Hybrid cycling in inactive people with long-term spinal cord injury

Effects on fitness, physical activity and health

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Chapter 1

General introduction

Background

Physical activity provides fundamental health benefits in the general population, and appears to be even more essential in people with chronic physical disabilities [1]. Physical inactivity, observed in a large part of the general population, is a serious risk factor for developing several health complications (e.g. cardiovascular disease (CVD), obesity, diabetes type II) and an important cause of mortality [2]. Due to physical impairments, people with chronic disabilities are mostly less physically active and fit than the general population, and consequently have an even higher risk for developing these health complications [3,4].

Compared to other populations with physical disabilities, people with spinal cord injury (SCI) have among the lowest physical activity and fitness levels [5,6]. An SCI is a damage to the spinal cord, caused by a trauma (e.g. falls or traffic accidents) or non-trauma (e.g. cancer or infections) [7]. As a result of the injured spinal cord, the communication between the brain, spinal cord and peripheral nerves is disrupted, leading to senso-motoric and autonomic dysfunction below the lesion level. Due to the motoric dysfunction, manifested by muscle paralysis, many individuals with SCI (~80%) become lifetime wheelchair users [8]. As a consequence of the paralysis and wheelchair dependency, many people with SCI have a seriously inactive lifestyle, associated with deconditioning and a high incidence of secondary health complications (e.g. CVD, metabolic syndrome, chronic low-grade inflammation, visceral adiposity, osteoporosis and muscle atrophy) [9-12], negatively influencing functioning, participation and quality of life (QoL) [13].

Because of the improved medical care, life expectancy after SCI has considerably improved over the last few decades [48]. However, an additional problem is that people aging with SCI and those with long-term SCI have even greater difficulties with staying physically active and fit, consequently leading to a greater risk for the development of secondary health complications and a further reduction of participation and QoL [14,15]. Avoiding the above-described downward spiral, that appears to worsen with age and duration of injury, is crucial for people with long-term SCI.

A rehabilitation aftercare system that covers the lifespan in people with SCI has been suggested, including preventive actions and interventions to preserve a long-term active lifestyle and physical fitness, and to decrease the frequency, duration and severity of secondary health complications [13]. In this context, self-management and regular exercise seem to play an important role, since ‘self-management is power’ and ‘Exercise is Medicine’ [16-20]. It has been demonstrated that self-management is effective in preventing several health problems and modifying behavior, especially when active learning strategies are included [49]. Participation in regular exercise activities has also been shown to promote a range of health benefits, including improved physical fitness and prevention or reduction of several secondary complications [16, 30, 53, 54].

Currently, there is no structured SCI-specific aftercare system operational in the Netherlands, and there is insufficient knowledge on the relations between physical activity, fitness and secondary complications, and the effectiveness of intervention strategies to improve

these facets in people with long-term SCI. To get more insight in these relations and to examine different interventions, the multicenter and multidisciplinary research program 'Active LifestyLe Rehabilitation Interventions in long-term Spinal Cord injury (ALLRISC)' was conducted [21].

Research program ALLRISC

The research program ALLRISC was embedded in the active Dutch SCI clinical research network, financially supported by The Netherlands Organization for Health Research and Development (ZonMw). This well-organized network is a multicenter and multidisciplinary collaboration among the eight Dutch rehabilitation centers with a specialized SCI unit, academic research groups, the Dutch Flemish Spinal cord Society (DuFSCoS) and the Dutch SCI patient organization (Dwarslaesie Organisatie Nederland; DON). Fourteen years ago, it started as the multicenter research program 'Restoration of Mobility in SCI Rehabilitation' that mainly focused on the clinical rehabilitation phase and up to five years after discharge [50-52]. Building upon the outcomes and experience of this previous clinical research program, ALLRISC focused on the long-term impact of SCI on active lifestyle, fitness, health, participation and QoL, and on interventions to maintain and improve these facets in the context of lifelong rehabilitation follow-up care.

ALLRISC consisted of four research projects (one cross-sectional study and three randomized-controlled trials (RCTs)) focusing on the same program-wide outcome measures (i.e. physical activity, fitness, health, participation and QoL), as well as on project-specific measures, following the ICF model (Figure 1) [21, 22]. The primary aims of ALLRISC were (1) to obtain a better understanding of the importance and requirements of regular rehabilitation aftercare in the context of long-term preservation of an active lifestyle, fitness, health, participation and QoL in people with long-term SCI, and (2) to develop evidence-based components and guidelines for an adequate SCI-specific rehabilitation aftercare plan in the Netherlands.

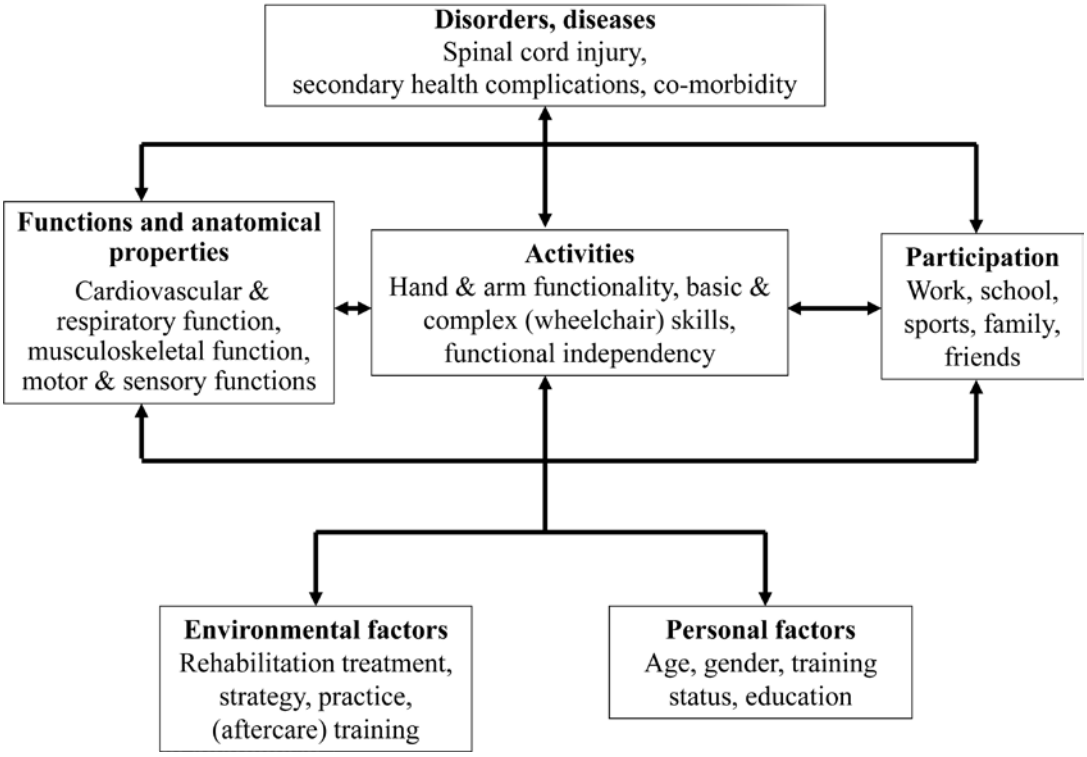

Figure 1. Health status in spinal cord injury, based on the ICF model [21,22]

The cross-sectional study (study 1, [23]) aimed to describe the prevalence of several secondary health complications (e.g. urinary tract and bowel problems, spasticity and pressure ulcers), and the impact of these complications on the program-wide outcome measures in a group of 300 individuals with long-term SCI. All eight Dutch rehabilitation centers with a specialized SCI unit participated in this study. Since the intervention studies were expected to be most relevant for people with low physical activity levels, Study 1 participants were invited to participate in one of the three RCTs if they met the inclusion criterion 'physically inactive' (i.e. score of <30 on the 'Physical Activities Scale for Individuals with Physical Disabilities (PASIPD)) [24].

The three RCTs aimed to investigate the effects of a 16-wk self-management (study 2, [25]), low-intensity wheelchair exercise (study 3, [26]) and hybrid cycle exercise (study 4, [27]) intervention on the program-wide and project-specific outcome measures. The self-management intervention, performed in four of the eight Dutch rehabilitation centers, focused on problem-solving ability, proactive coping, education and self-efficacy. The experimental group (N=40) received individual and group teaching and counselling sessions, while the control group (N=40) only received oral and written information (knowledge transfer). Study 3, performed in two other

rehabilitation centers, focused on the upper-body overuse paradigm. To avoid overuse of the upper-body musculoskeletal system, the intensity of exercise should not be too high in people with SCI. Therefore, a low-intensity (30% heart rate reserve) wheelchair exercise intervention (N=20) was evaluated, and compared with a non-trained control group (N=20). Study 4, performed in the final two rehabilitation centers, is central in the current thesis.

ALLRISC study 4: Effects of hybrid cycling

ALLRISC study 4 focused on the lower-body disuse paradigm. Due to paralysis of the lower limbs, exercise in people with long-term SCI predominantly involves activities of the non-paralyzed upper body [28]. Manual wheelchair exercise used to be one of the most frequently used exercise modes in people with SCI [55,56]. However, handrim wheelchair propulsion was found to be highly mechanically inefficient [57] and stressing to the upper body [58,59], often leading to overuse of the upper-body musculoskeletal system (including discomfort and pain), and consequently impaired functioning. To (partly) prevent these overuse problems, a handcycle can be used as a better alternative for upper-body exercise since handcycling is more mechanically efficient and less stressing to the upper-body than manual wheelchair propulsion [59, 60]. Nowadays, the handcycle is a commonly used mobility device and upper-body exercise mode in the Netherlands, already introduced during clinical rehabilitation [6]. Many Dutch people with SCI have an add-on handcycle together with their wheelchair that can be easily used for exercise and indoor and outdoor mobility (Figure 2).

However, several physiological factors related to SCI and upper-body exercise alone (e.g. handcycling), including the relatively small active muscle mass, inactivity of the skeletal muscle pump of the legs and insufficient cardiovascular reflex responses, may reduce desired (aerobic) training effects [61]. Moreover, due to the specificity principle, it is likely that upper-body training alone would not notably contribute to the prevention or improvement of several secondary complications in the lower limbs, such as osteoporosis, muscle atrophy, and vascular dysfunction [29,30].

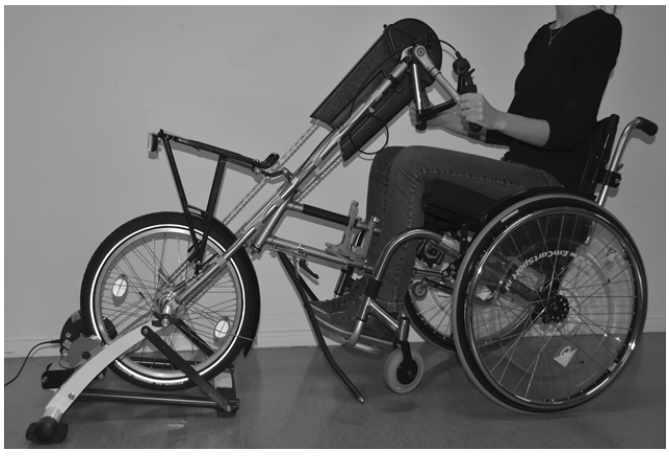

Figure 2 The add-on handcycle for voluntary upper-body exercise

Functional electrical stimulation (FES) can be used to reactivate the paralyzed lower-limb musculature and consequently reduce some of the above-mentioned problems. FES is a technique that uses computer-generated low-level electrical pulses to stimulate the contraction of targeted muscles through surface electrodes strategically placed over these muscles [63]. Since the early 1980s, this technique became a promising aid for the rehabilitation of people with SCI [61]. The most common system for lower-extremity FES exercise is the leg cycle ergometer, which is pedaled via FES-induced contractions of the paralyzed quadriceps, hamstrings and gluteus muscle groups [62]. The computer of the ergometer controls all the stimulation parameters, including the magnitude, frequency and sequence of the electrical stimulation in order to produce a fluid pedaling motion. The most common commercially available leg cycle ergometer in use is the ERGYS Clinical Rehabilitation System (Therapeutic Alliances, Inc., Fairborn, OH; Figure 3).

A major advantage of FES-induced leg exercise over voluntary arm exercise alone is that it can activate a large muscle mass that otherwise would be passive due to paralysis. This can potentially provide benefits to improve lower-limb integrity, increase the circulation by activating the skeletal muscle pump of the legs, and induce larger aerobic exercise responses. Various studies on FES-induced leg exercise have indeed found beneficial effects on aerobic fitness [30-34], lower-extremity bone mineral density (BMD) [35], muscle mass and strength [12,36] and vascular function [37]. Thus, these findings suggest that FES-induced leg exercise may positively influence deconditioning and secondary health complications (e.g. lower-body osteoporosis, muscle atrophy and vascular dysfunction) in people with SCI.

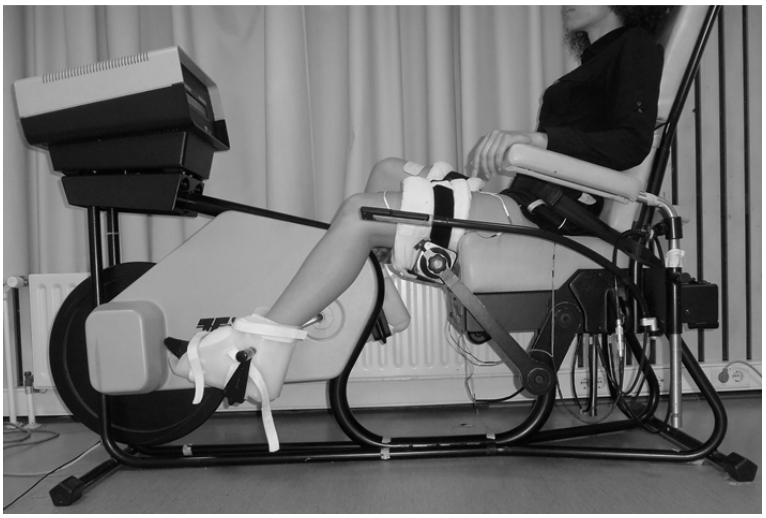

Figure 3 The cycle ergometer for FES-induced leg exercise.

To further increase the active muscle mass and subsequently provide greater aerobic exercise responses, a hybrid mode of exercise can be used in which voluntary arm exercise is combined with FES-induced leg exercise. This was previously done by attaching a separate arm crank ergometer to the FES system (e.g. the ERGYS) [38,40,64]. However, more recent technological developments have introduced more user-friendly hybrid exercise devices as alternatives for in- and outdoor exercise [39, 42]. One of these hybrid exercise devices is the BerkelBike (BerkelBike B.V., St, Michielsgestel, the Netherlands) that combines synchronous handcycling with asynchronous FES-induced leg cycling (Figure 4). Despite the potentially greater benefits of hybrid exercise over arm exercise alone, this commercially available hybrid cycle is not yet as commonly used as the handcycle in Dutch SCI rehabilitation.

Several intervention studies on hybrid exercise (i.e. rowing or cycling) showed positive effects on fitness [41-45] and vascular function [46,47]. However, limitations of these studies were the absence of a control group (except for Mutton et al. [44]), the relatively small number of participants, and the fact that only one aspect of hybrid exercise (i.e. fitness or vascular function) was investigated. To date, there is insufficient knowledge of (1) the integrated effects of hybrid exercise on the ICF levels of functions and anatomical properties, activities and participation in people with long-term SCI, and (2) the potential greater benefits over upper-body exercise alone.

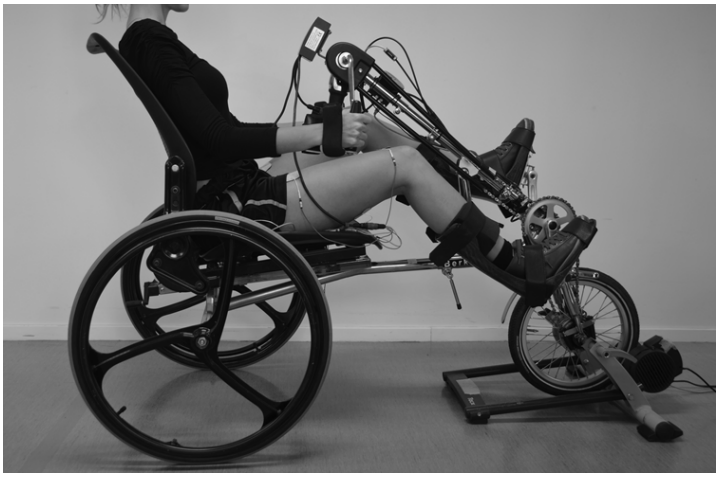

Figure 4 The hybrid cycle for combined FES-induced leg and voluntary arm exercise

Therefore, the purpose of ALLRISC study 4 was to investigate the effectiveness of a 16-wk hybrid cycle versus handcycle exercise program on the program-wide outcome measures (i.e. physical activity, fitness, health, participation and QoL), as well as on project-specific measures (i.e. metabolic syndrome, inflammatory status, visceral adiposity, immune function, lower-body soft tissue composition and BMD, bone turnover markers and vascular function) in inactive people with long-term SCI. During this 16-wk RCT, both the experimental (hybrid cycle) and control (handcycle) group trained twice a week for 18-30 min in one of the two rehabilitation centers with a specialized SCI unit (Reade Amsterdam or St. Maartenskliniek Nijmegen). Outcome measures were obtained in the week before the training program (T1), after 8 weeks of training (T2), in the week after (T3), and 26 weeks after the training program (T4).

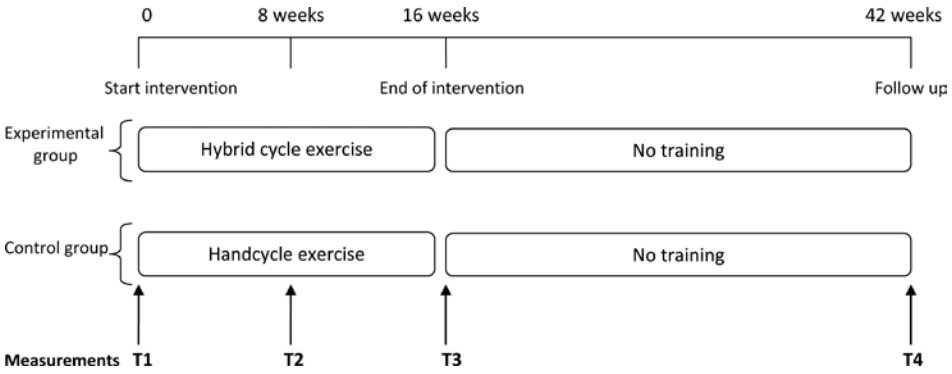

Figure 5 Design of ALLRISC study 4

Aim and outline of this thesis

The aim of the current thesis was to evaluate the effectiveness of the above-described 16-wk RCT on a selection of the obtained outcome measures (i.e. fitness, physical activity, CVD risk factors, and lower-body soft tissue composition and BMD).

In chapter 2 of this thesis, the experimental design of ALLRISC study 4 is extensively described. To get more insight in the metabolic and cardiorespiratory responses during hybrid cycling versus handcycling at equal subjective exercise intensity levels, a cross-sectional study was conducted parallel to the RCT, of which the results are presented in chapter 3. In chapter 4, the effects of the 16-wk RCT on fitness and physical activity are evaluated. Chapter 5 describes the effectiveness of the RCT on different CVD risk factors (i.e. metabolic syndrome, inflammatory status and visceral adiposity). To be able to examine training effects on knee BMD, we developed a new method to measure proximal tibia and distal femur BMD using dual-energy X-ray absorptiometry (DXA). This method, as well as the reliability of it, is described in chapter 6. Chapter 7 evaluates the effects of 16-wk hybrid cycle versus handcycle exercise on lower-body tissue composition and proximal tibia and distal femur BMD. Finally, in chapter 8, the main findings of this thesis are summarized and discussed, and implications for clinical practice and recommendations for future research are provided.

REFERENCES

1. Durstine JL, Painter P, Franklin BA. Morgan D, Pitetti KH, Roberts SO. Physical activity for the chronically ill and disabled. Sports Med 2000;30(3):207-19.
2. Bouchard C, Shephard R. Physical activity, fitness and health: the model and key to concepts. Champaign, IL: Human Kinetics;1994.
3. Rimmer JH, Chen MD, Hsieh K. A conceptual model for identifying, preventing, and managing secondary conditions in people with disabilities. Phys Ther 2011;91(12):1728-39.
4. Rimmer JH, Braddock D. Health promotion for people with physical, cognitive and sensory disabilities: an emerging national priority. Am J Health Promot 2002;16(4):220-4, ii.
5. Van den Berg-Emons RJ, Bussmann JB, Haisma JA, Sluis TA, van der Woude LH, Bergen MP, et al. A prospective study on physical activity levels after spinal cord injury during inpatient rehabilitation and the year after discharge. Arch Phys Med Rehabil 2008;89(11):2094-101.
6. Valent L, Dallmeijer AJ, Houdijk H, Slootman HJ, Post MW, Van der Woude LH. Influence of handcyling on physical capacity in the rehabilitation of persons with a spinal cord injury: a longitudinal cohort study. Arch Phys Med Rehabil 2008;89(6):1016-22.
7. Van den Berg ME, Castellote JM, de Pedro-Cuesta J, Mahillo-Fernandez I. Survival after spinal cord injury: a systematic review. J Neurotrauma 2010;27(8):1517-28.
8. Post MW, van Asbeck FW, van Dijk AJ, Schrijvers AJ. Services for spinal cord injured: availability and satisfaction. Spinal Cord 1997;35(2):109-15.
9. Myers J, Lee M, Kiratli J. Cardiovascular disease in spinal cord injury: an overview of prevalence, risk, evaluation, and management. Am J Phys Med Rehabil 2007;86(2):142-52.
10. Wang TD, Wang YH, Huang TS, Su TC, Pan SL, Chen SY. Circulating levels of markers of inflammation and endothelial activation are increased in men with chronic spinal cord injury. J Formos Med Assoc 2007;106(11):919-28
11. Zehnder Y, Lüthi M, Michel D, Knecht H, Perrelet R, Neto I, et al. Long-term changes in bone metabolism, bone mineral density, quantitative ultrasound parameters, and fracture incidence after spinal cord injury: a cross-sectional observational study in 100 paraplegic men. Osteoporos Int 2004;15(3):180-9.
12. Baldi JC, Jackson RD, Moraill R, Mysiw WJ. Muscle atrophy is prevented in patients with acute spinal cord injury using functional electrical stimulation. Spinal Cord 1998;36(7):463-9.
13. Priebe MM, Chiodo AE, Scelza WM, Kirshblum SC, Wuermser LA, Ho CH. Spinal cord injury medicine. 6. Economic and societal issues in spinal cord injury. Arch Phys Med Rehabil 2007;88(3 Suppl 1):S84-8.
14. Pentland W, McColl MA, Rosenthal C. The effect of aging and duration of disability on long term health outcomes following spinal cord injury. Paraplegia 1995;33(7):367-73.
15. Charlifue S, Lammertse DP, Adkins RH. Aging with spinal cord injury: changes in selected health indices and life satisfaction. Arch Phys Med Rehabil 2004;85(11):1848-53.
16. Manns PJ, McCubbin JA, Williams DP. Fitness, inflammation and the metabolic syndrome in men with paraplegia. Arch Phys Med Rehabil 2005;86(6):1176-81.
17. Fernhall B, Heffernan K, Jae SY, Hedrick B. Health implications of physical activity in individuals with spinal cord injury: a literature review. J Health Hum Serv Adm 2008;30(4):468-502.
18. Nash, M. Exercise as a health-promoting activity following spinal cord injury. J Neurol Phys Ther 2005;29(2):87-103, 106.
19. Hicks AL, Martin Ginis KA, Pelletier CA, Ditor DS, Foulon B, Wolfe DL. The effects of exercise training on physical capacity, strength, body composition and functional performance among adults with spinal cord injury: a systematic review. Spinal Cord 2011;49(11):1103-27.
20. Chiodo AE, Scelza WM, Kirshblum SC, Wuermser LA, Ho CH, Priebe MM. Spinal cord injury medicine. 5. Long-term medical issues and health maintenance. Arch Phys Med Rehabil 2007;88(3 Suppl 1):S76–S83.
21. Van der Woude LVH, de Groot S, Postema K, Bussmann JBJ, Janssen TWJ, ALLRISC, et al. Active LifestyLe Rehabilitation Interventions in aging Spinal Cord injury (ALLRISC): a multicenter research program. Disabil Rehabil 2013;35(13):1097-103.
22. WHO. International Classification of Functioning, Disability and Health. Geneva: World Health Organisation; 2001.
23. Adriaanse JJ, van Asbeck FW, Lindeman E, van der Woude LH, de Groot S, Post MW. Secondary health conditions in persons with a spinal cord injury for at least 10 years: design of a comprehensive long-term cross-sectional study. Disabil Rehabil 2013;35(13):1104-10.

24. Washburn RA, Zhu W, McAuley E, Frogley M, Figoni SF. The physical activity scale for individuals with physical disabilities: development and evaluation. Arch Phys Med Rehabil 2002;83(2):193-200.
25. Kooijmans H, Post MW, van der Woude LH, de Groot S, Stam HJ, Bussmann JB. Randomized controlled trial of a self-management intervention in persons with spinal cord injury: design of the HABITS (Healthy Active Behavioural Intervention in SCI) study. Disabil Rehabil 2013;35(13):1111-8.
26. Van der Scheer JW, de Groot S, Postema K, Veeger DH, van der Woude LH. Design of a randomized-controlled trial on low-intensity aerobic wheelchair exercise for inactive persons with chronic spinal cord injury. Disabil Rehabil 2013;35(13):1119-26.
27. Bakkum AJ, de Groot S, van der Woude LH, Janssen TW. The effects of hybrid cycle training in inactive people with long-term spinal cord injury: design of a multicentre randomized controlled trial. Disabil Rehabil 2013;35(13):1127-32.
28. Glaser RM. Arm exercise training for wheelchair users. Med Sci Sports Exerc 1989;21(5 Suppl):S149-57.
29. Glaser RM, Sawka MN, Durbin RJ, Foley DM, Suryaprasad AG. Exercise program for wheelchair activity. Am J Phys Med 1981;60(2):67-75.
30. Janssen TWJ, Glaser RM, Shuster B. Clinical efficacy of electrical stimulation exercise training: Effects on health, fitness, and function. Top Spinal Cord Inj Rehabil 1998;3(3):33-49.
31. Goss FL, McDermott A, Robertson RJ. Changes in peak oxygen uptake following computerized functional electrical stimulation in the spinal cord injured. Res Q Exerc Sport 1992;63(1):76-9.
32. Hooker SP, Figoni SF, Rodgers MM, Glaser RM, Mathews T, Suryaprasad AG, et al. Physiologic effects of electrical stimulation leg cycle exercise training in spinal cord injured persons. Arch Phys Med Rehabil 1992;73(5):470-6.
33. Hooker SP, Figoni SF, Glaser RM, Rodgers MM, Ezenwa BN, Faghri PD. Physiologic responses to prolonged electrically stimulated leg-cycle exercise in the spinal cord injured. Arch Phys Med Rehabil 1990;71(11):863-9.
34. Pollack SF, Axen K, Spielholz N, Levin N, Haas F, Ragnarsson KT. Aerobic training effects of electrically induced lower extremity exercises in spinal cord injured people. Arch Phys Med Rehabil 1989;70(3):214-9.
35. Chen SC, Lai CH, Chan WP, Huang MH, Tsai HW, Chen JJ. Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. Disabil Rehabil 2005;27(22):1337-41.
36. Sloan KE, Bremner LA, Byrne J, Day RE, Scull ER. Musculoskeletal effects of an electrical stimulation induced cycling program in the spinal injured. Paraplegia 1994;32(6):407-15.
37. Gerrits HL, de Haan A, Sargeant AJ, van Langen H, Hopman MT. Peripheral vascular changes after electrically stimulated cycle training in people with spinal cord injury. Arch Phys Med Rehabil 2001;82(6):832-9.
38. Raymond J, Davis GM, Climstein M, Sutton JR. Cardiorespiratory responses to arm cranking and electrical stimulation leg cycling in people with paraplegia. Med Sci Sports Exerc 1999;31(6):822-8.
39. Laskin JJ, Ashley EA, Olenik LM, Burnham R, Cumming DC, Steadward RD, et al. Electrical stimulation-assisted rowing exercise in spinal cord injured people. A pilot study. Paraplegia 1993;31(8):534-41.
40. Hooker SP, Figoni SF, Rodgers MM, Glaser RM, Mathews T, Suryaprasad AG, et al. Metabolic and hemodynamic responses to concurrent voluntary arm crank and electrical stimulation leg cycle exercise in quadriplegics. J Rehabil Res Dev 1992;29(3):1-11.
41. Brurok B, Helgerud J, Karlsen T, Leivseth G, Hoff J. Effect of aerobic high-intensity hybrid training on stroke volume and peak oxygen consumption in men with spinal cord injury. Am J Phys Med Rehabil 2011;90(5):407-14.
42. Heesterbeek PJC, Berkelmans HWA, Thijssen DHJ, van Kuppevelt HJM, Hopman MTE, Duysens J. Increased physical fitness after 4-week training on a hybrid FES-cycle in persons with spinal cord injury. Technology and Disability 2005;17(2):103-10.
43. Wheeler GD, Andrews B, Lederer R, Davoodi R, Natho K, Weiss C, et al. Functional electric stimulation-assisted rowing: increasing cardiovascular fitness through functional electric stimulation rowing training in persons with spinal cord injury. Arch Phys Med Rehabil 2002;83(8):1093-9.
44. Mutton DL, Scremin AM, Barstow TJ, Scott MD, Kunkel CF, Cagle TG. Physiologic responses during functional electrical stimulation leg cycling and hybrid exercise in spinal cord injured subjects. Arch Phys Med Rehabil 1997;78(7):712-8.
45. Krauss JC, Robergs RA, Depaepe JL, Kopriva LM, Aisenbury JA, Anderson MA, et al. Effects of electrical stimulation and upper body training after spinal cord injury. Med Sci Sports Exerc 1993;25(9):1054-61.
46. Thijssen DH, Ellenkamp R, Smits P, Hopman MT. Rapid vascular adaptations to training and detraining in persons with spinal cord injury. Arch Phys Med Rehabil 2006;87(4):474-81.
47. Thijssen DH, Heesterbeek P, van Kuppevelt DJ, Duysens J, Hopman MT. Local vascular adaptations after hybrid training in spinal cord-injured subjects. Med Sci Sports Exerc 2005;37(7):1112-8

48. Strauss DJ, Devivo MJ, Paculdo DR, Shavelle RM. Trends in life expectancy after spinal cord injury. Arch Phys Med Rehabil 2006;87(8):1079-85.
49. Devine EC. Meta-analysis of the effects of psychoeducational care in adults with asthma. Res Nurs Health 1996;19(5):367-76.
50. De Groot S, Dallmeijer AJ, Post MW, van Asbeck FW, Nene AV, Angenot EL, et al. Demographics of the Dutch multicentre prospective cohort study 'Restoration of mobility in spinal cord injury rehabilitation'. Spinal Cord 2006;44(11):668-75.
51. Kilkens OJ, Dallmeijer AJ, Nene AV, Post MW, van der Woude LH. The longitudinal relation between physical capacity and wheelchair skill performance during inpatient rehabilitation of people with spinal cord injury. Arch Phys Med Rehabil 2005;86(8):1575-81.
52. Haisma JA, Bussmann JB, Stam HJ, Sluis TA, Bergen MP, Post MW, et al. Physical fitness in people with a spinal cord injury: the association with complications and duration of rehabilitation. Clin Rehabil 2007;21(10):932-40.
53. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 2011; 11: 607-615.
54. Jacobs PL, Nash MS. Exercise recommendations for individuals with spinal cord injury. Sports Med 2004;34(11):727-51.
55. Hoffman MD. Cardiorespiratory fitness and training in quadriplegics and paraplegics. Sports Med 1986;3(5):312-30.
56. Valent L, Dallmeijer A, Houdijk H, Talsma E, van der Woude L. The effects of upper body exercise on the physical capacity of people with a spinal cord injury: a systematic review. Clin Rehabil 2007;21(4):315-30.
57. Van der Woude LH, Veeger HE, Dallmeijer AJ, Janssen TW, Rozendaal LA. Biomechanics and physiology in active manual wheelchair propulsion. Med Eng Phys 2001;23(10):713-33.
58. Van Drongelen S, van der Woude LH, Janssen TW, Angenot EL, Chadwick EK, Veeger HE. Glenohumeral joint loading in tetraplegia during weight relief lifting: a simulation study. Clin Biomech (Bristol, Avon) 2006;21(2):128-37.
59. Arnet U, van Drongelen S, Scheel-Sailer A, van der Woude LH, Veeger DH. Shoulder load during synchronous handcycling and handrim wheelchair propulsion in persons with paraplegia. J Rehabil Med 2012;44(3):222-8.
60. Dallmeijer AJ, Zentgraaf ID, Zijp NI, van der Woude LH. Submaximal physical strain and peak performance in handcycling versus handrim wheelchair propulsion. Spinal Cord 2004;42(2):91-8.
61. Figoni SF. Exercise responses and quadriplegia. Med Sci Sports Exerc 1993;25(4):433-41.
62. Cybulski GR, Penn RD, Jaeger RJ. Lower extremity functional neuromuscular stimulation in cases of spinal cord injury. Neurosurgery 1984;15(1):132-46.
62. Glenn WW, Phelps ML. Diaphragm pacing by electrical stimulation of the phrenic nerve. Neurosurgery 1985;17(6):974-84.
63. Wilder RP, Jones EV, Wind TC, Edlich RF. Functional electrical stimulation cycle ergometer exercise for spinal cord injured patients. J Long Term Eff Med Implants 2002;12(3):161-74.
64. Davis GM, Servedio FJ, Glaser RM, Gupta SC, Suryaprasad AG. Cardiovascular responses to arm cranking and FNS-induced leg exercise in paraplegics. J Appl Physiol 1990;69(2):671-4.

Chapter 2

The effects of hybrid cycle training in inactive people with long-term spinal cord injury: design of a multicenter randomized-controlled trial

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ABSTRACT

Purpose: Physical activity in people with long-term spinal cord injury (SCI) is important to stay fit and healthy. The purpose of this study is to evaluate the effects of hybrid cycle training (hand cycling in combination with functional electrical stimulation-induced leg cycling) on fitness, physical activity and health among a group of inactive people with long-term SCI.

Method: This study will be a 16-week multicenter randomized controlled trial (RCT) with a 26-week follow-up. Forty inactive people, aged 28 to 65, with paraplegia or tetraplegia for at least 10 years, will be randomly assigned to either an experimental group (hybrid cycle group) or control group (hand cycle group). During 16 weeks, both groups will train twice a week 30 minutes at an intensity of 65-75% of their heart rate reserve. The primary outcome measure is fitness. Secondary outcome measures are physical activity and health-related parameters. The primary and secondary outcome measures will be assessed just before the training programme (T1), after 8 weeks of training (T2), directly after (T3), and 26 weeks after the training programme (T4).

Conclusion: The results of this RCT may provide future implications for exercise prescription that preserve long-term functioning in people with SCI.

INTRODUCTION

With today's specialized medical care, life expectancy of people with a spinal cord injury (SCI) has considerably improved. However, many people with long-term SCI show a seriously inactive lifestyle, associated with deconditioning and secondary health complications (e.g. pressure sores, osteoporosis, and cardiovascular disease), resulting in a reduced participation and quality of life [1-2]. It is important to avoid this downward spiral that threatens persons with long-term SCI. Therefore, the research programme "Active LifestyLe Rehabilitation Interventions in long-term Spinal Cord injury" (ALLRISC) was developed to address inactive lifestyle, deconditioning, and secondary complications in people who have a SCI for at least 10 years [3-4]. The current study is part of ALLRISC and focuses on the lower-body disuse paradigm [4]

Exercise for individuals with SCI has traditionally involved upper-body activities (e.g. hand cycling) due to their lower-limb paralysis. Unfortunately, this approach can limit successful health outcome since the dynamics of conventional arm exercise are not conducive to the development and maintenance of the superior levels of fitness that can be achieved with leg exercise. In addition, arm exercise alone may not markedly contribute to the prevention of some common secondary complications such as lower-limb muscle atrophy, osteoporosis, pressure sores, and a host of cardiovascular disorders [5-6]. Several physiological factors related to SCI and arm exercise may account for some of these problems including: the relatively small muscle mass available, deficient cardiovascular reflex responses, and inactivity of the skeletal muscle pump of the legs. Due to the specificity of exercise principle, arm exercise alone would be expected to do little to prevent lower-body deterioration.

Use of the paralyzed lower-limb musculature, accomplished through functional electrical stimulation (FES), could alleviate some of these problems. A major advantage of FES-induced

exercise of the paralyzed legs over voluntary arm exercise is that it can utilize a large muscle mass that otherwise would be dormant. This can potentially provide benefits to improve the integrity of the paralyzed lower limbs, augment the circulation by activating the skeletal muscle pump, as well as elicit relatively large exercise responses for better aerobic training capability. One of the developed exercise techniques uses a computer-controlled leg cycle ergometer which is pedalled via FES-induced contractions of the paralyzed lower-limb muscle groups. Several studies suggest benefits not only on physical capacity and endurance [7-11], but also on vascular [12], muscle [13-14], and bone systems [15] in the lower extremities. Altogether, these studies have shown evidence strongly suggesting that this type of exercise can offer multiple therapeutic benefits, encompassing improved physical fitness, as well as reduced risk of acquiring secondary health complications.

To further activate more muscle mass and subsequently provide greater exercise responses to enhance aerobic fitness training capability, a hybrid mode of exercise consisting of FES-induced leg exercise combined with voluntary arm exercise can be used (e.g. rowing or cycling) [16-18]. Several training studies performed on hybrid exercise suggest benefits on aerobic capacity [19-23] and vascular characteristics [24-25]. However, these studies had relatively small sample groups (6 to 11 participants) and investigated only one aspect of hybrid training (e.g. aerobic capacity or vascular function). Moreover, these studies had no control group (except for Mutton et al. [22] where participants acted as their own control). There are no randomized controlled trials (RCT's) to date that investigated multiple aspects of hybrid cycle training in people with long-term SCI.

Therefore, the aim of this RCT is to examine the effectiveness of a 16-week hybrid cycle training programme compared to a 16-week hand cycle training programme among a group of forty inactive people with long-term SCI on fitness health, and physical activity.

METHODS

Participants

The participant group will consist of forty inactive individuals, aged 28-65, with paraplegia or tetraplegia for at least 10 years (age at onset SCI $\geq$ 18 years). People will be qualified as 'inactive' if their score on the Physical Activities Scale for Individuals with Physical Disabilities (PASIPD) [26] is lower than the 75^{th} percentile of a Dutch cohort study population [27]. Individuals will be eligible to be included if they are dependent on a handrim-propelled wheelchair, and if they have a spastic paralysis as well as no or limited sense in the lower extremity. Individuals will be excluded if they have contra-indications for physical training and testing (such as pressure sores, serious cardiovascular problems, or severe musculoskeletal complaints), or psychiatric problems that could interfere with the study. Individuals will also be excluded if they have plans to start another lifestyle (e.g. changes in physical activity and diet) in the months that the experiment is going on or if they have insufficient knowledge of the Dutch language to understand the purpose and protocol of the study. These eligibility criteria will be

checked by the research assistant in a telephone interview with the participant and by the rehabilitation physician during a thorough screening.

Potential participants will be selected from the databases of the two participating SCI-specialized Dutch rehabilitation centres: Reade Amsterdam and St. Maartenskliniek Nijmegen. An information letter will be sent to these people to inform them about the study. All participants have to provide written informed consent indicating voluntary participation in the study. Participants can withdraw from the study at any time for any reason if they wish to do so, without any consequences. Reasons for withdrawal will be registered. The study has been approved by the Medical Ethics Committee of the VU University Medical Centre Amsterdam.

Design

This study will be a 16-week RCT with a 26-week follow up, performed in two rehabilitation centres between November 2011 and November 2013. Within each rehabilitation centre, participants will be randomly assigned to either the experimental group (hybrid cycle group) or control group (hand cycle group). A blinded independent researcher will provide the allocation in sealed envelopes. The experimental group will receive a 16-week hybrid cycle training programme, while the control group will receive a 16-week hand cycle training programme (figure 1). The primary outcome measure is fitness. Secondary outcome measures are physical activity and health-related parameters. The primary and secondary outcome measures will be assessed just before the training programme (T1), after 8 weeks of training (T2), directly after (T3), and 26 weeks after the training programme (T4).

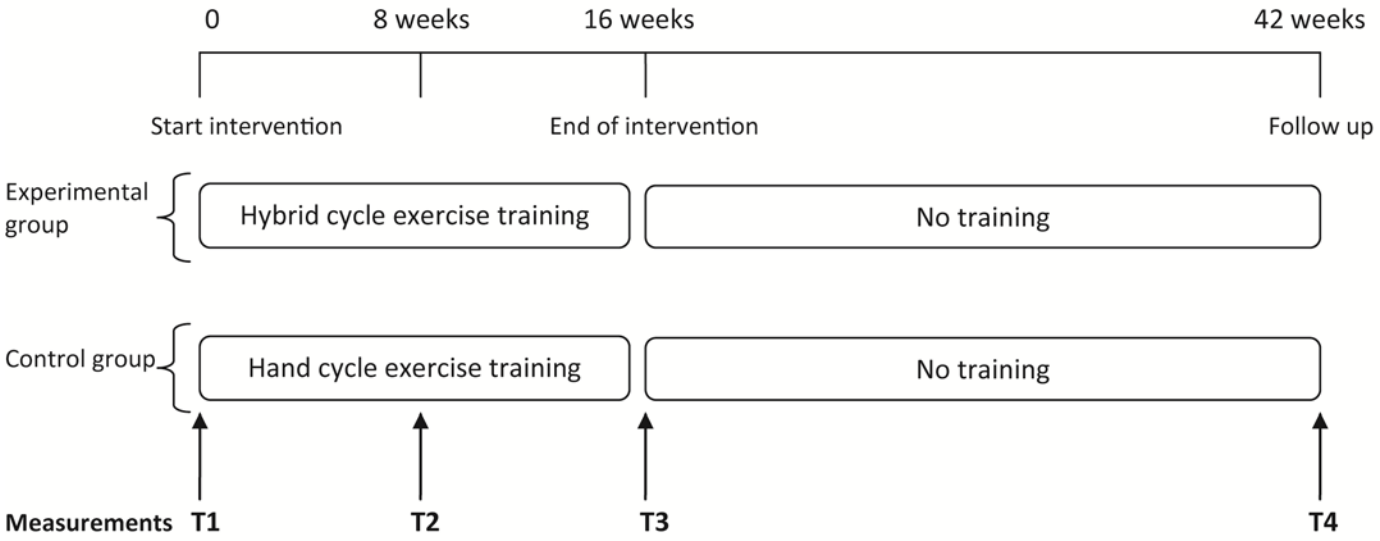

Figure 1 Experimental design of the study (intervention and measurements)

Training device

The hybrid cycle

The hybrid cycle (BerkelBike Pro, BerkelBike B.V., St. Michielsgestel, the Netherlands; figure 2) combines synchronous hand cycling with asynchronous FES-induced leg cycling. The backrest and seat position can be adjusted to the participant's anthropometry. The feet can be fastened in the foot pedals. A 6-channel stimulator (Impuls, BerkelBike B.V., St. Michielsgestel, the Netherlands; figure 2A) provides electrical stimulation via self-adhesive 50 x 90 mm surface electrodes (Stimex, Pierenkemper GmbH, Germany) placed bilaterally over the quadriceps, hamstrings and gluteus muscles. The stimulator receives information from the crank angle encoder (figure 2B) about pedal position and velocity to control the cyclic stimulation pattern. The stimulator has five preset stimulation programs (program test, 1, 2, 3 and 4), each with different FES firing angles and stimulation frequency (program test: 20 Hz; program 1-4: 35 Hz). In all programs, pulse duration is 400 µs and maximal current amplitude is 150 mA. During cycling, the legs move together with the arms and the current amplitude of the electrical stimulation can be changed manually with steps of 15 mA. When the leg musculature fatigues, arm activity can take over the entire propulsion. The hybrid cycle is equipped with 8 gears that can be changed manually. If necessary, it is possible to equip the hybrid cycle with quad grips.

The hand cycle

The hand cycle (Speedy-Bike, Reha-Technik GmbH, Delbrück, Germany; figure 3) is equipped with a wide synchronous bull-horn crank and with 8 gears that can be changed manually. The hand cycle can be equipped with quad grips, if necessary.

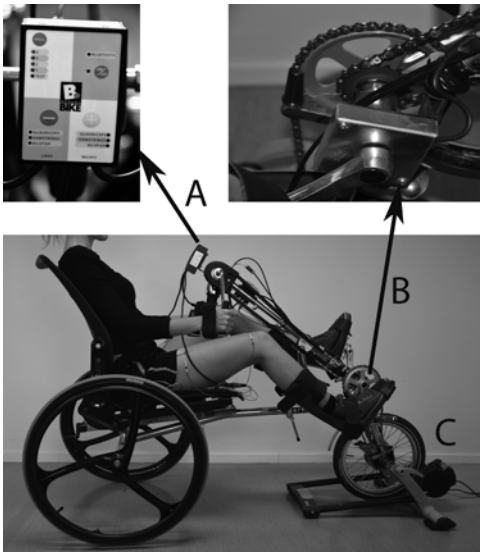

Figure 2 The hybrid cycle with stimulator (A) and crank angle encoder (B)

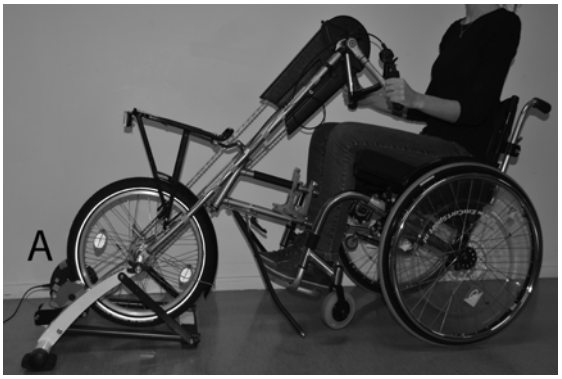

Figure 3 The hand cycle

Training protocol

Participants will perform 32 training sessions within a continuous period of 16 weeks. Each training session will consist of a short warm-up and cool-down period. After the warm up, the interval training protocol for that training session will start (table 1). During the training period, total cycle time will increase from 18 to 32 min. To provide sufficient recovery time, at least one day of rest will be scheduled in between training days. A week before the first training session, participants will perform a graded exercise test in their own handrim-propelled wheelchair to measure their maximal exercise responses (see section on 'Primary outcome measure'). Based on this test, the training load will be chosen such that the participant achieves an average heart rate response of 65-75% heart rate reserve (HRR) during training.

The first training will be a practice session, during which participants can become familiarized with cycling on either the hybrid cycle or hand cycle. This familiarization session is particularly important for the hybrid cycle group, since what tested here is the participant's response to the different stimulation programs. Based on this session, the trainer will choose a stimulation program that will be used in further training sessions.

Training sessions will be performed on an Ergotrainer (Tacx Flow, Technische Industrie Tacx B.V., Wassenaar, the Netherlands) adapted to the wheel size of the hybrid cycle and hand cycle. During training, heart rate will be monitored using radiotelemetry (Polar, Polar Electro Inc., Woodbury, NY) to ensure the proper training intensity is maintained as the training progresses. Since the use of heart rate as an indicator for training intensity can be unreliable in a part of the tetraplegic population [28], rating of perceived exertion (RPE) will serve as a subjective measure of training intensity. RPE will be measured after each training block and should be 4-7 on the Borg's 10-point scale [29].

Training intensity can be controlled by the participant making adjustments in cycle velocity or by the trainer adjusting the gear of the cycle or the resistance of the ergotrainer. In addition, during hybrid cycling the current amplitude of the stimulation can be adjusted manually by the trainer to control the degree of muscle activation. The trainer will try to induce strong muscle contractions during training. However, if the legs are moving too fiercely due to the stimulation or if the participant indicates that the stimulation is too intense, the trainer will decrease the current amplitude. Before and immediately after the training session, participants will be asked to report local pain and/or complaints. If serious musculoskeletal complaints occur, the researcher can decide to withdraw a participant from the study.

Table 1 Interval training protocol. Reps: repetitions

Session	Exercise bout (min)	Rest (min)	Reps	Total cycle time (min)
1-3	3	2	6	18
4-5	3	2	7	21
6-7	3	1.5	7	21
8-11	3	1.5	8	24
12-13	3	1	8	24
14-15	4	2	7	28
16-18	4	1.5	7	28
19-20	4	1	7	28
21-24	4	1.5	8	32
25-32	4	1	8	32

Primary outcome measure

The primary outcome measure in this study is fitness, which we define as the peak power output.

Peak power output (PO_{peak}) will be assessed during a graded exercise test in the participant's own handrim-propelled wheelchair on a motor-driven treadmill using the protocol of Dallmeijer et al. [4]. First, participants will perform a 3-min familiarization and warm-up session, followed by a 5-min rest interval. Then, two 3-min submaximal exercise blocks on two different constant workloads, with a 2-min rest period between blocks, will be performed to determine submaximal exercise responses. After the two submaximal blocks and a 2-min rest interval, the workload will be increased every minute by increasing the incline of the treadmill belt. The velocity of the treadmill belt will be held constant during testing, and depends on the participant's physical capability. The test will end when the participant can no longer maintain the velocity due to fatigue, or when the participant indicates that he/she wants to stop. Before the test, a separate drag test will be performed to determine the drag force (F_{drag}) of the wheelchair-user system on different inclines using the protocol of Van der Woude et al. [30]. Power output (PO) will be calculated from F_{drag} and the velocity of the belt (v), according to: PO (W) = F_{drag} (N) * v (m/s). PO_{peak} will be defined as the highest PO maintained for at least 30 s. During testing, respiratory gas exchange will be measured using open circuit spirometry (K4b², COSMED, Rome, Italy). Heart rate will be measured using radiotelemetry (Polar, Polar Electro Inc., Woodbury, NY).

Secondary outcome measures

The secondary outcome measures are physical activity and health-related parameters (metabolic syndrome, vascular structure and function, and bone mineral density of the distal femur and proximal tibia).

Physical activity will be measured objectively with an odometer as well as subjectively with the Dutch Physical Activities Scale for individuals with Physical Disabilities (PASIPD). The odometer will be mounted on the wheel of the participant's wheelchair to record every forward and backward revolution of the large wheels during 7 consecutive days [31]. Participants will be asked to keep a diary in which they register the number of wheel revolutions on a daily basis. The distance covered will be calculated by multiplying the number of wheel revolutions by the wheel circumference. The Dutch PASIPD will be used to subjectively assess physical activity [26]. This 12-item questionnaire requests the number of days a week and hours a day of participation in leisure (6 items), household (5 items), and occupational (1 item) activities over the past 7 days. Participants will be asked to fill in this questionnaire at home.

Metabolic syndrome is defined as having ≥ 3 of the following symptoms: abdominal obesity (waist circumference > 102 cm for males, > 88 cm for females), high blood pressure (> 130/85 mm Hg or use of medication for hypertension), high triglycerides (≥ 1.7 mmol/L), low high-density lipoprotein cholesterol (< 1.03 mmol/L for males, < 1.29 mmol/L for females), high fasting plasma glucose (≥ 5.6 mmol/L or use of medication for hyperglycemia) [32]. Waist circumference will be measured using a tape measure with the participant in supine position. Blood pressure will be taken on the right arm in a sitting position. Fasting blood samples will be taken to determine levels of triglycerides, high-density lipoprotein cholesterol, and plasma glucose.

Vascular structure and function will be measured under standardized conditions using high resolution ultrasound (T3000, Terason, Burlington, MA). Wall thickness and diameter will be examined across arteries in the neck, arm and leg [33]. Forearm blood flow and vascular resistance will be measured using venous occlusion plethysmography [34]. Physiological (flow-mediated dilation (FMD)) and pharmacological vasodilation (nitroglycerine (NTG)) will be examined after occlusion.

Bone mineral density (BMD) of the distal femur (DF) and proximal tibia will be measured using dual energy X-ray absorptiometry (DXA; Hologic Discovery, Hologic Inc., Waltham, Mass). DF and PT are common fracture sites in people with SCI [35]. However, PT and DF are not standard measurement sites and will therefore be scanned and analyzed as a 'forearm' [36]. In addition, biochemical markers of bone turnover (CTX and P1NP) will be determined from fasting blood samples [37-38].

Other outcome measures

Besides the primary and secondary outcomes, several other outcome measures will be assessed, among others things, for comparison with the other three ALLRISC studies. These other outcome measures will not be fully described, but will only be mentioned here: wheelchair skill performance [39-40], pulmonary function [41], immune function (immunoglobulin A [42]), inflammatory state (C-reactive protein, interleukins 6 and 10 [43]), health-related quality of life (World Health Organization Quality of Life- 5 [44]), participation (Utrecht Scale for Evaluation of Rehabilitation- Participation [45]), mood (Hospital Anxiety and Depression Scale [46]), sleep quality (Pittsburgh Sleep Quality Index [47]), fatigue (Fatigue Severity Scale [48]), upper extremity pain (Wheelchair User's Shoulder Pain Index [49-50]), bowel function (Neurogenic Bowel Dysfunction Score [51]), functional independence (Spinal Cord Independence Measure III [52]), self-efficacy (Spinal Cord Injury- Exercise Self-Efficacy Scale [53]; Self-Efficacy in Wheeled Mobility Scale [54]).

Statistical analysis

The sample size was calculated with the formulas given by Twisk [55] on the main outcome measure peak power output. This calculation, based on data of a preliminary study [41,56], revealed that a group size of 18 was required to detect a difference of 9 W between the experimental and control group on the main outcome measure. The power was 0.8 and the alpha was set at 0.05. With an expected drop-out of 10-15%, we aim to recruit at least 20 participants per group. Descriptive statistics will be used for the outcome measures and for the relevant participant characteristics. Student t-tests will be performed to evaluate group differences at baseline. Multifactor analysis of variance with repeated measures will be used to determine differences in change over time (treatment effect) between the experimental and the control group. To assess the potential relationship between outcome measures, a multivariate multi-level regression analysis will be performed. The level of significance will be set at 0.05. The data will be analyzed with the Statistical Package for the Social Science, version 18.0 (SPSS Inc, Chicago, Illinois, USA).

DISCUSSION

This paper outlines the design of a multicentre RCT that examines the integrated effects of a hybrid cycle training intervention in physically inactive people with long-term SCI on fitness, health, and physical activity. During hybrid cycling, upper-body exercise is combined with FES-induced exercise of the paralyzed lower body. We expect this training modality to be more effective in preventing deconditioning and several secondary health problems compared to arm exercise alone (e.g. hand cycling). The results of this study may provide future implications for exercise prescription that preserve long-term functioning in people with SCI.

REFERENCES

[1] Bloemen-Vrencken JH, de Witte LP, Post MW, van den Heuvel WJ. Health behaviour of persons with spinal cord injury. Spinal Cord 2007;45(3):243-9.

[2] Bloemen-Vrencken JH, Post MW, Hendriks JM, De Reus EC, De Witte LP. Health problems of persons with spinal cord injury living in the Netherlands. Disabil Rehabil 2005;27(22):1381-9.

[3] van der Woude LVH, de Groot S, Postema K, Bussmann JBJ, Janssen TWJ, ALLRISC, Post MWM. Active LifestyLe Rehabilitation Interventions in aging Spinal Cord injury (ALLRISC): a multicenter research program. Disabil Rehabil 2012.

[4] Dallmeijer AJ, Kilkens OJ, Post MW, de Groot S, Angenot EL, van Asbeck FW, Nene AV, van der Woude LH. Handrim wheelchair propulsion capacity during rehabilitation of persons with spinal cord injury. J Rehabil Res Dev 2005;42(3 Suppl 1):S55-63.

[5] Glaser RM. Arm exercise training for wheelchair users. Med Sci Sports Exerc 1989;21(5 Suppl):S149-57.

[6] Glaser RM, Sawka MN, Durbin RJ, Foley DM, Suryaprasad AG. Exercise program for wheelchair activity. Am J Phys Med 1981;60(2):67-75.

[7] Janssen TWJ, Glaser RM, Shuster B. Clinical efficacy of electrical stimulation exercise training: Effects on health, fitness, and function. Top Spinal Cord Inj Rehabil 1998;3(3):33-49.

[8] Goss FL, McDermott A, Robertson RJ. Changes in peak oxygen uptake following computerized functional electrical stimulation in the spinal cord injured. Res Q Exerc Sport 1992;63(1):76-9.

[9] Hooker SP, Figoni SF, Rodgers MM, Glaser RM, Mathews T, Suryaprasad AG, Gupta SC. Physiologic effects of electrical stimulation leg cycle exercise training in spinal cord injured persons. Arch Phys Med Rehabil 1992;73(5):470-6.

[10] Hooker SP, Figoni SF, Glaser RM, Rodgers MM, Ezenwa BN, Faghri PD. Physiologic responses to prolonged electrically stimulated leg-cycle exercise in the spinal cord injured. Arch Phys Med Rehabil 1990;71(11):863-9.

[11] Pollack SF, Axen K, Spielholz N, Levin N, Haas F, Ragnarsson KT. Aerobic training effects of electrically induced lower extremity exercises in spinal cord injured people. Arch Phys Med Rehabil 1989;70(3):214-9.

[12] Gerrits HL, de Haan A, Sargeant AJ, van Langen H, Hopman MT. Peripheral vascular changes after electrically stimulated cycle training in people with spinal cord injury. Arch Phys Med Rehabil 2001;82(6):832-9.

[13] Baldi JC, Jackson RD, Moraill R, Mysiw WJ, . Muscle atrophy is prevented in patients with acute spinal cord injury using functional electrical stimulation. Spinal Cord 1998;36(7):463-9.

[14] Sloan KE, Bremner LA, Byrne J, Day RE, Scull ER. Musculoskeletal effects of an electrical stimulation induced cycling program in the spinal injured. Paraplegia 1994;32(6):407-15.

[15] Chen SC, Lai CH, Chan WP, Huang MH, Tsai HW, Chen JJ. Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. Disabil Rehabil 2005;27(22):1337-41.

[16] Raymond J, Davis GM, Climstein M, Sutton JR. Cardiorespiratory responses to arm cranking and electrical stimulation leg cycling in people with paraplegia. Med Sci Sports Exerc 1999;31(6):822-8.

[17] Laskin JJ, Ashley EA, Olenik LM, Burnham R, Cumming DC, Steadward RD, Wheeler GD. Electrical stimulation-assisted rowing exercise in spinal cord injured people. A pilot study. Paraplegia 1993;31(8):534-41.

[18] Hooker SP, Figoni SF, Rodgers MM, Glaser RM, Mathews T, Suryaprasad AG, Gupta SC. Metabolic and hemodynamic responses to concurrent voluntary arm crank and electrical stimulation leg cycle exercise in quadriplegics. J Rehabil Res Dev 1992;29(3):1-11.

[19] Brurok B, Helgerud J, Karlsen T, Leivseth G, Hoff J. Effect of aerobic high-intensity hybrid training on stroke volume and peak oxygen consumption in men with spinal cord injury. Am J Phys Med Rehabil 2011;90(5):407-14.

[20] Heesterbeek PJC, Berkelmans HWA, Thijssen DHJ, van Kuppevelt HJM, Hopman MTE, Duysens J. Increased physical fitness after 4-week training on a hybrid FES-cycle in persons with spinal cord injury. Technology and Disability 2005;17(2):103-10.

[21] Wheeler GD, Andrews B, Lederer R, Davoodi R, Natho K, Weiss C, Jeon J, Bhambhani Y, Steadward RD. Functional electric stimulation-assisted rowing: increasing cardiovascular fitness through functional electric stimulation rowing training in persons with spinal cord injury. Arch Phys Med Rehabil 2002;83(8):1093-9.

[22] Mutton DL, Scremin AM, Barstow TJ, Scott MD, Kunkel CF, Cagle TG. Physiologic responses during functional electrical stimulation leg cycling and hybrid exercise in spinal cord injured subjects. Arch Phys Med Rehabil 1997;78(7):712-8.
[23] Krauss JC, Robergs RA, Depaepe JL, Kopriva LM, Aisenbury JA, Anderson MA, Lange EK. Effects of electrical stimulation and upper body training after spinal cord injury. Med Sci Sports Exerc 1993;25(9):1054-61.
[24] Thijssen DH, Ellenkamp R, Smits P, Hopman MT. Rapid vascular adaptations to training and detraining in persons with spinal cord injury. Arch Phys Med Rehabil 2006;87(4):474-81.
[25] Thijssen DH, Heesterbeek P, van Kuppevelt DJ, Duysens J, Hopman MT. Local vascular adaptations after hybrid training in spinal cord-injured subjects. Med Sci Sports Exerc 2005;37(7):1112-8.
[26] Washburn RA, Zhu W, McAuley E, Frogley M, Figoni SF. The physical activity scale for individuals with physical disabilities: development and evaluation. Arch Phys Med Rehabil 2002;83(2):193-200.
[27] de Groot S, van der Woude LH, Niezen A, Smit CA, Post MW. Evaluation of the physical activity scale for individuals with physical disabilities in people with spinal cord injury. Spinal Cord 2010;48(7):542-7.
[28] Valent LJ, Dallmeijer AJ, Houdijk H, Slootman J, Janssen TW, Hollander AP, van der Woude LH. The individual relationship between heart rate and oxygen uptake in people with tetraplegia during exercise. Spinal Cord 2007;45(1):104-11.
[29] Noble BJ, Borg GA, Jacobs I, Ceci R, Kaiser P. A category-ration perceived exertion scale: relationship to blood and muscle lactates and heart rate. Med Sci Sports Exerc 1983;15(6):523-8.
[30] van der Woude LH, de Groot G, Hollander AP, van Ingen Schenau GJ, Rozendal RH. Wheelchair ergonomics and physiological testing of prototypes. Ergonomics 1986;29(12):1561-73.
[31] Janssen TW, van Oers CA, van der Woude LH, Hollander AP. Physical strain in daily life of wheelchair users with spinal cord injuries. Med Sci Sports Exerc 1994;26(6):661-70.
[32] Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109(3):433-8.
[33] Thijssen DHJ, Willems L, van den Munckhof I, Scholten R, Hopman MTE, Dawson EA, Atkinson G, Cable NT, Green DJ. Impact of wall thickness on conduit artery function in humans: Is there a “Folkow” effect? Atherosclerosis 2011;217(2):415-9.
[34] Groothuis JT, Thijssen DH, Rongen GA, Deinum J, Danser AH, Geurts AC, Smits P, Hopman MT. Angiotensin II contributes to the increased baseline leg vascular resistance in spinal cord-injured individuals. J Hypertens 2010;28(10):2094-101.
[35] Biering-Sorensen F, Hansen B, Lee BS. Non-pharmacological treatment and prevention of bone loss after spinal cord injury: a systematic review. Spinal Cord 2009;47(7):508-18.
[36] Henderson RC, Berglund LS, May R, Zemel BS, Grossberg RI, Johnson J, Plotkin H, Stevenson RD, Szalay E, Wong B and others. The relationship between fractures and DXA measures of BMD in the distal femur of children and adolescents with cerebral palsy or muscular dystrophy. J Bone Miner Res 2010;25(3):520-6.
[37] Rosen HN, Moses AC, Garber J, Iloputaife ID, Ross DS, Lee SL, Greenspan SL. Serum CTX: a new marker of bone resorption that shows treatment effect more often than other markers because of low coefficient of variability and large changes with bisphosphonate therapy. Calcif Tissue Int 2000;66(2):100-3.
[38] Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J. The use of biochemical markers of bone turnover in osteoporosis. Osteoporos Int 2000;11(18 Suppl 6):S2-17.
[39] Kilkens OJ, Dallmeijer AJ, De Witte LP, Van Der Woude LH, Post MW. The wheelchair circuit: construct validity and responsiveness of a test to assess manual wheelchair mobility in persons with spinal cord injury. Arch Phys Med Rehabil 2004;85(3):424-31.
[40] Kilkens OJ, Post MW, van der Woude LH, Dallmeijer AJ, van den Heuvel WJ. The wheelchair circuit: reliability of a test to assess mobility in persons with spinal cord injuries. Arch Phys Med Rehabil 2002;83(12):1783-8.
[41] Valent LJ, Dallmeijer AJ, Houdijk H, Slootman HJ, Janssen TW, Post MW, van der Woude LH. Effects of hand cycle training on physical capacity in individuals with tetraplegia: a clinical trial. Phys Ther 2009;89(10):1051-60.
[42] Fahlman MM, Engels HJ. Mucosal IgA and URTI in American college football players: a year longitudinal study. Med Sci Sports Exerc 2005;37(3):374-80.

[43] Wang TD, Wang YH, Huang TS, Su TC, Pan SL, Chen SY. Circulating levels of markers of inflammation and endothelial activation are increased in men with chronic spinal cord injury. J Formos Med Assoc 2007;106(11):919-28.
[44] Geyh S, Fellinghauer BA, Kirchberger I, Post MW. Cross-cultural validity of four quality of life scales in persons with spinal cord injury. Health Qual Life Outcomes 2010;8:94.
[45] van der Zee CH, Priesterbach AR, van der Dussen L, Kap A, Schepers VP, Visser-Meily JM, Post MW. Reproducibility of three self-report participation measures: The ICF Measure of Participation and Activities Screener, the Participation Scale, and the Utrecht Scale for Evaluation of Rehabilitation-Participation. J Rehabil Med 2010;42(8):752-7.
[46] Woolrich RA, Kennedy P, Tasiemski T. A preliminary psychometric evaluation of the Hospital Anxiety and Depression Scale (HADS) in 963 people living with a spinal cord injury. Psychol Health Med 2006;11(1):80-90.
[47] Iliescu EA, Coo H, McMurray MH, Meers CL, Quinn MM, Singer MA, Hopman WM. Quality of sleep and health-related quality of life in haemodialysis patients. Nephrol Dial Transplant 2003;18(1):126-32.
[48] Anton HA, Miller WC, Townson AF. Measuring fatigue in persons with spinal cord injury. Arch Phys Med Rehabil 2008;89(3):538-42.
[49] Curtis KA, Drysdale GA, Lanza RD, Kolber M, Vitolo RS, West R. Shoulder pain in wheelchair users with tetraplegia and paraplegia. Arch Phys Med Rehabil 1999;80(4):453-7.
[50] Curtis KA, Roach KE, Applegate EB, Amar T, Benbow CS, Genecco TD, Gualano J. Development of the Wheelchair User's Shoulder Pain Index (WUSPI). Paraplegia 1995;33(5):290-3.
[51] Christensen P, Bazzocchi G, Coggrave M, Abel R, Hultling C, Krogh K, Media S, Laurberg S. A randomized, controlled trial of transanal irrigation versus conservative bowel management in spinal cord-injured patients. Gastroenterology 2006;131(3):738-47.
[52] Catz A, Itzkovich M, Tesio L, Biering-Sorensen F, Weeks C, Laramee MT, Craven BC, Tonack M, Hitzig SL, Glaser E and others. A multicenter international study on the Spinal Cord Independence Measure, version III: Rasch psychometric validation. Spinal Cord 2007;45(4):275-91.
[53] Kroll T, Kehn M, Ho PS, Groah S. The SCI Exercise Self-Efficacy Scale (ESES): development and psychometric properties. Int J Behav Nutr Phys Act 2007;4:34.
[54] Fliess-Douer O, van der Woude LH, Vanlandewijck YC. Development of a new scale for percieved self-efficacy in manual wheeled mobility – a pilot study. J Rehabil Med 2011;43(7):602-8.
[55] Twisk JWR. Sample size calculations. In: Twisk JWR. Applied longitudinal data analysis for epidemiology. A practical guide. Cambridge: Cambridge University Press; 2003:280-5.
[56] van den Berg R, de Groot S, Swart KM, van der Woude LH. Physical capacity after 7 weeks of low-intensity wheelchair training. Disabil Rehabil 2010;32(21):1717-21.

Chapter 3

Metabolic rate and cardiorespiratory response during hybrid cycling versus handcycling at equal subjective exercise intensity levels in people with a spinal cord injury

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ABSTRACT

Objective: To compare the metabolic rate and cardiorespiratory response during hybrid cycling versus handcycling at equal subjective exercise intensity levels in people with a spinal cord injury (SCI).

Design: Cross-sectional study.

Setting: Amsterdam Rehabilitation Research Centre | Reade, Amsterdam, the Netherlands.

Methods: On separate days, nine individuals with a motor complete paraplegia or tetraplegia (eight men, age 40±13 years, time since injury 12±10 years) performed 5-minute bouts of hybrid cycling (day 1) and handcycling (day 2) at moderate (level 3 on a 10-point rating of perceived exertion (RPE) scale) and vigorous (RPE level 6) subjective exercise intensity while respiratory gas exchange was measured by open-circuit spirometry and heart rate was monitored using radiotelemetry.

Outcome measures: Metabolic rate (calculated with the Weir equation) and cardiorespiratory response (heart rate, oxygen pulse and ventilation).

Results: Overall, the metabolic rate during hybrid cycling was 3.4 kJ (16%) higher ($P = 0.006$) than during handcycling. Furthermore, compared to handcycling, the overall heart rate and ventilation during hybrid cycling was 11 bpm (11%) and 5.3 l/minute (18%) higher ($P = 0.004$ and 0.024), respectively, while the oxygen pulse was the same ($P = 0.26$).

Conclusion: Hybrid cycling induces a higher metabolic rate and cardiorespiratory response at equal RPE levels than handcycling, suggesting that hybrid cycling is more suitable for fighting obesity and increasing cardiorespiratory fitness in individuals with a SCI.

INTRODUCTION

People with a spinal cord injury (SCI) have a reduced total daily energy expenditure, which can partly be explained by reduced physical activity levels as a result of their paralysis and subsequent wheelchair dependency.[1] The serious inactive lifestyle in people with a SCI is associated with low cardiorespiratory fitness levels, obesity, and obesity-related disorders (e.g. diabetes and cardiovascular disease).[2-4] Furthermore, it is known that the work intensity of activities of daily life is not sufficient to improve or maintain the cardiorespiratory fitness and fight obesity in individuals with a SCI.[5-6] Therefore, it is important that people with a SCI perform exercise training at sufficiently high metabolic rates.

However, due to the lower-limb paralysis, exercise training in people with a SCI often involves upper-body activities (e.g. handcycling),[7-8] which may limit successful health outcome due to the relatively small active muscle mass, inactivity of the skeletal muscle pump of the legs and deficient cardiovascular reflex response.[9] To alleviate these problems, the paralyzed lower-limb musculature can be added to the upper-body exercise by functional electrical simulation (FES). Compared to upper-body exercise alone, this hybrid mode of exercise training (e.g. hybrid cycling) has the potential to induce higher levels of metabolic rate.[9-11]

The metabolic rate an individual is able to exercise at for a certain period is largely dependent on the subjectively experienced exercise intensity, which can easily be assessed with a

rating of perceived exertion (RPE) scale.[12] In people with a SCI, this method seemed to be an appropriate measure for exercise intensity during moderate to vigorous steady-state exercise.[13-14] Due to the limited active muscle mass, upper-body exercise alone may provoke high RPE levels at relatively low metabolic rates. Hybrid exercise might be a way to increase the metabolic rate as well as the cardiorespiratory response while exercising at equal RPE levels; however, this has not been investigated yet.

Therefore, the aim of this study was to compare the metabolic rate and cardiorespiratory response during hybrid cycling versus handcycling at equal RPE levels in a group of individuals with a SCI. It was hypothesized that, due to the larger muscle mass available, hybrid cycling would lead to a higher metabolic rate and cardiorespiratory response and would therefore be more effective in fighting obesity and increasing cardiorespiratory fitness.

METHODS

Participants

Nine individuals with a motor complete paraplegia or tetraplegia (Table 1) were recruited from the database of the local rehabilitation center, and participated in this study which was approved by the Medical Ethics Committee of the VU University Medical Centre Amsterdam. All participants provided written informed consent indicating voluntary participation in this study. Individuals with a spastic paralysis and absent or limited sense in the lower body were eligible to be included if they responded well (visible muscle contractions and no discomfort in the lower extremities) to FES for at least 5 consecutive minutes. Individuals were excluded if they had contra-indications for physical testing, such as pressure sores, serious cardiovascular problems, or severe musculoskeletal complaints. Participants refrained from strenuous exercise for at least 48 hours before the tests. Furthermore, participants were requested to consume their last meal at least two hours prior to testing, and to avoid caffeine and alcohol consumption in the 24 hours before testing.

Table 1 Demographics of the participants

Participant	Gender	Age (yrs)	TSI (yrs)	Lesion level	AIS	Height (cm)	Weight (kg)	BMI (kg/m²)
1	m	53	11	C7	C	180	65	20
2	m	40	19	T6	A	187	66	19
3	m	56	4	T7	A	176	85	27
4	m	25	4	T8	A	193	70	19
5	m	55	34	C3	C	175	91	30
6	m	30	12	T11	A	185	74	22
7	f	40	4	C7	C	186	68	20
8	m	31	6	C8	A	180	59	18
9	m	26	10	C6	A	189	78	22
Mean (SD)		40 (13)	12 (10)			183 (6)	73 (10)	22 (4)

Abbreviations: m: male; f: female; yrs: years; TSI; time since injury; AIS: ASIA (American Spinal Injury Association) Impairment Scale; BMI: body mass index; SD: standard deviation

Study design

This cross-sectional study was performed in the local rehabilitation center. During the first measurement occasion, all participants performed an exercise protocol on a hybrid cycle; during the second measurement occasion, an exercise protocol was performed on a handcycle (see section on "Protocol" and Figure 3 for more details regarding the different exercise protocols). To provide sufficient recovery time, 48-72 hours of relative rest was scheduled in between measurement occasions.

Exercise modalities

Hybrid cycle

The hybrid cycle (BerkelBike Pro, BerkelBike B.V., St. Michielsgestel, the Netherlands; Figure 1) combines synchronous handcycling with asynchronous FES-induced leg cycling. A 6-channel stimulator (Impuls, BerkelBike B.V., St. Michielsgestel, the Netherlands; Figure 1A) provides the electrical stimulation via 12 self-adhesive 50 x 90 mm surface electrodes (Stimex, Pierenkemper GmbH, Ehringshausen, Germany) placed bilaterally over the quadriceps, hamstrings and gluteus muscles. The stimulator receives information from the crank angle

encoder (Figure 1B) about pedal position and velocity to control the cyclic stimulation pattern. The stimulator has five preset stimulation programs, each with the same pulse duration (400 μs) and maximal current amplitude (150 mA), but with different stimulation frequencies (20-35 Hz) and FES firing angles. During cycling, the current amplitude of the electrical stimulation can be changed manually with steps of 15 mA. The hybrid cycle is equipped with 8 gears, and if necessary, quad grips can be mounted.

The handcycle

The handcycle (Speedy-Bike, Reha-Technik GmbH, Delbrück, Germany; Figure 2) is equipped with a wide synchronous bull-horn crank and with 8 gears that can be changed manually. If necessary, the handcycle can also be equipped with quad grips.

The front wheel of both cycles was mounted on an ergotrainer (Tacx Flow, Technische Industrie, Tacx B.V., Wassenaar, The Netherlands; Figure 1C and 2A) that was adapted to the wheel size of the cycles.

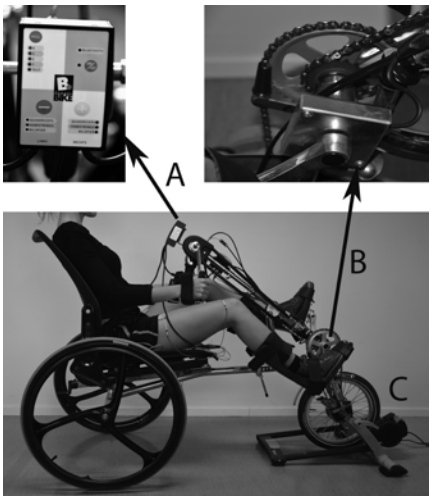

Figure 1 The hybrid cycle with the stimulator (A) and crank angle encoder (B) mounted on a ergotrainer (C).

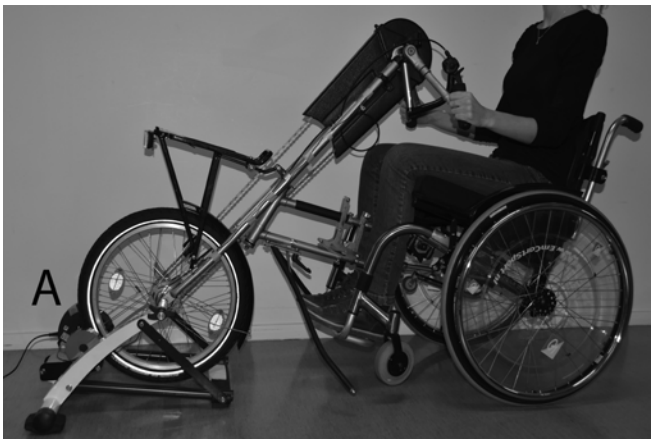

Figure 2 The handcycle mounted on a ergotrainer (A).

Protocol

Each measurement session consisted of a 2-minute warm-up and cool-down session of voluntary handcycling in the specific test cycle (in case of the hybrid cycle this meant that the legs were moved passively). After the warm up, the first 5-minute exercise bout was performed at moderate subjective exercise intensity (RPE level 3 on the Borg category-ratio 10 (CR10) scale),[12] and after a 5-minute rest interval, the second 5-minute exercise bout was performed at vigorous subjective exercise intensity (RPE level 6; Figure 3).

Before starting with the hybrid cycle test, first the participant's response to the five different stimulation programs was tested to examine the most suitable program for exercise testing. Since each program has different stimulation parameters (as described in the section on 'Exercise modalities), individuals may response differently to these programs; for example, it might be that a specific stimulation program induces discomfort in the lower limbs or a less smooth cycling motion. Based on subjective observations of the researcher and the perception of the participant, the program that produced the smoothest cycling motion without inducing discomfort was selected.

Before testing, the researcher extensively explained the Borg CR10 scale to the participants and indicated that the imposed RPE levels should reflect their overall perceived exertion (integrated sensation of central and peripheral stress). The participants were asked to maintain the imposed RPE levels as good as possible during all 5-minute exercise bouts. In order to do so, at any time during cycling participants were able to adjust the cycle velocity or ask the researcher to adjust the gear of the cycle or the resistance of the ergotrainer; in addition, during hybrid cycling the current amplitude of the stimulation could be adjusted manually by the researcher to control the degree of muscle activation. The researcher tried to induce strong lower-body muscle contractions; however, the current amplitude was decreased if the legs were moving too fiercely due to the stimulation or if the participants indicated that the stimulation was too intense.

During testing, respiratory gas exchange was measured using open-circuit spirometry (K4b², COSMED, Rome, Italy), heart rate was monitored using radiotelemetry (Polar, Polar Electro Inc., Woodbury, NY, USA), and power output was measured using a power meter (PowerTap Pro+, CycleOps, Madison, WI, USA) that was mounted on the front wheel of both cycles.

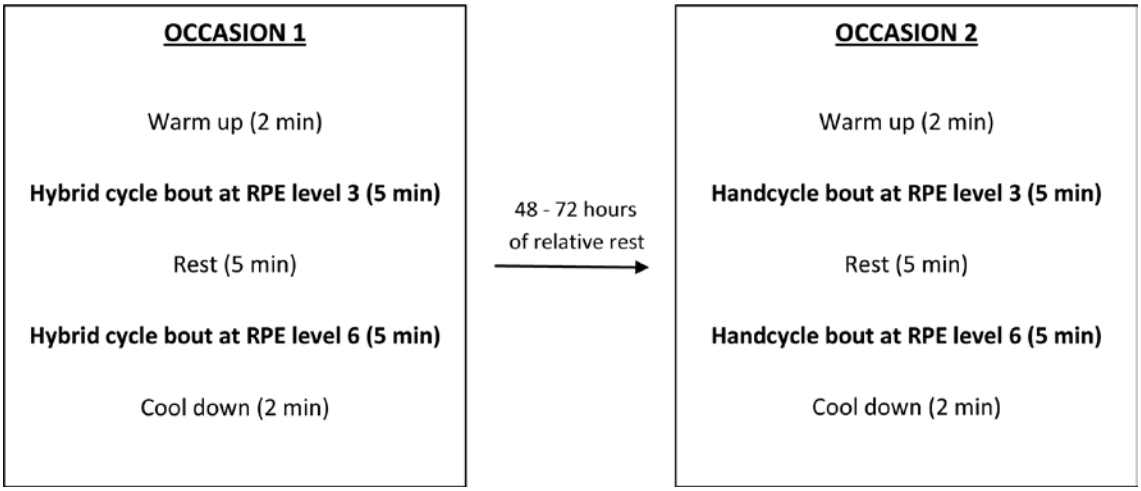

Figure 3 Exercise protocol. Warm-up and cool-down sessions consisted of voluntary handcycling alone in the specific test cycle.

Outcome measures

The main outcome measures of this study were the metabolic rate and cardiorespiratory response. The metabolic rate (kJ/minute) was calculated with the Weir method: 3.942 × VO_2 (l/minute) + VCO_2 (l/minute) × 4.182,[15] where VO_2 (l/minute) and VCO_2 (l/minute) were the average oxygen uptake and carbon dioxide emission during the last minute of the steady-state exercise bouts, respectively. Measures for cardiorespiratory response were heart rate, oxygen pulse (a surrogate for stroke volume and arteriovenous oxygen difference) and ventilation (V_E); the average heart rate (bpm) and V_E (l/minute) over the last minute of the bouts were used for analysis. Oxygen pulse (ml/beat) was calculated by dividing VO_2 (l/minute) by the heart rate (bpm). A secondary outcome measure was the power output (W) over the last minute of the exercise bouts.

Statistics

The assumption of normality was checked by visual inspection of the q-q plot and box plot of the data within the groups.; in addition, a Shapiro-Wilks test was performed on the data. Since there were no violations of these assumptions, the effect of exercise modality (hybrid cycling, handcycling) and subjective exercise intensity (RPE level 3 , RPE level 6) on the outcome measures was examined with two-way repeated measures ANOVA. If there was a significant interaction (or tendency to an interaction), paired t-tests were used to examine this interaction and to calculate the 95% confidence interval for each difference between the means. Partial eta squared (η_p^2) was calculated to determine the effect size.

RESULTS

Metabolic rate

There was a significant main effect for both exercise modality ($F(1,8) = 13.55$, $P = 0.006$, $\eta_p^2 = 0.63$) and exercise intensity ($F(1,8) = 23.73$, $P = 0.001$, $\eta_p^2 = 0.75$). Overall, compared to handcycling, the metabolic rate during hybrid cycling was 3.4 kJ/minute [1.3, 5.6] higher; and compared to RPE level 3, the metabolic rate at level 6 was 6.7 kJ/minute [3.5, 9.9] higher (Figure 4). The interaction between exercise modality and exercise intensity was also significant ($F(1,8) = 5.98$, $P = 0.04$, $\eta_p^2 = 0.43$). Follow-up analyses on the significant interaction revealed that the difference in metabolic rate between hybrid cycling and handcycling was higher at RPE level 6 (4.4 kJ/minute [1.8, 7.0]) than at level 3 (2.5 kJ/minute [0.4, 4.5]). Furthermore, the difference in metabolic rate between RPE level 3 and 6 was higher for hybrid cycling (7.7 kJ/minute [3.9, 11.4]) than for handcycling (5.8 kJ/minute [3, 8.5]).

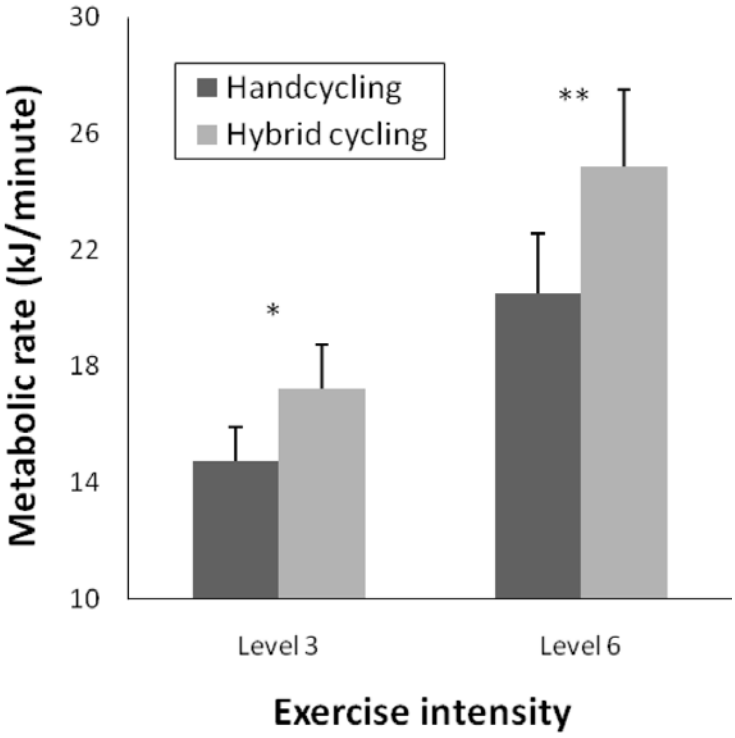

Figure 4 Absolute metabolic rate (mean + standard error) for handcycling (dark grey) and hybrid cycling (light grey) at RPE levels 3 and 6 (*P < 0.05; **P < 0.01).

Cardiorespiratory response

Heart rate

A significant main effect was found for both exercise modality ($F(1,7) = 18.18$, $P = 0.004$, $\eta_p^2 = 0.72$) and exercise intensity ($F(1,7) = 19.28$, $P = 0.003$, $\eta_p^2 = 0.73$). Overall, compared to handcycling, mean heart rate during hybrid cycling was 11 bpm [5, 18] higher; and compared to RPE level 3, mean heart rate at level 6 was 21 bpm [10, 32] higher (Figure 5A). A tendency to an interaction effect was found ($F(1,7) = 4.18$, $P = 0.08$, $\eta_p^2 = 0.37$). Follow-up analyses revealed that the difference in heart rate between hybrid cycling and handcycling was higher at RPE level 6 (17 bpm [7, 27]) than at level 3 (3 bpm [-6, 12]). Furthermore, the difference in heart rate between RPE level 3 and 6 was higher for hybrid cycling (27 bpm [12, 41]) than for handcycling (15 bpm [7, 23]).

Oxygen pulse

There was a significant main effect for exercise intensity ($F(1,7) = 15.96$, $P = 0.005$, $\eta_p^2 = 0.70$). Overall, the mean oxygen pulse at RPE level 6 was 1.25 ml/beat [0.51, 1.99] higher than at level 3 (Figure 5B). No significant main effect for exercise modality ($F(1,7) = 1.49$, $P = 0.26$, $\eta_p^2 = 0.18$) or interaction effect ($F(1,7) = 0.47$, $P = 0.51$, $\eta_p^2 = 0.06$) was found.

Ventilation

There was a significant main effect for both exercise modality ($F(1,8) = 7.77$, $P = 0.024$, $\eta_p^2 = 0.49$) and exercise intensity ($F(1,8) = 65.22$, $P < 0.001$, $\eta_p^2 = 0.89$). Overall, compared to handcycling, mean V_E during hybrid cycling was 5.3 l/minute [0.9, 9.6] higher; and compared to RPE level 3, mean V_E at level 6 was 12.9 l/minute [9.3, 16.7] higher (Figure 5C). The interaction between exercise modality and exercise intensity was also significant ($F(1,8) = 11.315$ $P = 0.01$, $\eta_p^2 = 0.59$). Follow-up analyses on the significant interaction revealed that the difference in V_E between hybrid cycling and handcycling was higher at RPE level 6 (7.7 l/minute [2.6, 12.8]) than at level 3 (2.8 l/minute [-1.4, 6.9]). Furthermore, the difference in V_E between RPE level 3 and 6 was higher for hybrid cycling (15.5 l/minute [10.4, 20.5]) than for handcycling (10.5 l/minute [7.7, 13.3].

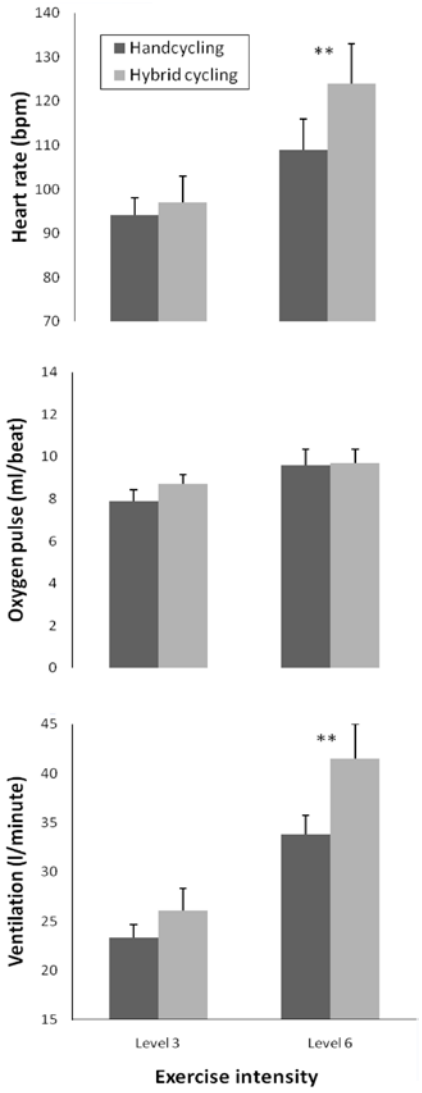

Figure 5 Cardiorespiratory response (heart rate (A), oxygen pulse (B) and V_E (C)) during handcycling (dark grey) and hybrid cycling (light grey) at RPE levels 3 and 6 (*$P < 0.05$; **$P < 0.01$). Values are mean + standard error.

Power output

There was a significant main effect for exercise intensity ($F(1,7) = 35.21$, $P = 0.001$, $\eta_p^2 = 0.83$). Overall, compared to RPE level 3, the power output at RPE level 6 was 13.86 W [8.34, 19.38], higher. No significant main effect for exercise modality ($F(1,7) = 1.12$, $P = 0.32$, $\eta_p^2 = 0.14$) or interaction effect ($F(1,7) = 1.60$, $P = 0.25$, $\eta_p^2 = 0.19$) was found.

DISCUSSION

An important result of this study was that the metabolic rate during hybrid cycling was higher than during handcycling at equal RPE levels (Figure 4). Several other studies also found higher metabolic rates during hybrid exercise versus arm exercise alone,[9,16-17] and stated that this was caused by the larger active muscle mass during hybrid exercise. In these studies, power output was used to standardize the exercise intensity; however, since RPE was not measured, it remained unclear how the participants subjectively experienced the exercise intensity during the relatively short (i.e. 10 minutes) exercise bouts. It might be possible that the higher metabolic rates in the above-mentioned studies also coincided with higher RPE levels. If this was the case, it is likely that these metabolic rates could not be maintained during a longer exercise period (e.g. 30-60 minutes), resulting in a necessary decrease in metabolic rate to be able to finish the exercise period. Eventually, it might be possible that the average metabolic rate over that certain exercise period will be nearly the same for both exercise modalities. The additional value of the current study is that it was demonstrated that the higher metabolic rate during hybrid cycling was achieved while 'feeling the same' as during the handcycling bouts. A secondary finding was that the absolute difference in metabolic rate between both exercise modalities was higher at RPE level 6 compared with level 3 (Figure 4). Hence, the above-described results show that people with a SCI expend more energy during hybrid cycling than during handcycling, and that this benefit becomes higher at increased RPE levels. These findings suggest that hybrid exercise might be more suitable for fighting obesity than arm exercise alone (when energy intake is kept constant). However, more research is needed regarding the required duration, frequency and intensity of exercise to fight obesity.

The higher metabolic rate during hybrid cycling coincided with a higher V_E and heart rate (Figure 5). Since other studies[9,16,18-19] found higher stroke volumes during hybrid exercise compared with arm exercise alone, indicating an increased cardiac volume loading as a result of the activation of the leg muscle pump, oxygen pulse was also expected to be higher during hybrid cycling; However, in this study, oxygen pulse did not differ between exercise modalities (Figure 5). Nevertheless, the higher V_E and heart rate at a similar oxygen pulse indicate that hybrid cycling gives a higher training stimulus to the heart and lungs compared with handcycling, suggesting that hybrid cycling is more suitable for increasing cardiorespiratory fitness.

Despite the higher metabolic rate during hybrid cycling, no difference in external power output was observed, which can be explained by the fact that hybrid cycling is less efficient than handcycling.[16]

A possible limitation of this study was that the type of cycling was not randomized (each participant started with the hybrid cycle protocol). This might have caused systematic differences between measurement occasions (e.g. learning effect regarding Borg scale interpretation). However, it was not expected that randomization of the exercise modes would have changed the results and outweighed the positive effects of the much larger muscle mass that is used during hybrid cycling. Another limitation was that the exercise bouts during which the outcome measures were determined were relatively short (i.e. 5 minutes). During the 5-minute bouts, all participants responded very well to the FES, but we know that this response often decreases over time. In daily practice, people should exercise for a much longer period to obtain desirable training effects.[20] From the current study, it remained unclear whether the metabolic rate and cardiorespiratory response during hybrid cycling are still higher during a longer exercise period where relatively untrained lower-limb muscles become fatigued over time. Therefore, future research is needed to examine whether the beneficial effects of hybrid cycling on metabolic rate and cardiorespiratory response still hold during longer exercise periods (e.g. 30 minutes), keeping in mind that it might be necessary to first properly train the lower-limb musculature to ensure strong muscle contractions over the entire exercise period.

Altogether, the results of the current study suggest that people with a SCI should implement hybrid exercise training in daily life. Hybrid/FES exercise is not only good to lose weight and to become and stay fit, many other studies also suggest benefits on vascular,[21-23] muscle[24-25] and bone systems[26] in the lower extremities.

CONCLUSION

This study demonstrated that hybrid cycling induces a higher metabolic rate and cardiorespiratory response at equal RPE levels compared with handcycling, suggesting that hybrid cycling is more suitable for fighting obesity and increasing cardiorespiratory fitness in individuals with SCI.

REFERENCES

1. Monroe MB, Tataranni PA, Pratley R, Manore MM, Skinner JS, Ravussin E. Lower daily energy expenditure as measured by a respiratory chamber in subjects with spinal cord injury compared with control subjects. Am J Clin Nutr 1998;68(6):1223-7.
2. Bloemen-Vrencken JH, de Witte LP, Post MW, van den Heuvel WJ. Health behaviour of persons with spinal cord injury. Spinal Cord 2007;45(3):243-9.
3. Bloemen-Vrencken JH, Post MW, Hendriks JM, De Reus EC, De Witte LP. Health problems of persons with spinal cord injury living in the Netherlands. Disabil Rehabil 2005;27(22):1381-9.
4. Krum H, Howes LG, Brown DJ, Ungar G, Moore P, McNeil JJ, et al. Risk factors for cardiovascular disease in chronic spinal cord injury patients. Paraplegia 1992;30(6):381-8.
5. Janssen TW, van Oers CA, van der Woude LH, Hollander AP. Physical strain in daily life of wheelchair users with spinal cord injuries. Med Sci Sports Exerc 1994;26(6):661-70.

6. Hjeltnes N, Vokac Z. Circulatory strain in everyday life of paraplegics. Scand J Rehabil Med 1979;11(2):67-73.
7. Jacobs PL. Effects of resistance and endurance training in persons with paraplegia. Med Sci Sports Exerc 2009;41(5):992-7.
8. Valent L, Dallmeijer A, Houdijk H, Talsma E, van der Woude L. The effects of upper body exercise on the physical capacity of people with a spinal cord injury: a systematic review. Clin Rehabil 2007;21(4):315-30.
9. Hooker SP, Figoni SF, Rodgers MM, Glaser RM, Mathews T, Suryaprasad AG, et al. Metabolic and hemodynamic responses to concurrent voluntary arm crank and electrical stimulation leg cycle exercise in quadriplegics. J Rehabil Res Dev 1992;29(3):1-11.
10. Brurok B, Helgerud J, Karlsen T, Leivseth G, Hoff J. Effect of aerobic high-intensity hybrid training on stroke volume and peak oxygen consumption in men with spinal cord injury. Am J Phys Med Rehabil 2011;90(5):407-14.
11. Heesterbeek PJC, Berkelmans HWA, Thijssen DHJ, van Kuppevelt HJM, Hopman MTE, Duysens J. Increased physical fitness after 4-week training on a hybrid FES-cycle in persons with spinal cord injury. Technology and Disability 2005;17(2):103-10.
12. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377-81.
13. Goosey-Tolfrey V, Lenton J, Goddard J, Oldfield V, Tolfrey K, Eston R. Regulating intensity using perceived exertion in spinal cord-injured participants. Med Sci Sports Exerc 2010;42(3):608-13.
14. Lenton JP, Fowler NE, van der Woude L, Goosey-Tolfrey VL. Wheelchair propulsion: effects of experience and push strategy on efficiency and perceived exertion. Appl Physiol Nutr Metab 2008;33(5):870-79.
15. McArdle WD, Katch FI, Katch VL. Exercise physiology: energy, nutrition, & human performance. Baltimore: Lippincott Williams & Wilkins; 2007.
16. Raymond J, Davis GM, Climstein M, Sutton JR. Cardiorespiratory responses to arm cranking and electrical stimulation leg cycling in people with paraplegia. Med Sci Sports Exerc 1999;31(6):822-8.
17. Raymond J, Davis GM, Fahey A, Climstein M, Sutton JR. Oxygen uptake and heart rate responses during arm vs combined arm/electrically stimulated leg exercise in people with paraplegia. Spinal Cord 1997;35(10):680-5.
18. Davis GM, Servedio FJ, Glaser RM, Gupta SC, Suryaprasad AG. Cardiovascular responses to arm cranking and FNS-induced leg exercise in paraplegics. J Appl Physiol 1990;69:671-4.
19. Phillips W, Burkett LN. Arm crank exercise with static leg FNS in persons with spinal cord injury Med Sci Sports Exerc 1995;27:530-35.
20. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 6th ed. Baltimore, Md: Lippincott Williams & Wilkins; 2000.
21. Thijssen DH, Ellenkamp R, Smits P, Hopman MT. Rapid vascular adaptations to training and detraining in persons with spinal cord injury. Arch Phys Med Rehabil 2006;87(4):474-81.
22. Thijssen DH, Heesterbeek P, van Kuppevelt DJ, Duysens J, Hopman MT. Local vascular adaptations after hybrid training in spinal cord-injured subjects. Med Sci Sports Exerc 2005;37(7):1112-8.
23. Gerrits HL, de Haan A, Sargeant AJ, van Langen H, Hopman MT. Peripheral vascular changes after electrically stimulated cycle training in people with spinal cord injury. Arch Phys Med Rehabil 2001;82(6):832-9.
24. Baldi JC, Jackson RD, Moraill R, Mysiw WJ. Muscle atrophy is prevented in patients with acute spinal cord injury using functional electrical stimulation. Spinal Cord 1998;36(7):463-9.
25. Sloan KE, Bremner LA, Byrne J, Day RE, Scull ER. Musculoskeletal effects of an electrical stimulation induced cycling program in the spinal injured. Paraplegia 1994;32(6):407-15.
26. Chen SC, Lai CH, Chan WP, Huang MH, Tsai HW, Chen JJ. Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. Disabil Rehabil 2005;27(22):1337-41.

Chapter 4

Effects of 16-wk hybrid cycle vs. handcycle exercise on fitness and physical activity in inactive people with long-term spinal cord injury

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ABSTRACT

Study Design: Open randomized-controlled trial.

Objective:: To investigate the effects of a 16-wk hybrid cycle versus handcycle exercise program on fitness, pulmonary function and physical activity in inactive people with long-term SCI.

Setting: Two rehabilitation centres.

Methods: Twenty individuals (SCI ≥ 8 years) were randomly assigned to either the hybrid cycle (voluntary arm exercise combined with functional electrical stimulation (FES)-induced leg exercise) or handcycle group. During 16 weeks, both groups trained twice a week for 30 minutes at 65-75% heart rate reserve. Outcome measures obtained pre, mid and post the program were fitness (peak power output (PO_{peak}), peak oxygen consumption (VO_{2peak}), resting heart rate (HR_{rest}) and wheelchair skill performance time score (PTS)), pulmonary function, and physical activity (distance travelled in wheelchair (WC_{dist}) and Physical Activities Scale for Individuals with Physical Disabilities (PASIPD) score). Changes were examined using a two-factor mixed-measures ANOVA.

Results: For all outcome measures, there were no significant interaction effects. Overall, ~40% and ~65% of the participants showed (non-significant) improvements in PO_{peak} (P=0.11) and VO_{2peak} (P=0.14) following the 16-wk training program, respectively. Furthermore, an overall reduction in HR_{rest} (5 ± 2 bpm; P=0.03) and an overall increase in PASIPD score (6.5 ± 2.1; P=0.002) were found after 16 weeks of training. No training effects were found for PTS, pulmonary function and WC_{dist}.

Conclusion: In the current study, hybrid cycling and handcycling showed similar effects on fitness, pulmonary function and physical activity, indicating that there were no additional benefits of the FES-induced leg exercise over handcycle training alone.

INTRODUCTION

Many people with long-term spinal cord injury (SCI) show a seriously inactive lifestyle, associated with decreased fitness levels and several secondary health complications (e.g. cardiovascular disease and respiratory problems)[1,2]. Exercise training plays an important role in improving fitness, health and active lifestyle in this population[3].

Typically, exercise training in people with SCI involves upper-body activities due to the paralysis of the lower body. However, important limitations of arm exercise alone are the relatively small muscle mass available, inactivity of the venous muscle pump and deficient cardiovascular reflex responses[4]. Exercise modes that combine voluntary arm exercise with functional electrical stimulation (FES)-induced leg exercise (i.e. hybrid exercise) have the potential to alleviate some of these problems by activating more muscle mass and subsequently providing greater exercise responses to improve fitness and health[5,6]. Nevertheless, to date there are no randomized controlled trials (RCTs) that investigated multiple aspects (i.e. fitness,

pulmonary function and physical activity) of hybrid exercise versus arm exercise alone in physically inactive people with SCI.

Therefore, the purpose of this study was to investigate the effects of a 16-wk hybrid cycle versus handcycle exercise program on fitness, pulmonary function and physical activity in inactive people with long-term SCI. It was hypothesized that both training programs would result in an improvement of fitness, pulmonary function and physical activity. Furthermore, it was hypothesized that hybrid cycle exercise would provide a greater benefit on fitness and pulmonary function than handcycle exercise alone, due to the larger muscle mass utilized during hybrid exercise.

MATERIALS AND METHODS

Design

The current study is part of a larger study of which the design was previously described by Bakkum et al. (2013)[7] Briefly, this study was a 16-wk open RCT performed in two Dutch rehabilitation centers with a specialized SCI-unit. Within each center, participants were randomly assigned to either the hybrid cycle group or handcycle group. The sample size calculation was performed on the main outcome measure of the larger study (i.e. peak power output) and revealed a group size of 18 participants. Outcome measures in the current study were obtained in the week before the training program (pre), after 8 weeks of training (mid), and in the week after (post) the program.

Participants

As previously described[7], participants were recruited from the databases of two Dutch rehabilitation centres. Inclusion criteria were: spastic SCI $\geq$ 10 years; age 28-65 years; age at onset SCI $\geq$ 18 years; physically inactive (Physical Activities Scale for Individuals with Physical Disabilities (PASIPD)[8] score $<$ 30); wheelchair dependent. Exclusion criteria were: contraindications for physical training and testing; psychiatric problems; plans to start another lifestyle (e.g. diet changes); insufficient knowledge of the Dutch language.

Training devices

The hybrid cycle (BerkelBike Pro, BerkelBike B.V., St. Michielsgestel, the Netherlands; Figure 1A) combines synchronous voluntary handcycling with asynchronous FES-induced leg cycling. A 6-channel stimulator (Impuls, BerkelBike B.V., St. Michielsgestel, the Netherlands; Figure 1A-I) provided electrical stimulation via self-adhesive 50 x 90 mm surface electrodes placed bilaterally over the quadriceps, hamstrings and gluteus muscles. During cycling, the stimulator received information from the crank angle encoder (Figure 1A-II) about pedal position and velocity to control the cyclic stimulation pattern.

The handcycle (Speedy-Bike, Reha-Technik GmbH, Delbrück, Germany; Figure 1B) was equipped with a wide synchronous bull-horn crank. Both cycles were equipped with 8 gears that could be changed manually, and with quad grips for the participants who needed them. The front

wheel of both devices was mounted on an ergotrainer (Tacx Flow, Technische Industrie Tacx B.V., Wassenaar, the Netherlands; Figure 1A-III and 1B-III) adapted to the wheel size of the cycles.

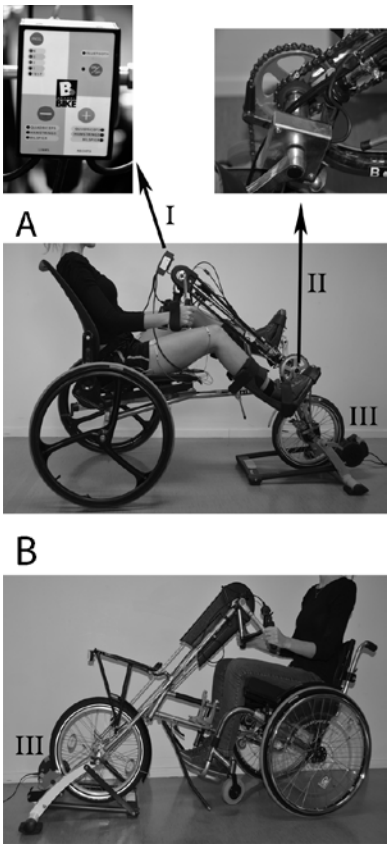

Figure 1 The hybrid cycle (A) with the stimulator (I) and crank angle encoder (II), and the handcycle (B), mounted on an ergotrainer (III).

Training protocol

The training protocol was also previously described by Bakkum et al. (2013)[7]. Briefly, during 16 weeks, participants trained twice a week for 18 to 32 min (the duration of the training sessions increased during the program) at an intensity of 65-75% heart rate reserve (HRR) and/or a score of 4-7 on a 10-point rating of perceived exertion (RPE) scale[9]. Exercise intensity was controlled by the participant making adjustments in cycle velocity or by the trainer adjusting the gear of the cycle or the resistance of the ergotrainer. In addition, during hybrid cycling the current amplitude of the stimulation was adjusted manually by the trainer to control the degree of muscle activation. The trainer tried to induce strong lower-body muscle contractions during training; however, the current amplitude was decreased if the participant indicated that the stimulation was too intense or if the legs were moving too fiercely due to the stimulation. Heart rate was recorded constantly during each training session using radiotelemetry (Polar, Polar Electro Inc., Woodbury, NY), and RPE was assessed after each training block.

Outcome measures

Fitness

Wheelchair exercise capacity, expressed as the peak power output (PO_{peak}) and peak oxygen consumption (VO_{2peak}), was assessed during a graded exercise test in the participant's own handrim-propelled wheelchair (within participants, tire pressure, seating position etc. were kept constant over time) on a motor-driven treadmill, using the protocol of Dallmeijer et al. (2005)[10]. Briefly, this protocol consisted of a 3-min warm-up session, a 5-min rest interval, two submaximal exercise blocks, and an incremental test in which every minute the incline of the treadmill belt was increased with 0.36°. The velocity of the belt was kept constant during testing, and was dependent on the participant's physical capability. The test was ended when the participant could no longer maintain the velocity due to fatigue, or when the participant indicated that he/she wanted to stop. Directly after the warm-up session, a separate drag test was performed to determine the drag force (F_{drag}), and subsequently the PO of the wheelchair-user system on different treadmill inclines, using custom made software (Technical Department Faculty of Human Movement Sciences, VU University Amsterdam)[11]. During testing, respiratory gas exchange was measured using open circuit spirometry (K4b², COSMED, Rome, Italy), and heart rate was measured using radiotelemetry (Polar, Polar Electro Inc., Woodbury, NY). PO_{peak} and VO_{2peak} were defined as the highest PO maintained for at least 30 s and the highest VO_2 (averaged over 30 s) attained during the test, respectively. Resting heart rate (HR_{rest}) was defined as the lowest heart rate (averaged over 30 s) of the 5-min rest interval.

In addition, for indirect determination of fitness, wheelchair skill performance was assessed using two elements (i.e. 15 m sprint and figure-of-8 task) of a wheelchair circuit[12]. The performance time score (PTS; total time needed for these two tasks) was used for analysis. Furthermore, at the end of the training program, subjectively experienced fitness level was measured using one multiple-choice question where participants were asked if they thought their fitness level had changed due to the training sessions (answers ranged from 'very much reduced' to 'very much improved').

Pulmonary function

The forced vital capacity (FVC), forced expiratory volume in the first sec (FEV1) and peak expiratory flow (PEF) were obtained using spirometry (K4b², COSMED, Rome, Italy). Each participant completed the test at least three times. If the FVC's agreed within 10%, no additional trials were performed. The best test was used for analysis.

Physical activity

Physical activity was measured objectively with an odometer as well as subjectively with the Dutch PASIPD[8]. The odometer was mounted on the wheel of the participant's daily-use wheelchair to record every forward and backward revolution of the large wheels during 7 consecutive days pre and post the training program[13]. Participants were asked to keep a diary in which they registered the number of wheel revolutions on a daily basis. The distance covered

was calculated by multiplying the number of wheel revolutions by the wheel circumference. The PASIPD is a 12-item questionnaire that requests the number of days a week and hours a day of participation in leisure (6 items), household (5 items), and occupational (1 item) activities over the past 7 days. Participants were asked to digitally fill out this questionnaire at home.

Statistical analysis

The assumption of normality of the data within groups was checked by visual inspection of the q-q plot and box plot; in addition, a Shapiro-Wilks test was performed. Homogeneity of variance was checked using the Levene's test. In case of violations of these assumptions, the statistical analyses were performed on the log-transformed data. Independent t-tests were used to determine possible baseline differences in the outcome measures between groups. Differences between pre, mid and post outcome measures were examined using a two-factor (time x group) mixed-measures ANOVA. Paired t-tests with Bonferroni correction were used to identify where the specific differences occurred between the three time points. One-way within-subjects ANOVAs with Bonferroni correction were used to examine the interaction effect if significant. Data are presented as mean ± standard error (SE), and significance was set a priori at $p < 0.05$.

Statement of ethics

All participants provided written informed consent indicating voluntary participation in this study, approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

RESULTS

Initially, 36 participants were included, of which 20 people completed the 16-wk study (Table 1). The reasons for drop-out were illness (N=8) and lack of adherence to the training (N=8). All 20 participants who completed the study recorded 100% compliance to the program and trained at the target exercise intensity during the program. Normal distribution and homogeneity of error variance were confirmed for all variables except for PO_{peak}, PTS, WC_{dist} and PASIPD score. No significant baseline differences were present for any outcome measure or personal and lesion characteristics between the two training groups and between participants who dropped out and participants who completed the training program. Due to limited hand function, one participant was not able to perform the graded wheelchair exercise test (no PO_{peak} and VO_{2peak} values were obtained). Furthermore, for VO_{2peak} and WC_{dist}, one and five participants were excluded from the analysis due to missing samples, respectively.

Table 1 Participants' characteristics

Participant	Sex	Age (yrs)	TSI (yrs)	Lesion level	AIS	Height (cm)	Body mass (kg)	BMI (kg/m^2)
HYB								
1	M	55	34	C3	C	178	90.7	28.5
2	M	40	12	C5	A	177	65.2	20.9
3	M	39	13	C6	B	184	84.4	24.9
4	M	49	31	C7	A	174	55.5	18.3
5	M	53	10	C7	C	182	63.4	19.1
6	M	49	27	T1	A	186	67.2	19.4
7	M	40	18	T6	A	188	66.6	18.9
8	M	58	24	T8	A	172	83.0	28.1
9	M	64	18	T9	A	174	80.2	26.5
10	M	31	14	T10	A	173	73.5	24.6
Mean (SD)		48 (10)	20 (8)			179 (6)	73.0 (11.2)	22.9 (4.0)
HC								
1	M	63	10	C2	D	180	73.6	22.9
2	M	48	30	C6	C	171	91.6	31.3
3	M	47	12	C6	C	174	80.2	26.5
4	M	51	21	T3	A	181	72.6	22.2
5	M	30	11	T4	A	174	73.8	24.4
6	M	49	16	T5	A	174	75.0	24.8
7	M	47	18	T7	A	185	82.0	24.0
8	M	38	9	T9	A	173	60.5	20.2
9	M	49	15	T11	A	187	58.8	16.8
10	F	50	14	L2	A	166	67.2	24.5
Mean (SD)		47 (9)	16 (6)			177 (7)	73.5 (9.8)	23.8 (3.8)

Abbreviations: yrs, years; TSI, time since injury; AIS, ASIA (American Spinal Injury Association) Impairment Scale; BMI, body mass index; HYB, hybrid cycle group; HC, handcycle group; M, male; F, female; SD, standard deviation.

Fitness

There were no significant main effects for time for PO_{peak}, VO_{2peak} and PTS (Table 2). However, ~40% and ~65% of the participants showed improvements over time in PO_{peak} (Figure 2A) and VO_{2peak} (Figure 2B), respectively. For HR_{rest}, there was a significant main effect for time (Table 2). Post-hoc analysis revealed a significant reduction ($P = 0.03$) of 6 ± 2 bpm (8%) between the pre- and mid-test, and no further reduction ($P = 1.0$) between the mid- and post-test (Figure 2C and 2D). For all fitness parameters, no interaction effects were found (Table 2). Almost 90% of the participants indicated that their subjectively experienced fitness level was 'slightly' (50%) to 'very much' (40%) improved after 16 weeks of training; only 10% of the participants reported no change in subjectively experienced fitness level.

Pulmonary function

No significant main effects for time or interaction effects were found for FVC, FEV1 and PEF (Table 2).

Physical activity

Overall WC_{dist} increased with 23% following the exercise program, however, this increase was not significant (Table 2, Figure 2E). In contrast, there was a significant main effect for time for PASIPD score (Table 2, Figure 2F). Post-hoc analysis revealed a significant increase of 88% ($P = 0.002$) between the pre- and mid-test, and no further improvement ($P = 1.0$) between the mid- and post-test. For both WC_{dist} and PASIPD score, no significant interaction effects were found (Table 2).

Table 2 Fitness, pulmonary function and physical activity

N = 10 HYB, 10 HC	Whole group			HYB			HC			P values	
Fitness	Pre	Mid	Post	Pre	Mid	Post	Pre	Mid	Post	Main effect time	Interaction effect
PO_{peak} (W)[1]	45.4 (6.1)	50.3 (5.7)	49.2 (5.5)	39.5 (9.5)	44.5 (9.5)	45.4 (8.5)	50.7 (7.9)	55.6 (6.9)	52.5 (7.3)	0.11	0.39
VO_{2peak} (L/min)[2]	1.32 (0.12)	1.43 (0.13)	1.41 (0.12)	1.19 (0.20)	1.25 (0.24)	1.33 (0.21)	1.43 (0.16)	1.57 (0.12)	1.48 (0.14)	0.14	0.33
HR_{rest} (bpm)	76 (2)	70 (3)	71 (2)	73 (4)	68 (4)	70 (3)	78 (2)	71 (3)	72 (4)	0.03	0.82
PTS (s)	18.9 (3.1)	18.6 (2.8)	18.1 (2.6)	22.2 (5.9)	21.9 (5.3)	20.9 (4.9)	15.5 (1.6)	15.2 (1.2)	15.3 (1.3)	0.41	0.41
Pulmonary function											
FVC (L)	4.0 (0.2)	4.0 (0.2)	4.0 (0.2)	4.0 (0.4)	3.9 (0.4)	3.9 (0.4)	4.0 (0.2)	4.0 (0.2)	4.0 (0.2)	0.80	0.95
FEV1 (L)	3.3 (0.2)	3.3 (0.2)	3.3 (0.2)	3.3 (0.4)	3.3 (0.4)	3.2 (0.4)	3.2 (0.2)	3.2 (0.1)	3.2 (0.1)	0.52	0.83
PEF (L/s)	7.0 (0.3)	7.1 (0.4)	6.9 (0.4)	6.7 (0.5)	6.8 (0.7)	6.8 (0.8)	7.2 (0.3)	7.2 (0.3)	6.9 (0.3)	0.58	0.48
Physical activity											
WCdist (km)[3]	27.8 (6.9)	x	34.3 (7.1)	27.1 (12.1)	x	30.0 (6.9)	28.7 (6.7)	x	39 (13.5)	0.30	0.78
PASIPD score	8.0 (1.5)	15.1 (2.7)	14.5 (2.5)	6.3 (1.9)	16.6 (3.9)	15.5 (3.3)	9.7 (2.4)	13.6 (3.8)	13.5 (4.0)	0.002	0.10

Values are mean ± standard error (SE). Abbreviations: HYB, hybrid cycle group; HC, handcycle group; POpeak, peak power output; VO_{2peak}, peak oxygen consumption; HR_{rest}, resting heart rate; PTS, performance time score; FVC, forced vital capacity; FEV1, forced expiratory volume in the first sec; PEF, peak expiratory flow; WC_{dist}, distance travelled in the wheelchair; PASIPD, Physical Activity Scale for Individuals with Physical Disabilities; x, not measured at the mid-test; [1]N = 9 HYB, 10 HC; [2]N = 8 HYB, 10 HC; [3]N = 8 HYB, 7 HC.

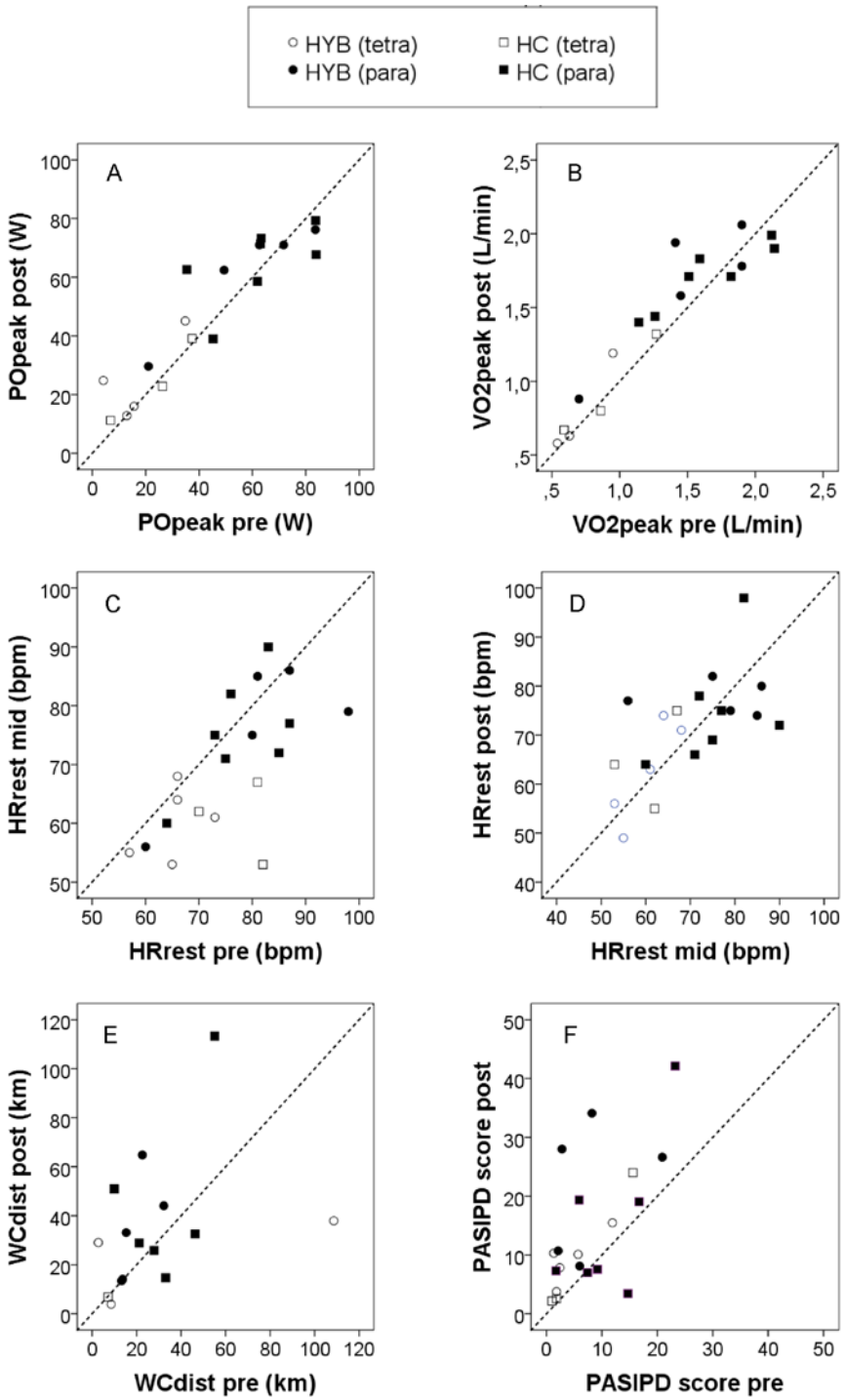

Figure 2 Individual values for: A, peak power output (PO_{peak}); B, peak oxygen consumption (VO_{2peak}); C, D, resting heart rate (HR_{rest}); E, distance travelled in the wheelchair (WC_{dist}); F, Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) score. HYB, hybrid cycle; HC, handcycle; tetra, tetraplegia; para, paraplegia.

DISCUSSION

An important finding of this study was that the wheelchair-specific fitness measures (i.e. PO_{peak}, VO_{2peak} and PTS) were not significantly improved following the 16-wk training program, while the other fitness measures (i.e. HR_{rest} and subjectively experienced fitness level) were, and that there were no differences over time between the two training groups for any of these measures. The peak exercise performance was measured in a handrim-propelled wheelchair since, in daily life, many people with SCI are dependent on such a wheelchair for mobility and will therefore benefit from an increased wheelchair-specific fitness. Moreover, from previous research, it is already known that both hybrid cycle[14,15] and handcycle[16] training lead to improvements in fitness (i.e. PO_{peak} and/or VO_{2peak}) if specific (i.e. hybrid cycle or handcycle) exercise testing is used to evaluate these outcome measures. The reduction in HR_{rest} (suggesting an improved cardiorespiratory fitness as an result of aerobic training[17]) and the increased subjectively experienced fitness observed in the current study, support these previously reported findings regarding the positive effects of hybrid cycle and handcycle training on fitness. However, peak wheelchair performance was not significantly improved, suggesting that hybrid cycling and handcyling may not be the best exercise modes to achieve desirable effects in wheelchair-specific fitness, and that it is better to train more specifically (i.e. wheelchair training). That said, ~40% and ~65% of the participants in this study showed improvements in PO_{peak} and VO_{2peak}, respectively, indicating that there were certainly beneficial effects of the training program on these fitness measures in a considerable part of the participant group. Moreover, based on normative values for PO_{peak} and VO_{2peak} in people with long-term SCI[18], at baseline, participants with tetraplegia and paraplegia in the current study were classified as 'average' and 'fair', respectively. It might be possible that greater training effects would have been found if we were able to include people with the poorest levels of fitness.

For pulmonary function, no significant changes were found after 16 weeks of hybrid cycle or handcycle training. These results were in agreement with other studies on exercise training in people with SCI from which it seems that clinically relevant improvements in pulmonary function are not commonly found[e.g.16].

Although there was no significant change over time in wheelchair activity measured with an odometer, the overall increased PASIPD score indicates an improved physical activity level. Moreover, participants subjectively indicated that various activities of daily living (e.g. transfers, transportation, housework) became easier due to an improved fitness level. The above-described findings regarding fitness and physical activity are supported by Nooijen et al.[19], who showed that increased physical activity levels are associated with increased fitness levels.

Future studies should focus on how to make this type of training more feasible and attractive for the SCI population. In the current study, it took two years to recruit 36 participants (313 invitation letters were sent) of which eventually 20 individuals completed the study. The most important reason that people were not willing to participate in this study was that the training program was too time-consuming for them. This was also the main reason for the eight participants who dropped out due to lack of adherence to the training. Better facilitation of the

training equipment might be a way to make these programs more feasible; if people have the possibility to exercise at home for example, they do not have to come to a rehabilitation centre which would save travel time. The fact that eight individuals (22%) dropped out due to health problems (e.g. urinary tract infections and kidney stones) indicates that people with SCI are vulnerable for illness, and that interventions aiming to increase fitness and health are important in this population.

In conclusion, in the current study, hybrid cycling and handcycling showed similar effects on fitness, pulmonary function and physical activity, indicating that there were no additional benefits of the FES-induced leg exercise over handcycle training alone.

REFERENCES

1. Manns PJ, Chad KE. Determining the relation between quality of life, handicap, fitness, and physical activity for persons with spinal cord injury. *Arch Phys Med Rehabil* 1999;**80:** 1566–1571.
2. Bloemen-Vrencken JH, De Witte LP, Post MW, van den Heuvel WJ. Health behaviour of persons with spinal cord injury. *Spinal Cord* 2007;**45:** 243-249.
3. Nash, M. Exercise as a health-promoting activity following spinal cord injury. *J Neurol Phys Ther* 2005**; 29:** 87-93.
4. Glaser RM. Arm exercise training for wheelchair users. *Med Sci Sports Exerc* 1989;**21**: S149-157.
5. Bakkum AJT, de Groot S, Onderwater M, de Jong J, Janssen TWJ. Metabolic rate and cardiorespiratory response during hybrid cycling versus handcycling at equal subjective exercise intensity levels in people with a spinal cord injury. *J Spinal Cord Med* 2013; **in press.**
6. Brurok B, Helgerud J, Karlsen T, Leivseth G, Hoff J. Effect of aerobic high-intensity hybrid training on stroke volume and peak oxygen consumption in men with spinal cord injury. *Am J Phys Med Rehabil* 2011;**90:** 407-414.
7. Bakkum AJ, de Groot S, van der Woude LH, Janssen TW. The effects of hybrid cycle training in inactive people with long-term spinal cord injury: design of a multicentre randomized controlled trial. *Disabil Rehabil* 2013;**35**: 1127-1132.
8. Washburn RA, Zhu W, McAuley E, Frogley M, Figoni SF. The physical activity scale for individuals with physical disabilities: development and evaluation. *Arch Phys Med Rehabil* 2002;**83**: 193–200.
9. Noble BJ, Borg GA, Jacobs I, Ceci R, Kaiser P. A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. *Med Sci Sports Exerc* 1983;**15:** 523-528.
10. Dallmeijer AJ, Kilkins OJ, Post MW, de Groot S, Angenot EL, van Asbeck FW et al. Handrim wheelchair propulsion capacity during rehabilitation of persons with spinal cord injury. *J Rehabil Res Dev* 2005;**42:** S55-63.
11. De Groot S, Zuidgeest M, van der Woude LH. Standardization of measuring power output during wheelchair propulsion on a treadmill Pitfalls in a multi-center study. *Med Eng Phys* 2006; **28:** 604-612.
12. Kilkens OJ, Dallmeijer AJ, De Witte LP, Van Der Woude LH, Post MW. The wheelchair circuit: construct validity and responsiveness of a test to assess manual wheelchair mobility in persons with spinal cord injury. *Arch Phys Med Rehabil* 2004;**85:** 424-431.
13. Janssen TW, van Oers CA, van der Woude LH, Hollander AP. Physical strain in daily life of wheelchair users with spinal cord injuries. *Med Sci Sports Exerc* 1994;**26:** 661-670.
14. Brurok B, Helgerud J, Karlsen T, Leivseth G, Hoff J. Effect of aerobic high-intensity hybrid training on stroke volume and peak oxygen consumption in men with spinal cord injury. *Am J Phys Med Rehabil* 2011;**90:**407-414.
15. Heesterbeek PJC, Berkelmans HWA, Thijssen DHJ, van Kuppevelt HJM, Hopman MTE, Duysens J. Increased physical fitness after 4-week training on a hybrid FES-cycle in persons with spinal cord injury. *Technol and Disabil* 2005;**17:**103-110.

16. Valent L, Dallmeijer AJ, Houdijk H, Slootman HJ, Post MW, Van der Woude LH. Influence of handcyling on physical capacity in the rehabilitation of persons with a spinal cord injury: a longitudinal cohort study. *Arch Phys Med Rehabil* 2008;**89:**1016-1022.
17. Wilmore JH, Stanforth PR, Gagnon J, Rice T, Mandel S, Leon AS et al. Heart rate and blood pressure changes with endurance training: the HERMITAGE Famlily Study. *Med Sci Sports Exerc* 2001;**33:**107-116.
18. Janssen TWJ, Dallmeijer AJ, Veeger HEJ, van der Woude LHV. Normative values and determinants of physical capacity in individuals with spinal cord injury. *J Rehabil Res Dev* 2002;**39:** 29-39.
19. Nooijen CF, de Groot S, Postma K, Bergen MP, Stam HJ, Bussmann JB, et al. A more active lifestyle in persons with a recent spinal cord injury benefits physical fitness and health. *Spinal Cord* 2012;**50:**320-323.

Chapter 5

Effects of hybrid cycle versus handcycle exercise on cardiovascular disease risk factors in people with spinal cord injury: a randomized-controlled trial

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ABSTRACT

Objective: Examine the effects of a 16-wk hybrid cycle versus handcycle exercise program on cardiovascular disease (CVD) risk factors in people with spinal cord injury (SCI).

Participants: Nineteen individuals with SCI≥8 years.

Design: Multicenter randomized-controlled trial. Both the hybrid cycle (n=9) and handcycle group (n=10) trained twice a week during 16 weeks in the specific cycle. Outcome measures obtained pre and post the program were MetS components (waist circumference (WC), systolic (SBP) and diastolic (DBP) blood pressure, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and insulin resistance), inflammatory status (C-reactive protein (CRP), interleukin (IL)-6 and 10, and visceral adiposity (trunk and android fat).

Results: Overall significant reductions were found for WC (p=0.001), DBP (p=0.03), insulin resistance (p=0.006), CRP (p=0.05), IL-6 (p=0.04), IL-6/IL-10 ratio (p=0.03), and trunk (p=0.04) and android (p=0.02) fat percentage. No significant main effects for time were observed for SBP, TG, HDL-C, IL-10, and trunk and android fat mass. For all outcome measures, there were no significant differences over time between groups.

Conclusion: Hybrid cycling and handcycling have similar beneficial effects on different MetS components, inflammatory status and visceral adiposity, indicating that there were no additional benefits of FES-induced leg exercise above handcycle training alone.

INTRODUCTION

With today's specialized medical care, life expectancy of people with spinal cord injury (SCI) has considerably improved (1). Despite this, mortality rates in people with SCI remain high compared with non-disabled people (2). Cardiovascular disease (CVD) is the leading cause of mortality in the SCI population and occurs more in this population than in people without SCI (3). An important contributor for this increased risk of CVD is the fact that several CVD risk factors, such as metabolic syndrome (MetS), chronic low-grade inflammation and visceral adiposity are more prevalent in people with SCI than in people without SCI (4, 5, 6). The inactive lifestyle observed in many individuals with SCI is strongly associated with the higher prevalence of these risk factors (7).

MetS is a condition characterized by clustering of the following CVD risk factors: abdominal obesity, hypertension, high triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C) and insulin resistance (8). The chronic low-grade elevation in plasma concentrations of pro-inflammatory mediators (e.g. C-reactive protein (CRP) and interleukin-6 (IL-6)) is suggested to play an important role in development of insulin resistance and atherosclerotic plaque (9, 10). Low-grade inflammation is therefore strongly associated with the abnormalities experienced in MetS and the pathophysiology of CVD development (11). Consequently, the suppression of chronic inflammation is an important factor in reducing CVD risk in people with SCI.

Participation in regular exercise training has been shown to promote a range of anti-inflammatory benefits in non-disabled individuals, including reduced visceral adiposity (12). However, in SCI, the anti-inflammatory benefits of exercise training may be lower due to the lower-limb paralysis and the reliance on the relatively small muscle mass activated during upper-body activities (e.g. handcycling and wheelchair propulsion) (13). Despite this, cross-sectional analyses have shown positive relationships between chronic inflammation and physical activity levels in this population (5, 14). The circulating cytokine response to upper-body exercise in non-SCI and thoracic SCI is also of a similar magnitude to that observed following lower-body exercise (15). Therefore, increasing physical activity by participating in regular exercise training may provide a protective effect against chronic inflammation and CVD risk in people with long-term SCI.

To date, no intervention studies have examined the effect of long-term upper-body exercise training on chronic inflammation in people with SCI. The activation of the paralyzed lower-limb musculature via functional electrical stimulation (FES)-evoked cycle training has previously been shown to significantly reduce plasma concentrations of the inflammatory mediators CRP, IL-6 and tumor necrosis factor-alpha (TNF-α) (16). The performance of combined FES-evoked leg exercise and voluntary upper-body exercise (i.e. hybrid exercise) has the potential to augment the anti-inflammatory response even further since a larger muscle mass is activated than during FES-evoked leg exercise or upper-body exercise alone (17).

The potential greater effect of hybrid exercise training over handcycle training on CVD risk factors requires investigation. Therefore, the aim of this study was to examine the effects of a 16-wk hybrid cycle versus handcycle training program on MetS components, resting inflammatory status and visceral adiposity in people with long-term SCI.

METHODS

Trial design

The experimental design of the current study (which is part of a larger study) was previously described by Bakkum et al. (18). Briefly, this study was a 16-wk open, explanatory, parallel-group randomized-controlled trial (RCT) performed in two Dutch rehabilitation centers (Reade Amsterdam and St. Maartenskliniek Nijmegen). Within each rehabilitation center, block randomization (fixed block size of 6; allocation ratio of 1:1; no stratification) was used to assign the participants to either the experimental group (hybrid cycle group) or control group (handcycle group). A blinded independent researcher provided the allocation in sequentially numbered, opaque, sealed and stapled envelopes. After the included participants completed all baseline measurements, the principal investigator opened the envelopes and allocated the participants to the intervention. The sample size calculation was performed on the main outcome measure of the larger study (i.e. peak power output) and revealed a group size of 18 participants.

Participants

As previously described (18), participants were recruited from the databases of two Dutch rehabilitation centers with a specialized SCI-unit (Reade Amsterdam and St. Maartenskliniek Nijmegen) and were eligible for inclusion if they met the following criteria: time since injury (TSI) ≥ 10 years, age at onset SCI ≥ 18 years, age 26-65 years, dependent on a wheelchair for daily mobility, spastic paralysis, no or limited sensation in the lower body, physically inactive. People were qualified as 'physically inactive' if their score on the Physical Activities Scale for Individuals with Physical Disabilities (PASIPD) (19) was lower than the 75th percentile (<30) of a Dutch cohort study population (20). Exclusion criteria were: contraindications for physical training and testing (e.g. pressure sores, severe cardiovascular problems), psychiatric problems that could interfere with study participation, plans to change current lifestyle habits (e.g. physical activity or diet) during the experimental training period, insufficient knowledge of the Dutch language to understand the purpose and protocol of the study. Due to difficulties with recruiting the intended number of participants, one year after trial commencement, the inclusion criterion TSI ≥ 10 years was reduced to TSI ≥ 8 years. All participants provided written informed consent indicating voluntary participation in this study, approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam.

Training devices

Hybrid cycle

The hybrid cycle (BerkelBike Pro, BerkelBike B.V., St. Michielsgestel, the Netherlands; Figure 1A) combines synchronous voluntary handcycling with asynchronous FES-induced leg cycling. A 6-channel stimulator (Impuls, BerkelBike B.V., St. Michielsgestel, the Netherlands; Figure 1A-I) provided electrical stimulation via self-adhesive 50 x 90 mm surface electrodes placed bilaterally over the quadriceps, hamstrings and gluteus muscles. During cycling, the stimulator received information from the crank angle encoder (Figure 1A-II) about pedal position and velocity to control the cyclic stimulation pattern.

The handcycle (Speedy-Bike, Reha-Technik GmbH, Delbrück, Germany; Figure 1B) was equipped with a wide synchronous bull-horn crank. The front wheel of both devices was mounted on an ergotrainer (Tacx Flow, Technische Industrie Tacx B.V., Wassenaar, the Netherlands; Figure 1A-III and 1B-III) that was adapted to the wheel size of the cycles. Both cycles were equipped with 8 gears that could be changed manually, and quad grips for those participants who needed them.

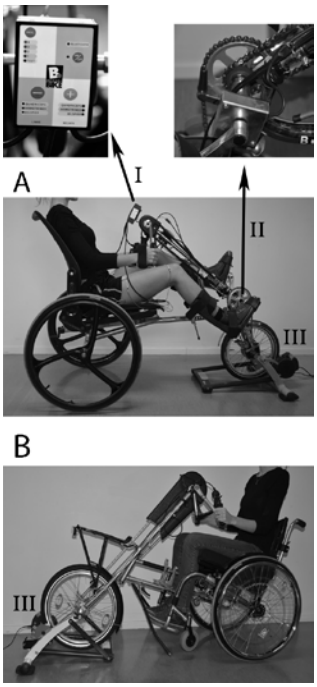

Figure 1 The hybrid cycle (A) with the stimulator (I) and crank angle encoder (II), and the handcycle (B), mounted on an ergotrainer (III).

Training protocol

The training protocol was previously described by Bakkum et al. (18). Briefly, participants performed 32 interval training sessions within a continuous period of 16 weeks. During the program, the duration of the training sessions increased from 18 to 32 minutes. To provide sufficient recovery time, at least one day of rest was scheduled in between training days. Following a graded exercise test to exhaustion, the training intensity was set to attain a heart rate response of 65-75% heart rate reserve during training. Since the use of heart rate as an indicator for training intensity can be unreliable in some individuals with tetraplegia (21), rating of perceived exertion (RPE) served as a supplementary measure of training intensity; a target RPE of 4-7 on the Borg's 10-point scale (22) was required during training. Training intensity was controlled by the participants making adjustments in cycle velocity or by the trainer adjusting the gear of the cycle or the resistance of the ergotrainer. In addition, during hybrid cycling the current amplitude of the electrical stimulation was adjusted manually by the trainer to control the degree of muscle activation. The trainer tried to induce strong muscle contractions throughout training, however, if the legs were moving too fiercely due to the stimulation or if the participant indicated that the stimulation was too intense, the trainer decreased the current amplitude. Heart rate was recorded constantly during each training session using radiotelemetry (Polar, Polar Electro Inc., Woodbury, NY), and RPE was assessed after each training block.

Outcome measures

The outcome measures in the current study (i.e. MetS, inflammatory status and visceral adiposity) were obtained in the week before (pre) and after (post) the 16-wk training program.

Metabolic syndrome

MetS was defined as having ≥ 3 of the following symptoms: abdominal obesity (waist circumference (WC) > 102 cm for males, > 88 cm for females); high blood pressure (> 130/85 mm Hg or use of medication for hypertension); high TG (≥ 1.7 mmol/L); low HDL-C (< 1.03 mmol/L for males, < 1.29 mmol/L for females); insulin resistance, identified by ≥ 1 of the following: high fasting glucose (≥ 5.6 mmol/L) or insulin (≥ 139 pmol/L) levels, homeostasis model assessment of insulin resistance (HOMA-IR) ≥ 4.0, or use of medication for hyperglycemia (8, 23). Supine WC was measured three times at the level of the umbilicus using a tape measure, and the average was used for data analysis. Blood pressure was taken on the left arm in a sitting position using an automatic device; the average blood pressure of three measurements was used for data analysis. After a 12-hour overnight fast, blood samples were taken from an antecubital vein into 3 mL lithium heparin (HDL-C and TG), 2 mL fluoride/oxalate (glucose) and 6.0 mL clot activator (insulin) tubes (BD Vacutainer). Within 2 hours after collection, the blood samples were spun down in a centrifuge at 1800g for 10 minutes at room temperature. Subsequently, plasma TG and HDL-C were determined using an enzymatic colorimetric assay, using the reagents GPO-PAP and HDL-C plus, respectively (Roche diagnostics, Mannheim, Germany). Determination of plasma glucose was done by the hexokinase method (Gluco-quant, Roche diagnostics, Mannheim, Germany). Serum concentrations of insulin were determined using an immunometric assay (Luminescence, Advia Centaur, Siemens Medical Solutions Diagnostics, USA). Glucose and insulin values were used to calculate HOMA-IR (24).

Inflammatory status

Fasting blood samples were collected from an antecubital vein into 6 mL BD Vacutainer K2E (EDTA) tubes. Within 2 hours of blood collection, plasma was isolated by centrifugation at 1800g for 10 minutes at room temperature, and subsequently aliquoted and stored at -80 ºC. At the end of the study, plasma concentrations of CRP, IL-6 and IL-10 were determined using quantitative sandwich-type enzyme-linked immunosorbant assay (ELISA) kits (CRP: IBL international, Hamburg, Germany; IL-6 and IL-10: R&D systems, Abingdon, UK), according to the manufacturers' instructions. The resting pro/anti-inflammatory ratio was calculated by dividing resting plasma IL-6 concentration by resting plasma IL-10 concentration. All samples were analyzed in duplicate. The within assay coefficients of variation for the analyses performed were as follows: CRP: 3.65%; IL-6: 3.83%; IL-10: 2.71%.

Visceral adiposity

Dual-energy X-ray absorptiometry (DXA; Hologic Discovery, Hologic Inc., Waltham, Mass) was used to determine trunk and android fat, which highly correlates (R = 0.65 to 0.90) with visceral fat measured by computed tomography (CT) (25, 26 , 27). Whole-body imaging was acquired according to the manufacturer's instructions with the participants in the supine position. The trunk and android region were automatically defined using the analytic software accompanying the system (Apex 13.3.3). Since the DXA device was only available in Amsterdam, DXA measurements were only performed in the group that trained in Reade Amsterdam (Table 1).

Statistical analysis

The assumption of normality was checked by visual inspection of the q-q plot and the box plot of the data within the groups. A Shapiro-Wilks test was also performed on the data. Homogeneity of variance was checked using the Levene's test. In case of violations of these assumptions, the statistical analyses were performed on the log-transformed data. Normal distribution and homogeneity of error variance were confirmed for all variables except for insulin, HOMA-IR, CRP, IL-6, IL-10 and IL6/IL10-ratio. Independent sample t-tests were employed to determine potential baseline differences in the outcome measures between the hybrid cycle and handcycle group. Differences between pre and post exercise training measurements were examined using a two-factor (time x group) mixed measures ANOVA. Data are presented as mean ± standard error (SE). Significance was set a priori at $p < 0.05$. All data were analyzed using the statistical package IBM SPSS for Windows version 20 (SPSS inc, Chicago, IL).

RESULTS

Between November 2011 (start recruitment) and August 2013 (end recruitment), 36 participants (17 hybrid cycle, 19 handcycle) were included of which 19 people (9 hybrid cycle; 10 handcycle) completed the 16-wk study (Table 1). The main reasons for drop-out were illness and lack of adherence to the training. All 19 participants who completed the study (32 sessions) recorded 100% compliance to the program. For the insulin and HOMA-IR analysis, 3 participants (1 hybrid cycle; 2 handcycle) were excluded due to missing samples. For the inflammatory status, 3 participants (2 hybrid cycle; 1 handcycle) were excluded due to the presence of underlying urinary tract infection or missing sample. No significant baseline differences were present for any of the outcome measures and demographic and clinical characteristics between the two intervention groups.

Table I Participants' characteristics

Participant	Sex	Age (yrs)	TSI (yrs)	Lesion level	AIS	Height (cm)	Body mass (kg)	BMI (kg/m^2)	PASIPD score
Hybrid cycle									
1*	M	55	34	C3	C	178	90.7	28.5	5.7
2	M	39	13	C6	B	184	84.4	24.9	2.4
3*	M	49	31	C7	A	174	55.5	18.3	1.3
4*	M	53	10	C7	C	182	63.4	19.1	2.1
5	M	49	27	T1	A	186	67.2	19.4	2.8
6*	M	40	18	T6	A	188	66.6	18.9	1.8
7	M	58	24	T8	A	172	83.0	28.1	20.9
8*	M	64	18	T9	A	174	80.2	26.5	6.0
9	M	31	14	T10	A	173	73.5	24.6	8.2
Mean (SE)		49 (3)	21 (3)			179 (2)	73.8 (3.8)	23.1 (1.4)	5.7 (2.1)
Handcycle									
1*	M	63	10	C2	D	180	73.6	22.9	5.9
2*	M	48	30	C6	C	171	91.6	31.3	9.2
3	M	47	12	C6	C	174	80.2	26.5	1.7
4*	M	51	21	T3	A	181	72.6	22.2	1.8
5	M	30	11	T4	A	174	73.8	24.4	15.6
6	M	49	16	T5	A	174	75.0	24.8	16.7
7*	M	47	18	T7	A	185	82.0	24.0	1.0
8	M	38	9	T9	A	173	60.5	20.2	23.2
9	M	49	15	T11	A	187	58.8	16.8	14.7
10*	F	50	14	L2	A	166	67.2	24.5	7.4
Mean (SE)		47 (3)	16 (2)			176 (2)	73.5 (3.1)	23.8 (1.2)	9.7 (2.4)

Abbreviations: yrs, years; TSI, time since injury; AIS, ASIA (American Spinal Injury Association) Impairment Scale; BMI, body mass index; PASIPD, Physical Activities Scale for Individuals with Physical Disabilities; M, male; F, female; SE, standard error. *Dual-energy X-ray absorptiometry (DXA) data available.

Metabolic syndrome

As shown in Table 2, an overall significant reduction of 3.1 cm (3.5%) in WC was found following the 16-wk training program. Figure 2A shows that the training benefits were greater in individuals with a high WC at the beginning of the training program. For diastolic blood pressure (DBP), an overall significant reduction of 4 mm Hg (7.0%) was observed (Table 2). Furthermore, there was an overall significant decrease of 26% in both insulin and HOMA-IR (Table 2). As shown in Figure 2C, the reduction in HOMA-IR was achieved in almost all participants. No significant main effects for time were found for systolic blood pressure (SBP), TG, HDL-C and glucose (Table 2). However, in ~65% of the participants TG was reduced (Figure 2B). For all the MetS components, no significant differences over time between groups were found (Table 2).

Inflammatory status

Overall, significant reductions of 0.45 mg/L (16.1%), 0.64 pg/mL (26.1%) and 2.97 (31.2%) were found for CRP, IL-6 and IL-6/IL-10 ratio, respectively; for IL-10, there was no significant main effect of time (Table 2). For all the inflammatory markers, no significant differences over time between groups were found (Table 2). Figure 2D shows that almost all participants showed a decrease in CRP. As demonstrated in Figure 2E and 2F, participants with high pre-training IL-6 values and IL-6/IL-10 ratios showed greater reductions than participants with low pre-training values.

Visceral adiposity

An overall significant reduction of 3.6% and 4.7% was observed for trunk and android fat percentage, respectively; however, there were no significant differences over time between the two training groups for these outcome measures (Table 2; Figure 2G and 2H). No significant main effects or interaction effects were found for trunk and android fat mass (Table 2).

Table II Metabolic syndrome, inflammatory status and visceral adiposity

	Whole group			HYB			HC			P values	
MetS components	Pre	Post	Δ	Pre	Post	Δ	Pre	Post	Δ	Main effect time	Interaction effect
(N = 9 HYB, 10 HC) WC (cm)	90.7 (2.8)	87.5 (2.4)	-3.1 (0.8)	91.8 (4.7)	87.8 (4.0)	-3.9 (1.3)	89.7 (3.5)	87.3 (2.9)	-2.5 (1.0)	0.001	0.38
SBP (mm Hg)	116 (3)	120 (4)	+4 (3)	112 (6)	117 (9)	+5 (5)	119 (4)	123 (3)	+4 (4)	0.18	0.92
DBP (mm Hg)	71 (2)	66 (3)	-4 (2)	69 (3)	63 (4)	-6 (3)	72 (3)	70 (4)	-3 (3)	0.03	0.31
TG (mmol/L)	1.4 (0.1)	1.3 (0.1)	-0.2 (0.1)	1.7 (0.2)	1.4 (0.2)	-0.3 (0.1)	1.2 (0.2)	1.1 (0.1)	-0.1 (0.2)	0.15	0.49
HDL-C (mmol/L)	1.2 (0.1)	1.3 (0.1)	+0.1 (0.1)	1.1 (0.1)	1.2 (0.1)	+0.1 (0.1)	1.4 (0.2)	1.4 (0.2)	0.0 (0.1)	0.30	0.35
Glucose (mmol/L)	5.5 (0.2)	5.4 (0.2)	-0.1 (0.1)	5.7 (0.3)	5.8 (0.4)	+0.1 (0.1)	5.3 (0.2)	5.1 (0.2)	-0.2 (0.2)	0.68	0.17
Insulin (pmol/L)*	63.6 (6.9)	47.4 (6.0)	-16.5 (4.8)	72.7 (10.6)	56.0 (9.5)	-18.9 (9.4)	54.6 (8.5)	40.5 (7.3)	-14.3 (4.0)	0.004	0.65
HOMA-IR*	2.3 (0.3)	1.7 (0.3)	-0.6 (0.2)	2.8 (0.5)	2.2 (0.6)	-0.6 (0.4)	1.9 (0.3)	1.3 (0.2)	-0.5 (0.2)	0.006	0.44
Inflammatory status											
(N: 7 HYB, 9 HC)											
CRP (mg/L)	3.32 (1.05)	2.79 (1.03)	-0.45 (0.17)	3.91 (1.75)	3.20 (1.68)	-0.71 (0.36)	2.86 (1.36)	2.47 (1.38)	-0.39 (0.18)	0.05	0.92
IL-6 (pg/mL)	2.45 (0.49)	1.81 (0.31)	-0.64 (0.32)	2.51 (0.91)	1.88 (0.58)	-0.63 (0.59)	2.40 (0.57)	1.76 (0.36)	-0.64 (0.36)	0.04	0.93
IL-10 (pg/mL)	0.27 (0.02)	0.31 (0.03)	+0.03 (0.02)	0.29 (0.03)	0.29 (0.04)	0.00 (0.02)	0.26 (0.02)	0.32 (0.05)	+0.06 (0.04)	0.29	0.16
IL-6/IL-10 ratio	9.52 (2.13)	6.55 (1.49)	-1.97 (1.45)	8.07 (2.33)	7.23 (2.47)	-0.84 (2.45)	10.65 (3.40)	5.96 (1.92)	-3.70 (2.07)	0.04	0.54
Visceral adiposity											
(N: 5 HYB, 5 HC)											
Trunk fat (kg)	11.5 (1.2)	11.0 (1.3)	-0.5 (0.3)	9.7 (1.6)	9.2 (1.5)	-0.5 (0.5)	13.2 (1.7)	12.7 (1.7)	-0.5 (0.5)	0.20	0.99
Trunk fat (%)	30.6 (2.0)	29.5 (2.0)	-1.1 (0.4)	27.5 (2.7)	25.9 (2.3)	-1.5 (0.7)	33.7 (2.5)	33.0 (2.5)	-0.7 (0.5)	0.04	0.41
Android fat (kg)	2.3 (0.3)	2.3 (0.3)	-0.1 (0.1)	2.0 (0.4)	1.9 (0.4)	-0.1 (0.1)	2.6 (0.4)	2.6 (0.4)	0.0 (0.2)	0.47	0.68
Android fat (%)	36.0 (2.4)	34.3 (2.2)	-1.7 (0.5)	33.4 (2.9)	31.3 (2.6)	-2.1 (0.5)	38.6 (3.7)	37.2 (3.3)	-1.3 (1.0)	0.02	0.52

Values are mean ± standard error (SE). Abbreviations: HYB, hybrid cycle group; HC, handcycle group; MetS, metabolic syndrome; Δ, mean pre-post difference; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-estimated insulin resistance; CRP, C-reactive protein; IL-6, interleukin-6; IL-10, interleukin-10. *Analysis was performed on N = 8 HYB, 8 HC

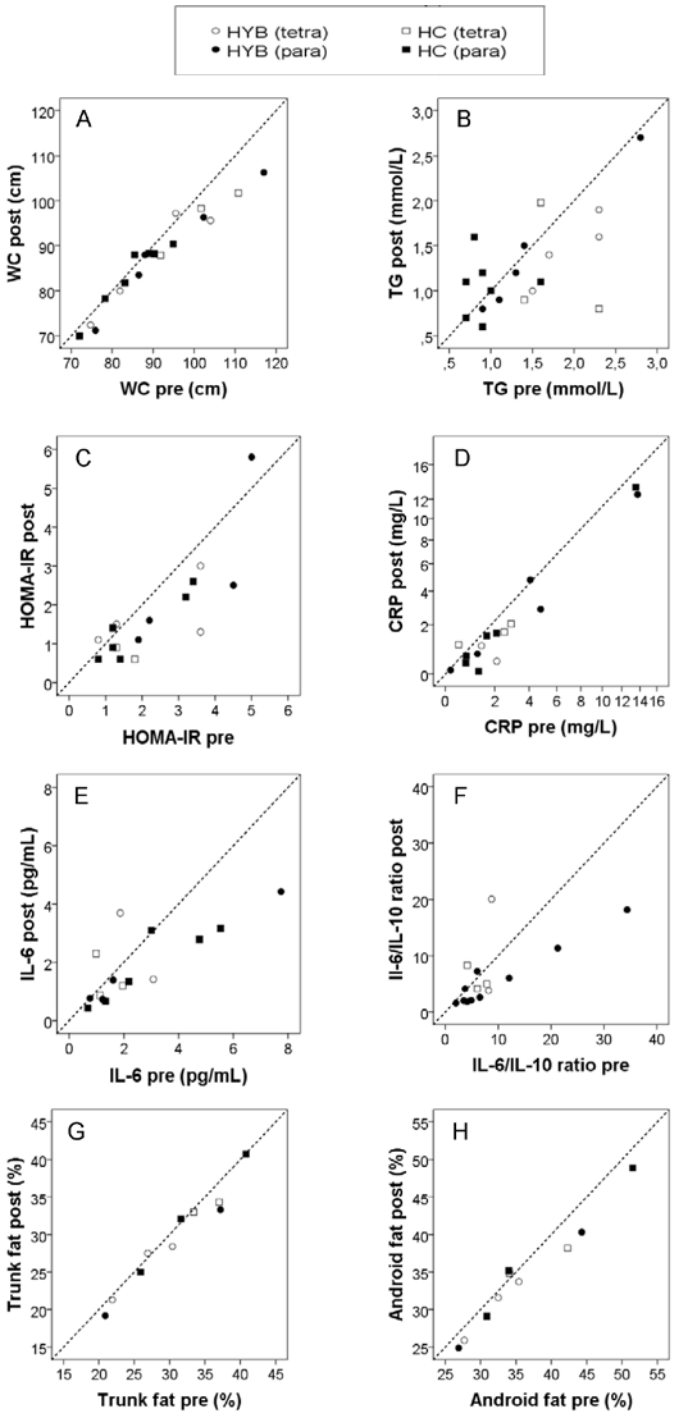

Figure 2 Individual values for metabolic syndrome, inflammatory status and visceral adiposity in the week before (pre) and after (post) the 16-wk training program. A, waist circumference (WC); B, homeostasis model assessment of insulin resistance (HOMA-IR); C, triglycerides (TG); D, C-reactive protein (CRP); E, interleukin (IL)-6; F, IL-6/IL-10 ratio; G, trunk fat percentage; H, android fat percentage. HYB, hybrid cycle; HC, handcycle; tetra, tetraplegia; para, paraplegia.

DISCUSSION

The main findings of this study were that both the 16-wk hybrid cycle and handcycle training program showed positive effects on different MetS components (WC, DBP, insulin and HOMA-IR), inflammatory status (CRP, IL-6 and IL-6/IL-10 ratio), and visceral adiposity (trunk and android fat percentage). Moreover, there were no notable benefits of the FES-induced leg exercise above handcycle training alone.

Metabolic syndrome

At the start of the intervention program, 16% of the participants who completed the program met the criteria for MetS. In comparison with cross-sectional studies on the prevalence of MetS in people with SCI (e.g. 23), this percentage is relatively low. As stated in the introduction, it is well documented that people with SCI have impaired levels of several MetS components (e.g. HDL-C and insulin) (5, 6). However, for the group of participants in this study, the mean values for all the MetS components were not elevated. Since there were no significant baseline differences between the individuals who dropped out and the individuals who completed the training program, it might be suggested that the participants who were enrolled in this study were relatively healthy compared to the average population with long-term SCI. Despite this, there were still positive training effects on different MetS components in this participant group. For example, the reduction in WC suggests that exercise training (i.e. hybrid cycling and handcycling) reduces abdominal obesity. At the start of this study, 3 of the 19 participants met the criteria of abdominal obesity. After 16 weeks of training, only 1 participant still met these criteria, but this person showed a reduction of 11 cm (9.4%) in WC. Another important result of this study was the reduction in insulin and HOMA-IR, indicating a reduced insulin resistance. Several other studies have also found positive effects of exercise on insulin resistance (28, 29, 30) while some studies have not (e.g. 31). In contrast, no significant changes were found for the lipids TG and HDL-C. That said, looking at the individual data, ~65% of the participants showed reductions in TG (Figure 2C). These findings are in accordance with a systematic review (22 studies were included) by Carlson et al. (32) who concluded that there is insufficient evidence that exercise alone improves lipid disorders in people with SCI. It requires further investigation to examine whether a combined exercise and dietary intervention is the optimal method for improving lipid spectrum in people with SCI. Together with the reduced DBP, the above-described findings suggest that exercise training has the potential to reduce several components within the MetS in inactive people with long-term SCI.

Inflammatory status

In the current cohort, resting inflammatory status was typical of untrained chronic SCI population groups (5, 33). Accordingly, 50% of the participants displayed resting inflammatory profiles symptomatic of an increased risk of CVD (IL-6 > 2 pg/mL; CRP > 3 mg/L). However, a large heterogeneity was present in resting values, suggesting SCI and physical inactivity alone are not solely responsible for a chronic inflammatory state. In this study, both exercise

interventions resulted in a significant improvement in inflammatory status. These findings are consistent with those of Griffin et al. (16), who reported a significant reduction in resting IL-6 and CRP concentration following 10-wk FES-cycling training. Hybrid exercise has previously been shown to induce a greater acute IL-6 response (17) and greater energy expenditure (34) than hand cycling exercise alone at a matched workload. However, both exercise modalities in the current study resulted in a similar significant reduction in inflammatory status (IL-6 and CRP).

Visceral adiposity

The mean values for visceral adiposity in this study were relatively low compared to the values reported in a study by Emmons et al. (35) who assessed visceral adiposity in people with SCI and able-bodied (AB) persons. This again supports the assumption that the participant group in the current study was relatively healthy. Despite this, a significant reduction in trunk and android fat percentage was found, suggesting that exercise training has the potential to reduce visceral adiposity. This finding was in accordance with a study by Gorgey et al. (36). Since DXA measurements are relatively expensive and time-consuming, researchers might also consider using the anthropometric measure WC (which is a reliable surrogate of visceral adiposity in able-bodied persons (5)) as a measure of visceral adiposity.

Hybrid cycle versus handcycle

The similar improvement in different CVD risk factors suggests that the relatively small available muscle mass during arm exercise alone is not a limiting factor for the reduction in CVD risk factors when exercise is performed on a regular basis at a sufficient intensity. The finding that handcycle exercise alone provides a sufficient training stimulus and that there were no notable benefits of the added FES-induced leg exercise, promote handcycling as a cheaper and more accessible exercise mode for reducing CVD risk factors than hybrid cycling. However, Bakkum et al. (34) have demonstrated that hybrid cycling induces higher metabolic and cardiorespiratory responses at equal subjective exercise intensity levels than handcycling, suggesting that hybrid cycling might be more suitable for fighting obesity and increasing cardiorespiratory fitness in individuals with SCI. Moreover, the addition of FES-induced leg exercise to handcycling has the potential to provide supplementary benefits on vascular (37) and musculoskeletal systems (38) in the lower extremities.

Limitations

A possible limitation of this study was that the lower-limb muscles of the participants in the hybrid group were relatively untrained at the beginning of the program, resulting in muscle fatigue during cycling. If the leg musculature becomes fatigued over time, the arms will take over the entire propulsion. To ensure strong lower-limb muscle contractions over the entire exercise period (i.e. 30 min), a conditioning phase for the paralyzed legs (i.e. FES-induced leg cycling only) for the participants in the hybrid group could have been performed. The training

effects might have been larger if all participants were able to complete 30 min of continuous leg exercise at the start of the hybrid cycle program. Another limitation was the relatively high drop-out rate (47%) in this study, however, it is not expected that this would have influenced the results since there were no baseline differences between the group that dropped out and the group that finished the training the program. Nevertheless, the high drop-out rate might also say something about the feasibility of this type of exercise intervention in people with long-term SCI. Firstly, it was difficult to recruit participants (only l1.5% of the people who received an invitation letter eventually participated), and secondly, it was hard to keep the participants in the program. The most mentioned reason for not participating and drop out was that the exercise intervention was too time consuming and could not easily be implemented in the daily life of these people. Therefore, future studies should consider how to make exercise interventions more feasible and attractive for this population. For example, better facilitation of the training equipment might save time; if people can exercise at home, this would mean that they do not have to travel to a rehabilitation center several days a week.

In conclusion, this study demonstrated that hybrid cycling and handcycling have similar beneficial effects on several CVD risk factors, including MetS components, inflammatory status and visceral adiposity, indicating that there were no notable benefits of the FES-induced leg exercise above handcycle training alone.

REFERENCES

1. Strauss DJ, Devivo MJ, Paculdo DR, Shavelle RM. Trends in life expectancy after spinal cord injury. Arch Phys Med Rehabil 2006; 87: 1079–1085.
2. Whiteneck GG, Charlifue SW, Frankel HL, Fraser MH, Gardner BP, Gerhart KA, et al. Mortality, morbidity, and psycho-social outcomes of persons spinal cord injured more than 20 years ago. Paraplegia 1992; 30:617–630.
3. Garshick E, Kelley A, Cohen SA, Garrison A, Tun CG, Gragnon D, et al. A prospective assessment of mortality in chronic spinal cord injury. Spinal Cord 2005; 43: 408–416.
4. Gibson AE, Buchholz AC, Martin Ginis KA; SHAPE-SCI Research Group. C-reactive protein in adults with chronic spinal cord injury: increased chronic inflammation in tetraplegia vs paraplegia. Spinal Cord 2008; 46: 616-621.
5. Manns PJ, McCubbin JA, Williams DP. Fitness, inflammation and the metabolic syndrome in men with paraplegia. Arch Phys Med Rehabil 2005; 86: 1176-1181.
6. Myers J, Lee M, Kiratli J. Cardiovascular disease in spinal cord injury: an overview of prevalence, risk, evaluation, and management. Arch Phys Med Rehabil 2007; 86: 142-152.
7. Washburn RA, Figoni SF. Physical activity and chronic cardiovascular disease prevention in spinal cord injury: a comprehensive literature review. Top Spinal Cord Inj Rehabil 1998; 3: 16–32.
8. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C; American Heart Association, et al. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issue related to definition. Circulation 2004; 109: 433-438.
9. Handschin C, Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. Nature 2008; 454: 463-469.
10. Tilg H, Morschen AR. Insulin resistance, inflammation, and non-alcoholic fatty liver disease. Trends Endocrinol Metab 2008; 19: 371-379.
11. Emanuela F, Grazia M, Marco de R, Maria Paola L, Giorgio F, Marco B. Inflammation as a link between obesity and metabolic syndrome. J Nutr Metab 2012; 2012: 476380.

12. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 2011; 11: 607-615.
13. Jacobs PL. Effects of resistance and endurance training in persons with paraplegia. Med Sci Sports Exerc 2009; 41: 992-997.
14. Buchholz AC, Martin Ginis KA, Bray SR, Craven BC, Hicks AL, Hayes KC, et al. Greater daily leisure time physical activity is associated with lower chronic disease risk in adults with spinal cord injury. Appl Physiol Nutr Metab 2009; 34: 640-647.
15. Paulson TA, Goosey-Tolfrey VL, Lenton JP, Leicht CA, Bishop NC. Spinal cord injury level and the circulating cytokine response to strenuous exercise. Med Sci Sports Exerc 2013; 45: 1649-1655.
16. Griffin L, Decker MJ, Hwang JY, Wang B, Kitchen K, Ding Z, et al. Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury. J Electromyogr Kines 2009; 19: 614–622.
17. Paulson TA, Bishop NC, Smith B, Goosey-Tolfrey VL. The inflammation-mediating cytokine response to acute handcycling exercise with/without functional electrical stimulation-evoked lower limb cycling. J Rehab Res Dev 2014; [Epub ahead of print].
18. Bakkum AJ, de Groot S, van der Woude LH, Janssen TW. The effects of hybrid cycle training in inactive people with long-term spinal cord injury: design of a multicentre randomized controlled trial. Disabil Rehabil 2013; 35: 1127-1132.
19. Washburn RA, Zhu W, McAuley E, Frogley M, Figoni SF. The physical activity scale for individuals with physical disabilities: development and evaluation. Arch Phys Med Rehabil 2002; 83:193–200.
20. De Groot S, van der Woude LH, Niezen A, Smit CA, Post MW. Evaluation of the physical activity scale for individuals with physical disabilities in people with spinal cord injury. Spinal Cord 2010; 48: 542–547.
21. Valent LJ, Dallmeijer AJ, Houdijk H, Slootman J, Janssen TW, Hollander AP, et al. The individual relationship between heart rate and oxygen uptake in people with a tetraplegia during exercise. Spinal Cord 2007; 45: 104-111.
22. Noble BJ, Borg GA, Jacobs I, Ceci R, Kaiser P. A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. Med Sci Sports Exerc 1983; 15: 523–528.

23. Nelson MD, Widman LM, Abresch RT, Stanhope K, Havel PJ, Styne DM, et al. Metabolic syndrome in adolescents with spinal cord dysfunction. J Spinal Cord Med 2007; 30 Suppl 1: S127-139.
24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412–419.
25. Clasey JL, Bouchard C, Teates CD, Riblett JE, Thorner MO, Hartman ML, et al. The use of anthropometric and dual-energy X-ray absorptiometry (DXA) measures to estimate total abdominal and abdominal visceral fat in men and women. Obes Res 1999; 7: 256-264.
26. Hill AM, LaForgia J, Coates AM, Buckley JD, Howe PR. Estimating abdominal adipose tissue with DXA and anthropometry. Obesity 2007; 15: 504–510.
27. Shuster A, Patlas M, Pinthus JH, Mourtzakis M. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. Br J Radiol 2012; 85:1-10.
28. D'Oliveira GL, Figueiredo FA, Passos MC, Chain A, Bezerra FF, Koury JC. Physical exercise is associated with better fat mass distribution and lower insulin resistance in spinal cord injured individuals. J Spinal Cord Med 2014; 37: 79-84.
29. Jeon JY, Weiss CB, Steadward RD, Ryan E, Burnham RS, Bell G, et al. Improved glucose tolerance and insulin sensitivity after electrical stimulation-assisted cycling in people with spinal cord injury. Spinal Cord 2002; 40:110-117.
30. Mohr T, Dela F, Handberg A, Biering-Sørensen F, Galbo H, Kjaer M. Insulin action and long-term electrically induced training in individuals with spinal cord injury. Med Sci Sports Exerc 2001; 33: 1247-1252.
31. Ryan TE, Brizendine JT, Backus D, McCully KK. Electrically induced resistance training in individuals with motor complete spinal cord injury. Arch Phys Med Rehabil 2013; 94: 2166-2173.
32. Carlson KF, Wilt TJ, Taylor BC, Goldish GD, Niewoehner CB, Shamliyan TA, et al. Effect of exercise on disorders of carbohydrate and lipid metabolism in adults with traumatic spinal cord injury: systematic review of the evidence. J Spinal Cord Med 2009; 32: 361-378.
33. Wang TD, Wang YH, Huang TS, Su TC, Pan SL, Chen SY. Circulating levels of markers of inflammation and endothelial activation are increased in men with chronic spinal cord injury. J Form Med Assoc 2007; 106: 919-928.

34. Bakkum AJT, de Groot S, Onderwater M, de Jong J, Janssen TWJ. Metabolic rate and cardiorespiratory response during hybrid cycling versus handcycling at equal subjective exercise intensity levels in people with a spinal cord injury. J Spinal Cord Med 2013; Nov 8 [Epub ahead of print].
35. Emmons RR, Garber CE, Cirnigliaro CM, Kirshblum SC, Spungen AM, Bauman WA. Assessment of measures for abdominal adiposity in persons with spinal cord injury. Ultrasound Med Biol 2011; 37: 734-741.
36. Gorgey AS, Mather KJ, Cupp HR, Gater DR. Effects of resistance training on adiposity and metabolism after spinal cord injury. Med Sci Sports Exerc 2012; 44: 165-174.
37. Thijssen DH, Heesterbeek P, van Kuppevelt DJ, Duysens J, Hopman MT. Local vascular adaptations after hybrid training in spinal cord-injured subjects. Med Sci Sports Exerc 2005; 37:1112–1118.
38. Sloan KE, Bremner LA, Byrne J, Day RE, Scull ER. Musculoskeletal effects of an electrical stimulation induced cycling programme in the spinal injured. Paraplegia 1994; 32: 407–415.

Chapter 6

A reliable method for measuring proximal tibia and distal femur bone mineral density using dual-energy X-ray absorptiometry

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ABSTRACT

Purpose: To assess the intra- and inter-rater reliability of a standardized protocol for measuring proximal tibia and distal femur bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA).

Methods: Ten able-bodied individuals (7 male) participated in this study. During one measurement session, the knee of each participant was scanned twice by rater 1 using DXA. Both scans were analyzed twice by rater 1 as well as once by a second rater. Intraclass correlation coefficients (ICCs), standard error of measurements (SEMs) and smallest detectable differences (SDDs) were calculated for the outcome measures proximal tibia and distal femur BMD. A decision study was performed to determine the effect of study protocol adjustments (i.e. increasing the number of scan repetitions, or scan analyses by the same rater) on SEM and SDD values.

Results: High intra- and inter-rater ICCs (0.97-0.98) were found for both proximal tibia and distal femur BMD. Low SEMs (0.017-0.028 g/cm²) and SDDs (0.047-0.077 g/cm²) were found, with a slightly better result for proximal tibia BMD. Increasing the number of scan analyses by the same rater did not markedly reduce SEM and SDD values, while increasing the number of scan repetitions did.

Conclusions: Proximal tibia and distal femur BMD can be reliably assessed with this method.

INTRODUCTION

Osteoporosis of the lower extremities is a severe secondary complication in people with a spinal cord injury (SCI) causing an increased risk of (low-impact) fractures, especially in the proximal tibia and distal femur[1-2]. To manage this so-called immobilization osteoporosis, bone mineral density (BMD) should therefore be measured at these specific sites[3].

Dual-energy X-ray absorptiometry (DXA) is a commonly used technique to measure BMD, to diagnose and manage osteoporosis, as well as to predict fracture risk[4]. There are standard clinical DXA protocols available to accurately measure whole body and regional (i.e. hip, lumbar spine and forearm) BMD[5]; however, the proximal tibia and distal femur are not standard measurement sites, and can therefore only be measured using a customized protocol.

In the literature, there is not much consistency regarding these customized protocols to measure knee BMD. A large variety was observed in: (1) type of DXA scan algorithm: several studies have used different modified lumbar spine[6-7] or forearm[8] scan protocols, while others have used the small-animal program[9-10]; (2) region of interest (ROI) settings: several studies have used anatomical markers for the ROI setting (e.g. the ROI's height is the same size as the fibular head)[6-8], while others have used the same fixed sizes for all participants (e.g. the proximal 7 cm of the tibia)[10-11]; (3) knee placement: in most studies the knee was scanned frontally with the participants in the supine position[6-7, 9-10], while in one study the participants were placed in the lateral position[8].

Besides the above-described inconsistency concerning the methods used to measure proximal tibia and distal femur BMD, many studies lack important methodological details (e.g.

regarding scan and analysis software used, and ROI settings), making it impossible for other researchers to reproduce these protocols[9, 11-13]. Moreover, most methods were not tested on reliability[7, 9-10, 12-13].

Therefore, the purpose of this study was to assess the intra- and inter-rater reliability of a standardized method for measuring proximal tibia and distal femur BMD using DXA. Moreover, it was investigated whether this protocol could be optimized. Results of this study might lead to better osteoporosis diagnosis and management in people with disabilities and diseases where the knee is affected (e.g. SCI, cerebral palsy, Duchenne muscular dystrophy and knee osteoarthritis).

METHODS

Participants

Ten able-bodied persons (7 male; mean age 35 (25-58) years; mean body mass 75.3 (56.4−91.2) kg; mean height 183.9 (167.0−193.7) cm; no history of knee fractures) provided written informed consent and participated in this study which was approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam.

Scan procedure

Proximal tibia and distal femur BMD measured using DXA (Hologic Discovery, Hologic Inc., Waltham, Massachusetts, USA). After thorough discussions with radiologists and Hologic, we hypothesized that an adapted forearm scan protocol is most suitable for knee measurements, since the knee anatomically has more similarities with the forearm than with the lumbar spine or a small animal. Moreover, since for many people with SCI it is inconvenient to maintain a lateral position, scans were performed with the participants in supine position.

A radiologic technologist (rater 1) positioned the participant's non-dominant leg into the correct alignment and rotation: the leg was placed in full extension, and the foot was endorotated (to reduce overprojection of the tibia and fibula as much as possible) and strapped in a foot positioner (Figure 1). The knee was scanned frontally using the forearm scan protocol, such that both the patella and fibular head were completely visible in the scan, and that the joint space of the knee was horizontal (Figure 2); participants were repositioned and scans were repeated by rater 1 until these criteria were met. In case of movement artefacts, the scan was also performed again.

During one measurement session, for each participant the above-described scan procedure was performed twice by rater 1 to obtain a total of two proper knee scans per person. Between repeated scans, the participants stepped down from the DXA table and were then completely repositioned by rater 1. Scan time was approximately 30 s, and exposure to radiation was less than 0.2 μSv per scan[14].

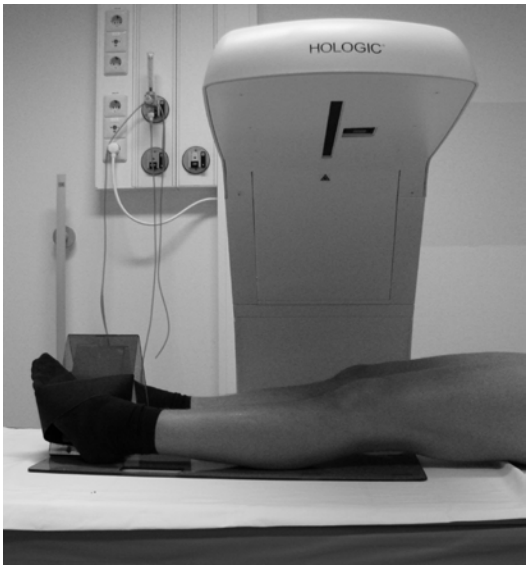

Figure 1. Scan position for measuring left proximal tibia and distal femur BMD using DXA; the participant was placed in the supine position with the left leg fully extended and the foot endorotated and strapped in a foot positioner.

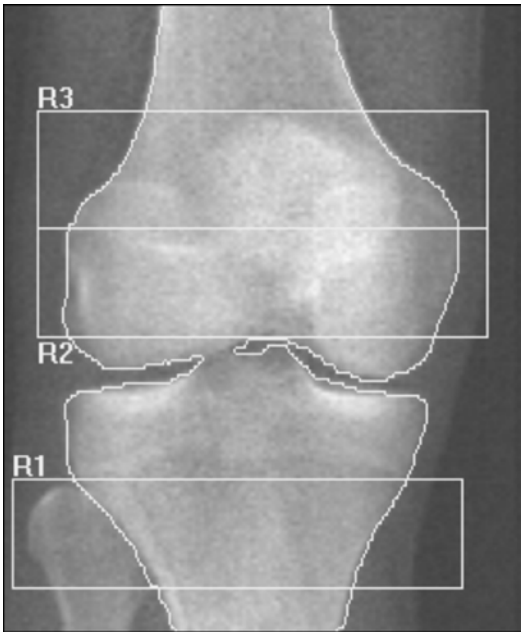

Figure 2. A frontally scanned knee where both the patella and fibular head are completely visible in the scan. R1 is the ROI of the proximal tibia; R2 and R3 are the ROIs of the distal femur, with the height of R2 matching the height of R1 and R3 including R2 and the entire patella.

Analysis

Following the advice of Hologic, the proximal tibia and distal femur were analyzed using the forearm subregion analysis protocol. The automatic bone detection function was used to shade all bone pixels in the scan and the image was corrected manually for erroneously included or excluded bone pixels; fibula bone pixels were excluded. To take anthropometrical differences among people into account, the ROIs were set to anatomical markers. The distal horizontal edge of the ROI of the proximal tibia (R1) was placed at the most distal point of contact between the fibular head and the tibia, and the proximal horizontal edge was placed at the upper edge of the fibular head (Figure 2). For the distal femur, two ROIs (R2 and R3) were set to also examine the effect of the patella on the reliability of the measurement, with R2 including only a part of the patella and R3 including R2 and the entire patella. The bottom horizontal edge of both R2 and R3 was positioned at the top of the space between the femoral condyles, with the height of R2 matching the height of R1, and the proximal horizontal edge of R3 placed at the upper edge of the patella (Figure 2). The width of R1-R3 was set outside the bone area but inside the soft tissue area (no air was included). After setting R1-R3, the analytic software accompanying the system (Apex 13.3.3) automatically performed the BMD calculations. The above-described scan and analysis method could also be applied with other types of DXA scanners (e.g. GE Lunar) that have the option for sub-regional forearm analysis.

To be able to assess the intra- and inter-rater reliability of the protocol, both scans of each participant (a total of 20 scans) were analyzed twice by rater 1, as well as once by a second radiologic technologist (rater 2). Both raters performed the analyses completely independent from each other and were first extensively trained in how to perform the analysis protocol.

Statistics

Descriptive statistics (model based mean and standard error) were calculated for proximal tibia (R1) and distal femur (R2 and R3) BMD. The intra- and inter-rater reliability were assessed according to generalizability theory, which is based on analysis of variance[15-16]. Variance components were obtained from a random effects design and the method of restricted maximum likelihood, using the VARCOMP procedure in IBM SPSS Statistics 20. With these variance components, the intra- and inter-rater intraclass correlation coefficient (ICC), standard error of measurement (SEM), and smallest detectable difference (SDD) were calculated for the outcome measures R1-R3. The meaning of the different variance components, and the formulas for calculating the intra- and inter-rater ICC, SEM and SDD are presented in Table 1.

To examine whether the study protocol could be optimized, a decision study was performed to determine the effect of study protocol adjustments (i.e. more scan repetitions, or more scan analyses by the same rater) on SEM and SDD values[15-16].

Table 1: Meaning of the variance components; and formulas for calculating the intra- and inter-rater intraclass correlation coefficient (ICC), standard error of measurement (SEM), and smallest detectable difference (SDD)

σ^2_p	Variance between participants
$\sigma^2_{s:p}$	Variance between scans within the participants
σ^2_r	Variance between raters
σ^2_{pr}	Variance due to interaction of participants and raters
$\sigma^2_{sr:p}$	Variance due to interaction of scans and raters within the participants
σ^2_e	Variance due to pure measurement error
ICC_{intra}	$(\sigma^2_p + \sigma^2_r + \sigma^2_{pr}) / (\sigma^2_p + \sigma^2_{s:p} + \sigma^2_r + \sigma^2_{pr} + \sigma^2_{sr:p} + \sigma^2_e)$
ICC_{inter}	$\sigma^2_p / (\sigma^2_p + \sigma^2_{s:p} + \sigma^2_r + \sigma^2_{pr} + \sigma^2_{sr:p} + \sigma^2_e)$
SEM_{intra}	$\sqrt{(\sigma^2_{s:p} + \sigma^2_r + \sigma^2_{pr} + \sigma^2_{sr:p} + \sigma^2_e)}$
SEM_{inter}	$\sqrt{(\sigma^2_{s:p} + \sigma^2_{sr:p} + \sigma^2_e)}$
$SDD_{intra/inter}$	$1.96 \times \sqrt{2} \times SEM_{intra/inter}$

RESULTS

Reliability

The estimates of the variance components obtained from the variance components analysis appear in appendix 1. The model based means, ICCs, SEMs and SDDs for proximal tibia (R1) and distal femur (R2, R3) BMD are presented in Table 2. High intra-rater ICCs (0.98) and low SEMs (0.017-0.028 g/cm²) and SDDs (0.047-0.077 g/cm²) were found for R1-R3, with a slightly better result for R1. No difference was found between R2 and R3. For the inter-rater reliability, almost identical ICC (0.97-0.98), SEM (0.018-0.028 g/cm²) and SDD (0.051-0.077 g/cm²) values were found (Table 2).

Optimization of the protocol

Increasing the number of scan analyses by the same rater only marginally improved (by a few thousandths) SEM and SDD values. However, increasing the number of scan repetitions did lead to markedly improved SEMs and SDDs (Table 3). For example, using 4 scans instead of one scan will reduce the SEMs and SDDs for R2 and R3 by half their size.

Table 2: Model based mean (SE), and intra- and inter-rater reliability parameters for proximal tibia and distal femur BMD measurements

BMD (g/cm²)	Model based mean (SE)	intra-rater			inter-rater		
		ICC	SEM	SDD	ICC	SEM	SDD
R1	0.770 (0.035)	0.98	0.017	0.047	0.97	0.018	0.051
R2	1.067 (0.062)	0.98	0.028	0.077	0.98	0.028	0.077
R3	1.026 (0.055)	0.98	0.028	0.077	0.98	0.028	0.077

SE: standard error; BMD: bone mineral density; R1: region of interest of the proximal tibia; R2 and R3: regions of interest of the distal femur; ICC: intraclass correlation coefficient; SEM: standard error of measurement; SDD: smallest detectable difference.

Table 3: Decision study results: the effect of increasing the number of scans on SEM and SDD values

BMD (g/cm²)	Model based mean (SE)	1 scan		2 scans		4 scans	
		SEM	SDD	SEM	SDD	SEM	SDD
R1	0.770 (0.035)	0.017	0.047	0.012	0.033	0.008	0.023
R2	1.067 (0.062)	0.028	0.077	0.020	0.054	0.014	0.038
R3	1.026 (0.055)	0.028	0.077	0.020	0.054	0.014	0.038

SE: standard error; BMD: bone mineral density; R1: region of interest of the proximal tibia; R2 and R3: regions of interest of the distal femur; SEM: standard error of measurement; SDD: standard detectable difference. Example: when the knee is scanned 4 times (hypothetical study protocol adjustment) instead of once, the SEMs and SDDs for R2 and R3 will be reduced by half their size.

Appendix: Estimates of the variance components

	R1	R2	R3
σ^2_p	122.46	380.30	299.12
$\sigma^2_{s:p}$	2.58	6.72	7.38
σ^2_r	0	0	0.03
σ^2_{pr}	0.55	0	0.08
$\sigma^2_{sr:p}$	0.04	0	0
σ^2_e	0.21	0.96	0.33

Values are $\times 10^{-4}$; R1: region of interest of the proximal tibia; R2 and R3: regions of interest of the distal femur.

DISCUSSION

The purpose of this study was to examine the intra- and inter-rater reliability of a standardized DXA protocol to assess proximal tibia and distal femur BMD. Our results demonstrate that, with this method, both sites can be reliably assessed (high intra- and inter-rater ICCs (0.97-0.98); Table 2). Moreover, small BMD differences can be detected with this protocol (SDDs: 0.047-0.077; Table 2), that can be optimized by increasing the number of scan repetitions (Table 3).

Shields et al. (2005)[6] have examined the inter-rater (4 raters) reliability of a standardized DXA-method for measuring proximal tibia and distal femur BMD in 22 people with a SCI, using a customized lumbar spine protocol. Compared to our study (Table 2), they have found a similar ICC for the distal femur (0.98), but a slightly lower ICC for the proximal tibia (0.89); no SEM and SDD values were reported. The difference in the ICC for the proximal tibia might be due to differences in the ROI settings; in the study of Shields et al. (2005), the height of the ROIs was based on the femur length while the height of the ROIs in our study was based on the fibular head; moreover, in their study different anatomical landmarks were used to set the horizontal edges of the ROIs.

In the current study, the intra and inter-rater SDDs were 0.047-0.051 for proximal tibia and 0.077 for distal femur BMD (Table 2), which means that an individual improvement of at least 0.047-0.051 g/cm² (≈6-7%) and 0.077 g/cm² (≈7-8%) in proximal tibia and distal femur BMD, respectively is necessary to detect a real improvement. In intervention studies where BMD changes of less than 6.6-7.2% are already expected to be clinically relevant, we would recommend performing more scan repetitions to reduce the SDDs. For example, the SDDs for R2 and R3 can be reduced to approximately half their size (≈3.7%) by performing four scans instead of one scan (Table 3). However, in intervention studies, it should be realized that soft tissue changes around the knee (e.g. as an effect of an intervention strategy[17]) can negatively influence the reliability of the measurement. Furthermore, repositioning the individual's leg from day to day may contribute to a reduced reliability[18]. To reliably assess real treatment effects, it is therefore important that repeated measures are performed by experienced radiologic technologists following a clearly standardized scan and analysis protocol.

Since the ICCs, SEMs and SDDs for R2 and R3 were the same in this study (Table 2), it would be sufficient to analyze only one of these two distal femur ROIs to reliably measure distal femur BMD. Since R2 is easier to set (only the bottom edge has to be set), we recommend using this region in further research. It seems that the patella did not affect the reliability of the distal femur measurement; however, including the patella in the analysis will lead to an overestimation of distal femur BMD. This problem was not mentioned in other studies that frontally scanned the knee to measure distal femur BMD[6-7, 11-13]. A possible way to exclude the patella from the analysis and purely measure distal femur BMD is to laterally scan the individuals, which was done by Henderson et al. (2010)[8]. However, as stated before, since scanning laterally can be inconvenient for people with a SCI, we choose to scan the knee frontally.

This study was performed in able-bodied persons whose legs could easily be positioned in the appropriate alignment and rotation and who were able to keep that position during

scanning. However, when scanning people with a SCI, it should be taken into account that the positioning of the legs can sometimes be difficult due to contractures or neurogenic heterotopic ossification in the hip, knee or ankle[19-20], which might influence the reliability of the measurement. In case of contractures or neurogenic heterotopic ossification, it should be ensured that the knee is extended and the foot is endorotated as far as possible (extra straps can be used if necessary). Another complication that can occur during scanning people with a SCI is (severe) spasticity of the legs[21], causing motion artefacts in the scan. In that case, the scan should be performed again immediately when the spasticity has disappeared. It is assumed that spasticity would not be a major problem during scanning since the very short scan time considerably reduces possible movement artefacts.

In conclusion, this standardized DXA scan protocol can: reliably measure proximal tibia and distal femur BMD; detect small BMD differences (6-8%); be optimized by increasing the number of scan repetitions. Therefore, this method has the potential to diagnose and manage osteoporosis in people with disabilities and diseases where the knee is affected (e.g. SCI, cerebral palsy, Duchenne muscular dystrophy and knee osteoarthritis).

REFERENCES

1. Jiang SD, Dai LY, Jiang LS. Osteoporosis after spinal cord injury. Osteoporos Int 2006:17(2): 180-192.
2. Ragnarsson KT, Sell GH. Lower extremity fractures after spinal cord injury: A retrospective study. Arch Phys Med Rehabil 1981:62(418-423.
3. Biering-Sorensen F, Hansen B, Lee BS. Non-pharmacological treatment and prevention of bone loss after spinal cord injury: A systematic review. Spinal Cord 2009:47(7): 508-518.
4. Mazess RB, Barden HS. Measurement of bone by dual-photon absorptiometry (dpa) and dual-energy x-ray absorptiometry (dexa). Ann Chir Gynaecol 1988:77(5-6): 197-203.
5. Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. Am J Clin Nutr 1990:51(6): 1106-1112.
6. Shields RK, Schlechte J, Dudley-Javoroski S, Zwart BD, Clark SD, Grant SA, Mattiace VM. Bone mineral density after spinal cord injury: A reliable method for knee measurement. Arch Phys Med Rehabil 2005:86(10): 1969-1973.
7. Bloomfield SA, Mysiw WJ, Jackson RD. Bone mass and endocrine adaptations to training in spinal cord injured individuals. Bone 1996:19(1): 61-68.
8. Henderson RC, Berglund LM, May R, Zemel BS, Grossberg RI, Johnson J, Plotkin H, Stevenson RD, Szalay E, Wong B et al. The relationship between fractures and dxa measures of bmd in the distal femur of children and adolescents with cerebral palsy or muscular dystrophy. J Bone Miner Res 2010:25(3): 520-526.
9. Broholm B, Pødenphant J, Biering-Sørensen F. The course of bone mineral density and biochemical markers of bone turnover in early postmenopausal spinal cord-lesioned females.
. Spinal Cord 2005:43(11): 674-677.
10. Mohr T, Podenphant J, Biering-Sorensen F, Galbo H, Thamsborg G, Kjaer M. Increased bone mineral density after prolonged electrically induced cycle training of paralyzed limbs in spinal cord injured man. Calcif Tissue Int 1997:61(1): 22-25.
11. Lai CH, Chang WH, Chan WP, Peng CW, Shen LK, Chen JJ, Chen SC. Effects of functional electrical stimulation cycling exercise on bone mineral density loss in the early stages of spinal cord injury. J Rehabil Med 2010:42(2): 150-154.
12. Chen SC, Lai CH, Chan WP, Huang MH, Tsai HW, Chen JJ. Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. Disabil Rehabil 2005:27(22): 1337-1341.

13. Bélanger M, Stein RB, Wheeler GD, Gordon T, Leduc B. Electrical stimulation: Can it increase muscle strength and reverse osteopenia in spinal cord injured individuals?
. Arch Phys Med Rehabil 2000:81(8): 1090-1098.
14. Lewis MK, Blake GM, Fogelman I. Patient dose in dual x-ray absorptiometry. Osteoporosis Int 1994:4(11-15.
15. Molenberghs G, Laenen A, Vangeneugden T. Estimating reliability and generalizability from hierarchical biomedical data. J Biopharm Stat 2007:17(4): 595-627.
16. Vangeneugden T, Laenen A, Geys H, Renard D, Molenberghs G. Applying concepts of generalizability theory on clinical trial data to investigate sources of variation and their impact on reliability. Biometrics 2005:61(1): 295-304.
17. Chilibeck PD, Jeon J, Weiss C, Bell G, Burnham R. Histochemical changes in muscle of individuals with spinal cord injury following functional electrical stimulated exercise training. Spinal Cord 1999:37(264-268.
18. Therbo M, Petersen MM, Schrøder HM, Nielsen PK, Zerahn B, Lund B. The precision and influence of rotation for measurements of bone mineral density of the distal femur following total knee arthroplasty: A methodological study using dexa. Acta Orthop Scand 2003:74(677-682.
19. Diong J, Harvey LA, Kwah LK, Eyles J, Ling MJ, Ben M, Herbert RD. Incidence and predictors of contracture after spinal cord injury—a prospective cohort study. Spinal Cord 2012:50(579-584.
20. van Kuijk AA, Geurts AC, van Kuppevelt HJ. Neurogenic heterotopic ossification in spinal cord injury. Spinal Cord 2002:40(7): 313-326.
21. Maynard FM, Karunas RS, Waring WPr. Epidemiology of spasticity following traumatic spinal cord injury. Arch Phys Med Rehabil 1990:71(8): 566.

Chapter 7

Effects of hybrid cycling on lower-body soft tissue composition and proximal tibia and distal femur bone mineral density in inactive people with long-term spinal cord injury: a 16-wk randomized-controlled trial

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ABSTRACT

Trial design: Open, explanatory, parallel-group randomized-controlled trial.

Setting: Rehabilitation center.

Participants: Physically inactive and wheelchair-dependent individuals (aged 26-65) with spastic spinal cord injury (SCI) ≥ 8 yrs (age at onset SCI ≥ 18 yrs).

Interventions: The experimental group received a 16-wk hybrid cycle (voluntary arm exercise combined with functional electrical stimulation (FES)-induced leg exercise) training program, while the control group received a 16-wk handcycle program. Outcome measures were obtained in the week before and after the training program.

Objective: Investigate the effects of hybrid cycle training on soft tissue composition (lean and fat mass) of the legs, proximal tibia and distal femur bone mineral density (BMD), and bone turnover markers (procollagen type 1 amino-terminal propeptide (P1NP) and cross-linked C-telopeptide (CTX)).

Randomization: block randomization (block size 6; allocation ratio 1:1).

Results: Thirty-six participants were included, of which 20 individuals (10 hybrid cycle, 10 handcycle) completed the study and were analyzed for all outcome measures. Following the 16-wk program, lean mass of the legs was increased with 0.86 ± 0.26 kg (P=0.029) in the hybrid cycle group, and decreased with 0.78 ± 0.27 kg (P=0.045) in the handcycle group. For fat mass of the legs, an overall reduction of 0.35 ± 0.13 kg (P=0.03) was found. For proximal tibia and distal femur BMD, no significant main effects for time were observed. Furthermore, there was an overall reduction of 3.6 ± 1.7 µg/L (P=0.05) in P1NP and no significant difference over time (P=0.53) for CTX. However, no significant differences over time between the two training groups were found for leg fat mass, proximal tibia and distal femur BMD, P1NP and CTX.

Conclusion: Hybrid cycling leads to improvements in soft-tissue composition of the legs but does not improve knee BMD and bone turnover makers.

Trial registration: Netherlands Trial Register (NTR), no. 2855.

INTRODUCTION

Adverse soft tissue composition changes and bone mineral density (BMD) loss in the lower extremities are common complications in people with long-term spinal cord injury (SCI) (1,2). The soft tissue composition changes (i.e. muscle atrophy and increased adiposity) are associated with several metabolic disorders, such as insulin resistance and cardiovascular disease (3,4). The BMD loss results in osteoporosis (5), leading to an increased risk of (low-impact) fractures, especially in the proximal tibia and distal femur (6,7).

Inactivity of the lower extremities is an important factor in this sublesional change in body composition. From previous research, it is known that reactivating the paralyzed lower-limb musculature by functional electrical stimulation (FES) can improve soft tissue composition in people with long-term SCI (8). Moreover, it is known that mechanically reloading the bones by activating the paralyzed muscles, alters the activity and balance between osteoblasts (bone

formation) and osteoclasts (bone resorption), which consequently results in BMD improvements (9). Therefore, exercise training of the lower limbs is important to prevent or reverse lower-body adverse soft tissue composition changes and BMD loss in people with long-term SCI.

Several studies were performed to examine the effects of FES-induced leg exercise alone on lower-body soft tissue composition (8) and knee (proximal tibia and/or distal femur) BMD (e.g. 10-12). In these studies, the outcome measures were assessed using dual-energy X-ray absorptiometry (DXA), a commonly used technique to measure whole body and regional body composition. Standard DXA protocols are available to accurately measure soft tissue composition of the legs. However, proximal tibia and distal femur BMD are not standard measurement sites, and can therefore only be measured using a customized DXA protocol. In literature, there is inconsistency regarding the adapted scan and analysis protocols used to measure knee BMD, and many of the described protocols lack important methodological details (e.g. 10,12) and were not tested on reliability (10-12). Therefore, Bakkum et al. (13) developed a reliable DXA method that can detect small proximal tibia (~0.05 g/cm^2) and distal femur (~0.08 g/cm^2) BMD changes over time. Besides the above-described inconsistency regarding the methods used to measure knee BMD, there is inconsistency regarding the effectiveness of FES training on knee BMD; some studies found positive training effects (10,11), while others did not (e.g. 12).

In addition to BMD measurements, biochemical markers of bone turnover can be determined in blood to assess metabolic activity of bone tissue (14). Unlike differences in BMD, changes in markers of bone formation (e.g. procollagen type 1 amino-terminal propeptide (P1NP)) and bone resorption (e.g. cross-linked C-telopeptide (CTX)) can occur in a relatively short period of time (15). Therefore, assessment of these bone turnover markers might be of additional value when investigating the effectiveness of a training intervention on knee BMD.

To activate more muscle mass and subsequently provide greater exercise responses, a hybrid mode of exercise can be used in which FES-induced leg exercise is combined with voluntary arm exercise (16). This type of exercise has not been extensively investigated yet, but has the potential to cause greater health benefits than arm exercise or FES-induced leg exercise alone due to the relatively large active muscle mass. To date, there are no studies that examined the effects of hybrid exercise on lower-extremity body composition and bone turnover markers in people with long-term SCI. Therefore, the aim of this randomized-controlled trial (RCT) was to investigate the effectiveness of a 16-wk hybrid cycle training program on soft tissue composition (lean and fat mass) of the legs, proximal tibia and distal femur BMD, and bone turnover markers (CTX and P1NP) in people with long-term SCI.

METHODS

Trial design

The current study is part of a larger clinical trial (registered in Netherlands Trial Register (NTR), no. 2855) of which the experimental design has previously been described by Bakkum et al. (17). Briefly, this study was a 16-wk open, explanatory, parallel-group RCT performed in two Dutch rehabilitation centers (Reade Amsterdam and St. Maartenskliniek Nijmegen). Within each rehabilitation center, block randomization (fixed block size of 6; allocation ratio of 1:1; no stratification) was used to assign participants to either the experimental group (hybrid cycle; voluntary arm exercise combined with FES-induced leg exercise) or control group (handcycle; voluntary arm exercise alone). A blinded independent researcher provided the allocation in sequentially numbered, opaque, sealed and stapled envelopes. After the included participants completed all baseline measurements, the principal investigator opened the envelopes and allocated the participants to the intervention. The sample size calculation was performed on the main outcome measure of the larger study (i.e. peak power output) and revealed a group size of 18 participants. Measurements in the current study were performed in the week before (pre) and after (post) the training program.

Participants

As previously described (17), participants were recruited from the databases of two Dutch rehabilitation centers with a specialized SCI-unit (Reade Amsterdam and St. Maartenskliniek Nijmegen). Inclusion criteria were: spastic tetraplegia or paraplegia; time since injury (TSI) $\geq$ 10 years; age 28-65 years; age at onset SCI $\geq$ 18 years; physically inactive; dependent on a wheelchair; and no or limited sensation in the lower extremity. Exclusion criteria were: contraindications for physical training and testing (e.g. severe cardiovascular or musculoskeletal complaints); psychiatric problems; plans to start another lifestyle (e.g. diet and physical activity changes); insufficient knowledge of the Dutch language. These eligibility criteria were checked by a research assistant in a telephone interview with the participant, and subsequently by a rehabilitation physician during a thorough screening. People were qualified as 'physically inactive' if their score on the Physical Activities Scale for Individuals with Physical Disabilities (PASIPD) (18) was lower than the 75th percentile of a Dutch cohort study population (19). Due to difficulties with recruiting the intended number of participants, one year after trial commencement, the inclusion criterion TSI $\geq$ 10 years was reduced to TSI $\geq$ 8 years.

Ethics statement

All participants provided written informed consent indicating voluntary participation in this study, approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam (registration no. 2011/90).

Training devices

The hybrid cycle (BerkelBike Pro, BerkelBike B.V., St. Michielsgestel, the Netherlands; Figure 1A) combines synchronous voluntary handcycling with asynchronous FES-induced leg cycling. A 6-channel stimulator (Impuls, BerkelBike B.V., St. Michielsgestel, the Netherlands; Figure 1A-I) provided electrical stimulation via self-adhesive 50 x 90 mm surface electrodes placed bilaterally over the quadriceps, hamstrings and gluteus muscles. During cycling, the stimulator received information from the crank angle encoder (Figure 1A-II) about pedal position and velocity to control the cyclic stimulation pattern.

The handcycle (Speedy-Bike, Reha-Technik GmbH, Delbrück, Germany; Figure 1B) was equipped with a wide synchronous bull-horn crank. Both cycles were equipped with 8 gears that could be changed manually, and with quad grips for those participants who needed them. The front wheel of both devices was mounted on an ergotrainer (Tacx Flow, Technische Industrie Tacx B.V., Wassenaar, the Netherlands; Figure 1A-III and 1B-III) that was adapted to the wheel size of the cycles.

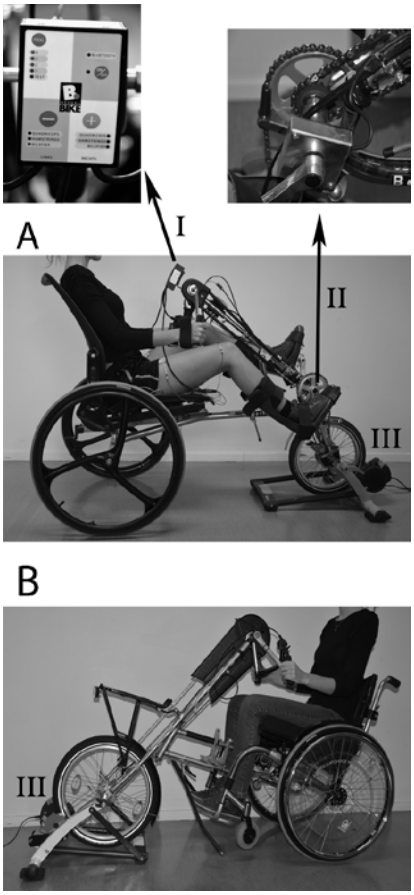

Figure 1 The hybrid cycle (A) with the stimulator (I) and crank angle encoder (II), and the handcycle (B), mounted on an ergotrainer (III).

Training protocol

The training protocol has also previously been described by Bakkum et al. (17). Briefly, participants performed 32 interval training sessions within a continuous period of 16 weeks. During the program, the total exercise time during the training sessions increased from 18 to 32 minutes. Following a graded exercise test to exhaustion, the training intensity was set to attain a heart rate response of 65-75% heart rate reserve (HRR) during training. Since the use of heart rate as an indicator for training intensity can be unreliable in individuals with tetraplegia (20), rating of perceived exertion (RPE) served as a supplementary measure of training intensity; a target RPE of 4-7 on the Borg's 10-point scale (21) was required during training. Exercise intensity was controlled by the participant making adjustments in cycle velocity or by the trainer adjusting the gear of the cycle or the resistance of the ergotrainer. In addition, during hybrid cycling the current amplitude of the stimulation was adjusted manually by the trainer to control the degree of muscle activation. Each session, the trainer tried to induce strong lower-limb muscle contractions; however, the current amplitude was decreased if the legs were moving too fiercely due to electrical stimulation or if the participants indicated that the stimulation was too intense. Heart rate was recorded constantly during each training session using radiotelemetry (Polar, Polar Electro Inc., Woodbury, NY), and RPE was assessed after each training block. Before and immediately after each training session, participants were asked to report local pain and/or complaints.

Outcome measures

Soft tissue composition

Whole-body DXA (Hologic Discovery, Hologic Inc., Waltham, Mass) imaging was used to measure lean and fat mass (kg) of the legs. Measurements were performed according to the manufacturer's instructions with the participants in the supine position. The left leg and right leg region were automatically defined using the analytic software accompanying the system (Apex 13.3.3). For data analysis, left and right leg measurements were summed.

Bone mineral density

Proximal tibia and distal femur BMD (g/cm^2) were measured using the method of Bakkum et al. (2014) (13), briefly explained here. Participants were placed in the supine position on the DXA table. The non-dominant leg was placed into the correct alignment and rotation: the knee was extended as far as possible, and the foot was endorotated (to reduce overprojection of the tibia and fibula) and strapped in a foot positioner. Then, the knee was scanned frontally using the forearm scan protocol of the DXA device, such that both the patella and fibular head were completely visible in the scan, and that the joint space of the knee was horizontal (Figure 2). Subsequently, proximal tibia and distal femur BMD were analyzed using the forearm subregion analysis protocol. The automatic bone detection function was used to shade all bone pixels in the scan, and the image was corrected manually for erroneously included or excluded bone pixels; fibula bone pixels were excluded. The distal edge of the region of interest (ROI) of the proximal

tibia (R1) was placed at the most distal point of contact between the fibular head and the tibia, and the proximal horizontal edge was placed at the upper edge of the fibular head (Figure 2). For the distal femur (R2), the bottom horizontal edge was positioned at the top of the space between the femoral condyles, with the height of R2 matching the height of R1 (Figure 2). The width of both ROIs was set outside the bone area but inside the soft tissue area (no air was included). After setting the ROIs, the analytic software of the system automatically performed the BMD calculations.

All above-described DXA scan procedures and analyses were performed by the same experienced radiologic technologist. Since the DXA device was exclusively available in Amsterdam, the measurements were only performed in the group that trained in rehabilitation center Reade Amsterdam (Table 1).

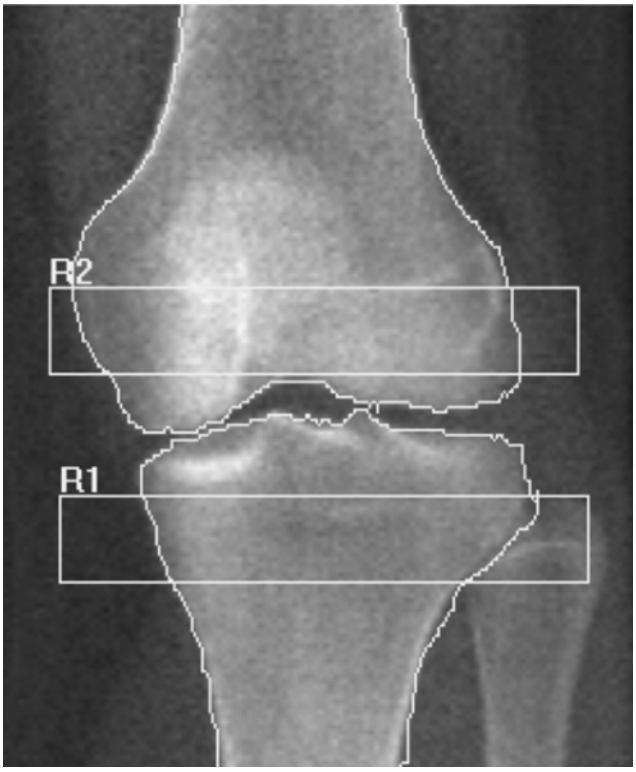

Figure 2 A frontally scanned knee. R1 is the region of interest (ROI) of the proximal tibia, and R2 is the ROI of the distal femur, with the height of R2 matching the height of R1.

Bone turnover markers

After a 12-hour overnight fast, blood samples were collected from an antecubital vein into 6.0-mL BD Vacutainer clot activator tubes. Within two hours of blood collection, the samples were centrifuged at 1800g for 10 minutes at room temperature. Subsequently, the serum was separated into aliquots and stored at -80°C. All serum specimens were assayed in one session at the end of the study to reduce inter-assay variability. Serum concentrations of P1NP (µg/L) and CTX

(ng/L) were determined using radioimmunoassay (Orion Diagnostica, Espoo, Finland) and immunometric assay (Roche Diagnostics Corporation, Indianapolis, IN, USA) kits, respectively, according to the manufacturer's instructions. All samples were analyzed in duplicate. The within assay coefficients of variation for P1NP and CTX were 4% and 5%, respectively.

Statistical analysis

The assumption of normality of the data within groups was checked by visual inspection of the q-q plot and box plot; in addition, a Shapiro-Wilks test was performed. Homogeneity of variance was checked using the Levene's test. In case of violations of these assumptions, the statistical analyses were performed on the log-transformed data. Independent t-tests were used to determine potential baseline differences in the outcome measures between groups. Differences between pre and post exercise measurements were examined using a two-factor (time of measurement x group) mixed-measures ANOVA. If an interaction effect was found, paired t-tests were used to examine this interaction. Data are presented as mean ± standard error (SE), and significance was set a priori at $p < 0.05$. All data were analyzed using the statistical package IBM SPSS for Windows version 21 (SPSS inc, Chicago, IL).

RESULTS

Between November 2011 (start recruitment) and August 2013 (end recruitment), 36 participants were included (17 hybrid cycle, 19 handcycle), of which 20 individuals (10 hybrid cycle, 10 handcycle) completed the study and were analyzed for all outcome measures (Figure 3). Reasons for drop out were illness (3 hybrid cycle, 5 handcycle) and lack of adherence to the training (4 hybrid cycle, 4 handcycle). Besides temporary muscle soreness due to exercise training, no serious adverse events were reported as a consequence of the training program. All 20 participants who completed the study (32 sessions) recorded 100% compliance to the program. DXA measurements were performed in 12 (7 hybrid cycle, 5 handcycle) individuals (Table 1). The assumptions of normality and homogeneity of error variance were confirmed for all variables except for proximal tibia and distal femur BMD. No significant baseline differences were present for any outcome measure or personal and lesion characteristics between the two training groups, and between the individuals who dropped out and the individuals who completed the 16-wk training program. For both soft tissue composition of the legs and bone turnover markers, 1 participant of the hybrid cycle group was excluded from the analysis due to missing data.

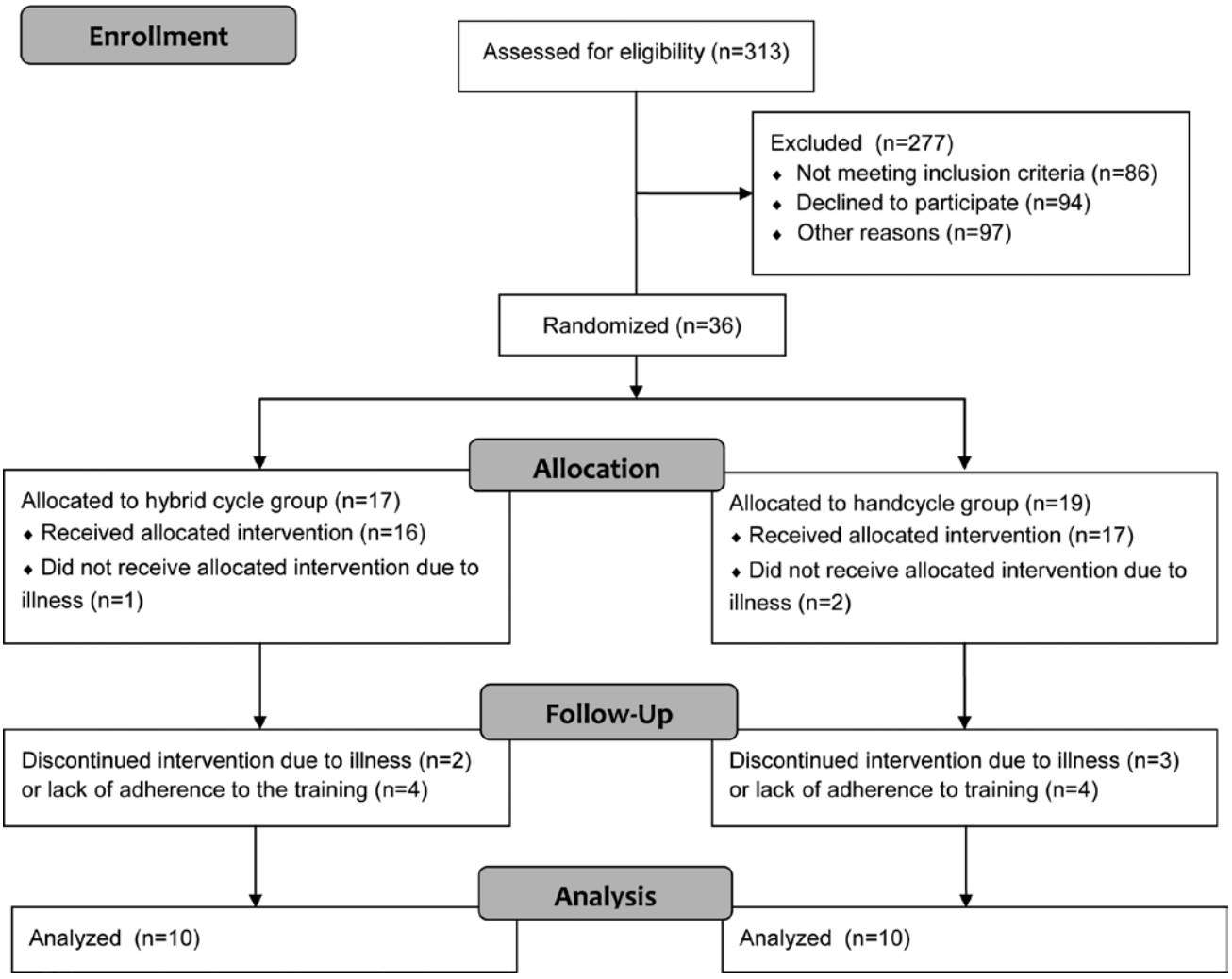

Figure 3 Flow diagram of the process through the phases of the randomized controlled trial.

Table 1 Participants' characteristics

Participant	Gender	Age (yrs)	TSI (yrs)	Lesion level	AIS	Height (cm)	Body mass (kg)	BMI (kg/m²)
HYB								
1*	M	55	34	C3	C	178	90.7	28.5
2*	M	40	12	C5	A	177	65.2	20.9
3	M	39	13	C6	B	184	84.4	24.9
4*	M	49	31	C7	A	174	55.5	18.3
5*	M	53	10	C7	C	182	63.4	19.1
6	M	49	27	T1	A	186	67.2	19.4
7*	M	40	18	T6	A	188	66.6	18.9
8*	M	58	24	T8	A	172	83.0	28.1
9*	M	64	18	T9	A	174	80.2	26.5
10	M	31	14	T10	A	173	73.5	24.6
Mean (SD)		48	20 (8)			179	73.0	22.9 (4.0)
HC								
1*	M	63	10	C2	D	180	73.6	22.9
2*	M	48	30	C6	C	171	91.6	31.3
3	M	47	12	C6	C	174	80.2	26.5
4*	M	51	21	T3	A	181	72.6	22.2
5	M	30	11	T4	A	174	73.8	24.4
6	M	49	16	T5	A	174	75.0	24.8
7*	M	47	18	T7	A	185	82.0	24.0
8	M	38	9	T9	A	173	60.5	20.2
9	M	49	15	T11	A	187	58.8	16.8
10*	F	50	14	L2	A	166	67.2	24.5
Mean (SD)		47 (9)	16 (6)			177	73.5 (9.8)	23.8 (3.8)

Abbreviations: yrs, years; TSI, time since injury; AIS, ASIA (American Spinal Injury Association) Impairment Scale; BMI, body mass index; HYB, hybrid cycle; HC, handcycle; M, male; F, female; SD, standard deviation. *Dual-energy X-ray absorptiometry (DXA) data available.

Soft tissue composition

For lean mass of the legs, a significant interaction effect was found; lean mass in the hybrid cycle group was increased with 0.86 ± 0.26 kg (P = 0.029), while lean mass in the handcycle group was reduced with 0.78 ± 0.27 kg (P = 0.045) following the 16-wk training program (Table 2, Figure 4). For fat mass of the legs, a significant overall reduction of 0.35 ± 0.13 kg, and no significant interaction effect (group x time) was observed (Table 2, Figure 2).

Bone mineral density

For both proximal tibia and distal femur BMD, no significant main effects for time or group x time interactions were found (Table 2).

Bone turnover markers

As shown in Table 2, there was a significant overall reduction of 3.6 ± 1.7 µg/L in P1NP and no significant main effect for time for CTX. For both P1NP and CTX, there were no significant differences over time between the training groups.

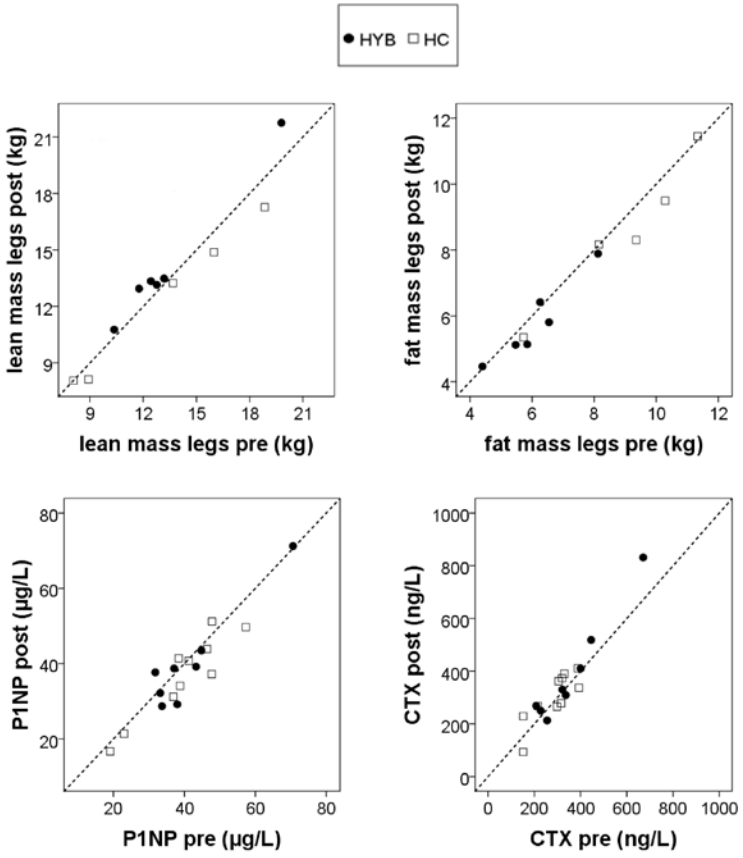

Figure 4 Individual pre and post training values for lean mass legs (A), fat mass legs, P1NP (C) and CTX (D). HYB, hybrid cycle; HC, handcycle.

Table 2 Soft tissue composition, bone mineral density and bone turnover markers

	Whole group		Δ	HYB		Δ	HC		Δ	P values	
	Pre	Post		Pre	Post		Pre	Post		Main effect time	Group x time interaction
STC-legs (kg)[1]											
Lean	13.25 (1.12)	13.37 (1.17)	+0.11 (0.31)	13.38 (1.34)	14.24 (1.56)	+0.86 (0.26)	13.10 (2.06)	12.32 (1.84)	-0.78 (0.27)	0.84	0.002
Fat	7.41 (0.67)	7.05 (0.66)	-0.35 (0.13)	6.10 (0.51)	5.81 (0.50)	-0.30 (0.15)	8.97 (0.97)	8.55 (0.99)	-0.41 (0.23)	0.03	0.67
BMD (g/cm^2)[2]											
Proximal tibia	0.448 (0.043)	0.445 (0.045)	-0.004 (0.005)	0.418 (0.054)	0.417 (0.054)	-0.001 (0.006)	0.492 (0.073)	0.483 (0.081)	-0.005 (0.009)	0.26	0.33
Distal femur	0.643 (0.070)	0.645 (0.069)	+0.001 (0.006)	0.563 (0.081)	0.572 (0.082)	+0.009 (0.005)	0.756 (0.114)	0.747 (0.111)	-0.006 (0.012)	0.92	0.25
BTM[3]											
P1NP (µg/L)	41.9 (3.0)	38.2 (2.7)	-3.6 (1.7)	44.4 (4.9)	39.8 (4.2)	-4.7 (3.3)	39.6 (3.6)	36.7 (3.6)	-2.9 (1.4)	0.05	0.63
CTX (ng/L)	326.3 (28.1)	337.9 (34.6)	+11.5 (17.0)	370.1 (48.5)	379.0 (64.5)	+8.9 (29.9)	287.0 (27.4)	300.9 (30.0)	+13.9 (17)	0.53	0.88

Values are mean ± SE. Δ: mean difference between pre and post; HYB, hybrid cycle; HC, handcycle; STC, soft tissue composition; BMD, bone mineral density; BTM, bone turnover markers; P1NP, procollagen type 1 amino-terminal propeptide; CTX, cross-linked C-telopeptide. [1]n=6 HYB; 5 HC; [2]n=7 HYB; 5 HC; [3]n=9 HYB; 10 HC.

DISCUSSION

Soft tissue composition

An important result of this study was that the soft tissue composition of the legs changed in both the hybrid cycle and handcycle group following the 16-wk training program; lean mass increased in the hybrid group and decreased in the handcycle group, and fat mass decreased in both groups. In contrast to the unexpected decrease in lean mass of the legs in the handcycle group, the increase in muscle mass as a consequence of the FES-induced leg cycling in the hybrid group is supported by previous research (8). Since muscle atrophy of the lower limbs is an important risk factor for developing pressure ulcers (a common secondary complication in SCI) (22), improving the lower-body musculature by hybrid cycling might be a way to reduce the risk of pressure sores. Furthermore, it seems that hybrid cycling has no additional beneficial effect on lower-body adiposity over handcycling alone (when exercising at a similar exercise intensity and for the same duration), suggesting that fat loss is a systemic effect of exercise training.

Bone mineral density

The overall baseline proximal tibia and distal femur BMD values of the participants in the current study (0.448 ± 0.043 g/cm^2 and 0.643 ± 0.070 g/cm^2, respectively) were only slightly lower than the baseline values of the participants with long-term SCI in the study of Chen et al. (0.553 ± 0.079 g/cm^2 and 0.718 ± 0.066 g/cm^2, respectively) (10). Compared to the able-bodied persons measured by Chen et al. (10), proximal tibia and distal femur BMD of the individuals in the current study was ~50% lower. This finding is in accordance with the literature, reporting a rapid and linear decrease in lower-body BMD in the acute phase, and a newly reached, ~50% lower steady-state BMD level two years post injury (23, 24).

With the DXA method used in this study, the smallest detectable difference over time is ~0.05 g/cm^2 for proximal tibia and ~0.08 g/cm^2 for distal femur BMD. The non-significant BMD changes over time found in this study ranged from +0.009 to -0.006 g/cm^2 and may therefore be attributed to measurement error. As stated in the introduction, some previous studies found positive effects of FES exercise on knee BMD in people with long-term SCI (10,11), while others did not (e.g. 12). From a systematic review about the non-pharmacological treatment and prevention of bone loss in SCI (25), it seems that the studies that found BMD improvements after FES training are those with a longer training period (12 months), or higher training frequency (5x/week) or stimulus intensity. Thus, possible explanations for the fact that no BMD improvements were found in this study, might be the relatively short training period (i.e. 16 weeks), or relatively low training frequency (i.e. twice a week) or stimulus intensity.

Bone turnover makers

In the current study, the P1NP and CTX values of the participants with long-term SCI were within age-related limits for able-bodied persons (26), indicating a normal rate of bone turnover. In contrast, Paker et al. (27) found that serum CTX levels were elevated in people with acute SCI (TSI < 1 year). Furthermore, 16 weeks of hybrid cycle or handcycle exercise training did not

improve PN1P and CTX. Moreover, the fairly small alterations observed in these bone turnover markers, including the significant reduction in P1NP, cannot be considered as clinically relevant. This finding was supported by Astorino et al. (28) who found that neither P1NP nor CTX levels were changed as a consequence of 6 months of exercise training. The above-described findings support the assumption that bone turnover reaches a new steady state in people with long-term SCI, now stabilizing around a ~50% lower bone mass.

Limitations

A limitation of this study was the relatively high drop-out rate (44%); 16 of the 36 enrolled individuals dropped out immediately after allocation to the training group (n=3) or during the experimental trial (n=13). Since no baseline differences for any outcome measure or personal and lesion characteristics were found between the individuals who dropped out and those who completed the 16-wk training program, it is not expected that the high drop-out rate would have affected the results of the current study. However, together with the difficulty of recruiting a sufficient number of participants (after two years, only 36 of the 313 invited people eventually participated), the fact that 44% of the included individuals dropped out, questions the feasibility of this type of training intervention in persons with long-term SCI. The most frequently heard reason for not willing to participate and withdrawal from the study due to lack of adherence to the training, was that the intervention was too time-consuming. Therefore, in future exercise intervention studies in people with SCI, it should be carefully considered how the interventions can be made as feasible and attractive as possible. For example, offering the opportunity to train at home would save travel time to a rehabilitation or training center. Moreover, 50% of the dropouts, had to stop due to health problems (e.g. kidney stones or urinary tract infections), suggesting that the current study population is vulnerable for illness.

Another limitation of this trial might be the relatively short training period (16 weeks), and low training frequency (2 times a week) and stimulus intensity. To realize improvements in bone metabolism (i.e. BMD and bone turnover markers), Biering-Sørensen et al. (23) recommended that the FES-induced leg exercise should be at least 2-3 times a week and probably has to be maintained for the long-term. However, considering the above-described difficulties with recruiting the intended number of participants and keeping the participants in the trial, it is questionable if an exercise program of a longer duration and higher training frequency would have been feasible. On the other hand, the stimulus intensity during the hybrid cycle exercise could have been increased by first conditioning the paralyzed legs (i.e. by FES-induced leg cycling only) of the participants in the hybrid group. The lower-limb musculature of the participants in this study was relatively deconditioned at the beginning of the trial, which sometimes resulted in rapid lower-limb muscle fatigue during hybrid cycling (the arms had to take over the entire propulsion). The training effects might have been larger if strong lower-limb muscle contractions were ensured over the entire exercise session from the beginning to the end of the training intervention.

Conclusion

The beneficial effect of hybrid cycling over handcycling observed in this study was the increased muscle mass of the legs. Furthermore, both the 16-wk hybrid cycle and handcycle training program led to a reduced fat mass of the legs, but did not improve proximal tibia and distal femur BMD and the bone turnover markers CTX and P1NP. Future studies on hybrid cycling that aim for improvements in knee BMD and markers of bone turnover should conduct training interventions of a longer duration, or higher training frequency or stimulus intensit

LITERATURE

1. Maimoun L, Fattal C, Micallef J-P, Peruchon E, Rabischong P (2006) Bone loss in spinal cord-injured patients: from physiopathology to therapy. Spinal Cord 44: 203-210.
2. Spungen AM, Adkins RH, Stewart CA, Wang J, Pierson RN Jr, et al. (2003) Factors influencing body composition in persons with spinal cord injury: a cross-sectional study. J Appl Physiol 95; 2398-2407.
3. Bauman WA, Spungen AM (2008) Coronary heart disease in individuals with spinal cord injury: assessment of risk factors. Spinal Cord 46: 466–476.
4. Bauman WA, Spungen AM (2001) Carbohydrate and lipid metabolism in chronic spinal cord injury. J Spinal Cord Med 24: 266–277.
5. Jiang SD, Dai LY, Jiang LS (2006) Osteoporosis after spinal cord injury. Osteoporos Int 17: 180–192.
6. Ragnarsson KT, Sell GH (1981) Lower extremity fractures after spinal cord injury: a retrospective study. Arch Phys Med Rehabil 62: 418–423.
7 Vestergaard P, Krogh K, Rejnmark L, Mosekilde L (1998) Fracture rates and risk factors for fractures in patients with spinal cord injury. Spinal Cord 36: 790–796.
8. Baldi JC Jr, Moraille R, Mysiw WJ (1998) Muscle atrophy is prevented in patients with acute spinal cord injury using functional electrical stimulation. Spinal Cord 36: 463–469.
9. Chillibeck P, Sale D, Webber C (1995) Exercise and bone mineral density. Sports Med 19: 103-122.
10. Chen SC, Lai CH, Chan WP, Huang MH, Tsai HW, et al. (2005) Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. Disabil Rehabil 27: 1337–1341.
11. Bélanger M, Stein RB, Wheeler GD, Gordon T, Leduc B (2000) Electrical stimulation: can it increase muscle strength and reverse osteopenia in spinal cord injured individuals? Arch Phys Med Rehabil 81: 1090–1098.
12. Shields RK, Dudley-Javoroski S (2007) Musculoskeletal adaptations in chronic spinal cord injury: effects of long-term soleus electrical stimulation training. Neurorehabil Neural Repair 21: 169–179.
13. Bakkum AJT, Janssen TWJ, Rolf MP, Roos JC, Burcksen J, et al. (2014) A reliable method for measuring proximal tibia and distal femur bone mineral density using dual-energy X-ray absorptiometry. Med Eng Phys 36: 387–390.
14. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J, et al. (2000) The use of biochemical markers of bone turnover in osteoporosis. Osteoporos Int 11 Suppl 6: 2-17.
15. Pagani F, Francucci CM, Moro L (2005) Markers of bone turnover: biochemical and clinical perspectives. J Endocrinol Invest 28 Suppl 10: 8-13.
16. Brurok B, Helgerud J, Karlsen T, Leivseth G, Hoff J (2011) Effect of aerobic high-intensity
hybrid training on stroke volume and peak oxygen consumption in men with spinal cord injury.
Am J Phys Med Rehabil 90: 407-414.
17. Bakkum AJ, de Groot S, van der Woude LH, Janssen TW (2013) The effects of hybrid cycle training in inactive people with long-term spinal cord injury: design of a multicentre randomized controlled trial. Disabil Rehabil 35: 1127-1132.
18. Washburn RA, Zhu W, McAuley E, Frogley M, Figoni SF (2002) The physical activity scale for individuals with physical disabilities: development and evaluation. Arch Phys Med Rehabil 83: 193–200.

19. De Groot S, van der Woude LH, Niezen A, Smit CA, Post MW (2010) Evaluation of the physical activity scale for individuals with physical disabilities in people with spinal cord injury. Spinal Cord 48: 542–547.
20. Valent LJ, Dallmeijer AJ, Houdijk H, Slootman J, Janssen TW, et al. (2007) The individual relationship between heart rate and oxygen uptake in people with a tetraplegia during exercise. Spinal Cord 45: 104-111.
21. Noble BJ, Borg GA, Jacobs I, Ceci R, Kaiser P (1983) A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. Med Sci Sports Exerc 15: 523-528
22. Krause JS, Vines CL, Farley TL, Sniezek J, Coker J (2001) An exploratory study of pressure ulcers after spinal cord injury: relationship to protective behaviors and risk factors. Arch Phys Med Rehabil 82: 107-113.
23. Biering-Sørensen F, Bohr H, Schaadt O (1990) Longitudinal study of bone mineral content in the lumbar spine, the forearm and the lower extremities after spinal cord injury. Eur J Clin Invest 20: 330-335.
24. Garland DE, Stewart CA, Adkins RH, Hu SS, Rosen C, et al. (1992) Osteoporosis after spinal cord injury. J Orthop Res 10: 371–378
25. Biering-Sørensen F, Hansen B, Lee BS (2009) Non-pharmacological treatment and prevention of bone loss after spinal cord injury: a systematic review. Spinal Cord 47: 508-518.
26. Jenkins N, Black M, Paul E, Pasco JA, Kotowicz MA, et al. (2013) Age-related reference intervals for bone turnover markers from an Australian reference population. Bone 55: 271-276.
27. Paker N, Bugdayci D, Ersoy S, Uysal E, Elbirlik S (2007) Bone loss and bone turnover in acute and chronic spinal cord injured patients. Neurosciences (Riyadh) 12: 232-235.
28. Astorino TA, Harness ET, Witzke KA (2013) Effect of chronic activity-based therapy on bone mineral density and bone turnover in persons with spinal cord injury. Eur J Appl Physiol 113: 3027-3037.

Chapter 8

General discussion

The aim of this thesis was to evaluate the integrated effects of hybrid cycling versus handcycling on fitness, physical activity and health in physically inactive people with long-term spinal cord injury (SCI). To achieve this goal, a 16-wk randomized controlled trial (RCT) was conducted in two Dutch rehabilitation centers with a specialized SCI unit. During 16 weeks, both the experimental (hybrid cycle) and control (handcycle) group trained twice a week for 18-30 min at an intensity of 65-75% of their heart rate reserve (HRR) or a score of 4-7 on a 10-point rating of perceived exertion (RPE) scale. Outcome measures were obtained in the week before the training program, after 8 weeks of training, and in the week after the training program. Parallel to this multicenter RCT, two cross-sectional studies were performed to (1) examine the metabolic and cardiorespiratory response during hybrid cycling versus handcycling at equal subjective exercise intensity levels, and (2) assess the reliability of a standardized method to measure proximal tibia and distal femur bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA). In the current chapter, the main findings of these studies are summarized and discussed in relation to the existing literature. Furthermore, implications for clinical practice and recommendations for future research are provided.

Effects of hybrid cycling versus handcycling

In chapters 4, 5 and 7, the effects of the current 16-wk RCT on fitness, physical activity and the health-related parameters cardiovascular disease (CVD) risk factors, lower-body soft tissue composition and knee BMD are presented. The most important findings of these chapters were that (1) following 16 weeks of twice-weekly exercise, both the hybrid cycle and handcycle group showed positive effects on aspects of fitness, physical activity, CVD risk factors and lower-body soft tissue composition, and (2) these positive effects over time were not significantly different between the two training groups (except for lean mass of the legs), indicating that for the outcome measures studied there were no additional benefits of the functional electrical stimulation (FES)-induced leg exercise over handcycling alone. Below, these findings are extensively discussed.

Fitness and physical activity

In chapter 3 it was demonstrated that hybrid cycling induces higher metabolic and cardiorespiratory responses than handcycling when exercising at equal subjective exercise intensity levels. Previous studies also found higher metabolic rates during hybrid exercise versus arm exercise alone and stated that this was caused by the larger active muscle mass during hybrid exercise [1-3]. However, in these studies, power output was used to standardize the exercise intensity and it remained unclear how the participants subjectively experienced the exercise intensity. It might be possible that the higher metabolic rates in these studies also coincided with higher RPE levels. Chapter 3 demonstrated that the higher metabolic and cardiorespiratory responses during hybrid cycling were achieved while ‘feeling the same’ as during handcycling. Based on these findings, it was hypothesized that hybrid cycling was more suitable for increasing cardiorespiratory fitness in people with long-term SCI than handcycling. However, as described

in chapter 4, no significant difference over time between the hybrid cycle and handcycle training group was found for fitness. A possible explanation for this finding is provided in the section on 'Training protocol'.

In chapter 4 it was also demonstrated that the wheelchair-specific fitness (wheelchair exercise capacity, expressed as peak power output (PO_{peak}) and peak oxygen consumption (VO_{2peak})) was not significantly improved following the 16-wk training program, while the cardiorespiratory fitness (expressed as resting heart rate) and subjectively experienced fitness were. In the current RCT, exercise capacity was determined during an incremental test in a manual wheelchair since, in daily life, many people with SCI are dependent on such a wheelchair for mobility [4] and were therefore expected to benefit from an increased wheelchair-specific fitness. Moreover, previous studies have already demonstrated that both hybrid cycle [5,6] and handcycle [7] exercise can lead to improvements in PO_{peak} and VO_{2peak} if these outcome measures are assessed during a specific exercise test (i.e. hybrid cycle or handcycle test, respectively). However, in the current trial, PO_{peak} and VO_{2peak} were not significantly increased following 16 weeks of training, suggesting that hybrid cycling and handcycling may not be the best exercise modes to improve wheelchair-specific fitness and that it might be better to train more specifically (i.e. wheelchair training). That said, ~40% and ~65% of the participants in this study showed improvements in PO_{peak} and VO_{2peak}, respectively, indicating that the training program certainly beneficially influenced these fitness measures in a considerable part of the participant group. Moreover, the significantly improved resting heart rate and subjectively experienced fitness also indicate beneficial effects of hybrid cycle and handcycle training on fitness.

Although there was no beneficial effect on objectively measured wheelchair activity following the 16-wk RCT, the overall increased score on the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) suggests an improved physical activity level (chapter 4). Moreover, many participants in our study indicated that several activities of daily living (e.g. transfers, transportation and housework) became easier due to a subjectively experienced improved fitness as a consequence of the training program. The above-described findings regarding fitness and physical activity are supported by Nooijen et al. [8], who showed that increased physical activity levels are associated with increased fitness levels in people with SCI.

Cardiovascular disease risk factors

Chapter 5 demonstrated that both the 16-wk hybrid cycle and handcycle exercise program led to improvements in several CVD risk factors, including metabolic syndrome components (waist circumference, diastolic blood pressure and insulin sensitivity), inflammatory status (C-reactive protein (CRP), interleukin (IL)-6 and IL-6/IL-10 ratio) and visceral adiposity (trunk and android fat percentage). In contrast to trunk and android fat mass, the fat percentage of these regions, as well as the waist circumference (a reliable surrogate of visceral adiposity [9]) significantly decreased, suggesting that both hybrid cycle and handcycle exercise have the potential to reduce

visceral fat and improve body composition in people with long-term SCI. This finding was in accordance with a study by Gorgey et al. [10], who found a reduced visceral adiposity after 12 weeks of twice-weekly FES-induced leg training in people with SCI. Furthermore, the overall significant improvement in insulin sensitivity was supported by several other studies on the influence of exercise on insulin sensitivity [11-13]. Finally, the improved inflammatory status was consistent with the findings of Griffin et al. [14], who reported a significant reduction in resting IL-6 and CRP following a 10-wk FES-induced leg cycle training program. In contrast to the above-described positive effects of exercise, no significant training effects were found for the lipids triglycerides and high-density lipoprotein cholesterol. In a systematic review by Carlson et al. [15], it was concluded that there is yet insufficient evidence that exercise alone improves lipid disorders in people with SCI and that it requires further investigation to examine whether a combined exercise and dietary intervention is the optimal method for improving the lipid spectrum in this population.

Lower-body soft tissue composition and bone mineral density

Of all outcome measures analyzed in this thesis, the only significant difference over time between the two training groups was found for lean mass of the legs; an increase was found in the hybrid cycle group, while a decrease was observed in the handcycle group (chapter 7). In contrast to the unexpected decrease in lean mass in the handcycle group, the increase in lean mass as a consequence of the FES-induced leg exercise in the hybrid cycle group is supported by the literature [16]. Since muscle atrophy of the lower limbs is an important risk factor for developing pressure ulcers (a common secondary complication in SCI, [17]), improving the lower-body musculature by hybrid cycling might be a way to reduce the risk of pressure sores. Since fat mass of the legs equally decreased in both groups, it seems that hybrid cycling has no additional beneficial effect on lower-body adiposity over handcycling alone, suggesting that fat loss is a systemic effect of exercise training.

In chapter 7 it was also shown that proximal tibia and distal femur BMD, assessed with the in chapter 6 described reliable DXA scan and analysis protocol, did not significantly change over time. In the literature, there is inconsistency regarding the effectiveness of FES-induced leg exercise on knee BMD in people with long-term SCI; some studies found positive training effects [18,19], while others did not [e.g. 20]. It seems that the studies that found improvements in knee BMD are those with a longer training period (12 months), higher training frequency (five times a week), or higher power output of the legs [21]. In addition to the BMD measurements, the bone turnover markers procollagen type 1 amino-terminal propeptide (P1NP) and cross-linked C-telopeptide (CTX) were determined in blood. The fairly small alterations observed in these bone turnover markers following the 16-wk training program, including the significant reduction in P1NP, cannot be considered as clinically relevant. This finding was supported by data from Astorino et al. [22] who found that neither P1NP nor CTX levels were changed as a consequence of 6 months of exercise in people with SCI.

Other outcome measures and long-term training effects

As presented in chapter 2, besides the outcome measures analyzed in this thesis, numerous other outcome measures were obtained in the current RCT (e.g. vascular structure and function, quality of life, participation and immune function). Moreover, to examine the long-term training effects, all outcome measures were obtained 26 weeks after the end of the exercise intervention. The other outcome measures obtained in this RCT as well as the 26-wk follow-up data have not been evaluated yet. For some of the other outcome measures, it is assumable that hybrid cycling would induce greater benefits than handcycling alone. For example, based on previous studies on hybrid cycling [23,24], it was hypothesized that the vascular structure (wall thickness and diameter) in the legs would improve in the hybrid cycle group, while it would remain unchanged in the handcycle group. Furthermore, it was hypothesized that possible beneficial effects of the 16-wk exercise intervention could only be preserved on the long-term if the participants stayed physically active after the intervention. However, for now this is only speculation. Therefore, in the coming years, all the other outcome measures obtained in this RCT as well as the long-term training effects are intended to be analyzed and published by researchers of the Dutch clinical SCI rehabilitation network (www.scionn.nl).

Randomized controlled trials in SCI research

There is a strong demand for clinical trials to determine the effectiveness of interventions on different health problems (e.g. deconditioning, CVD risk and osteoporosis) in people with long-term SCI. The focus of these trials should be on the underlying mechanisms responsible for adaptations to training in this vulnerable population, and a relatively long training period may be needed to detect substantial training effects [21,25]. Since the RCT is considered as the gold standard for a clinical trial, in the current thesis, the effects of hybrid cycle versus handcycle exercise on fitness, physical activity and health were investigated in a 16-wk RCT. However, in practice, carrying out this RCT turned out to be fairly difficult.

Beforehand, it was expected that it would not be easy to recruit the intended number of 40 participants for the trial. To increase our chances, we chose to conduct the RCT in two rehabilitation centers with a specialized SCI unit in different parts of the Netherlands. Potential participants were selected from the databases of these centers following strict inclusion criteria. Initially, 313 people were assessed for eligibility, of which eventually 36 persons were randomly assigned to one of the two intervention groups. The two most important reasons why people were excluded from trial participation were: (1) they did not meet the strict eligibility criteria of the study, and (2) they were not able or willing to participate since the training program was too time-consuming for them. Because of the problems with enrolling participants, after one year, a slight adaptation to the inclusion criteria was deemed necessary; the time since injury was reduced from 10 to 8 years and the age at onset of the SCI was reduced from 18 to 16 years. Thanks to these adjustments, eventually three more participants were enrolled.

Besides the difficulty of including a sufficient number of participants, it was hard to keep the participants in the training program. Of the 36 participants who were recruited over a period

of two years, 16 individuals dropped out immediately after allocation to the training group or during the experimental trial. Reasons for drop out were illness and lack of adherence to the training. Despite the thorough medical screening preceding inclusion and the relatively good health status of the participants (as discussed in chapter 4 and 5), almost 50% of the drop outs had to stop due to health problems not related to the training program (e.g. pressure ulcers, bowel problems and kidney stones), indicating that people with long-term SCI are vulnerable for illness, and that interventions aiming to promote health are important in this population. The people who dropped out due to lack of adherence to the training indicated that the program was too time-consuming for them. However, since no baseline differences for any of the outcome measures or personal and lesion characteristics were observed between the group that dropped out and the group that completed the training program, it is not expected that the relatively high drop-out rate (44%) would have affected the findings of this study. Nevertheless, the large number of drop outs, as well as the difficulty to recruit a sufficient number of participants, questions the feasibility of the current RCT.

Therefore, future studies should consider how to make clinical trials more feasible and attractive for people with long-term SCI. First, for each future clinical trial in people with SCI, it should be carefully considered whether the RCT is definitely the most suitable experimental design to examine treatment effects. As a matter of fact, clinical researchers are increasingly addressing questions for which the RCT may not be feasible, practical or ethical [44,45]. In case RCTs cannot be easily implemented in settings or with participants of interest, West et al. [45] suggest to use a strong alternative experimental design (e.g. a randomized encouragement design or observational study) instead of changing the treatment or study population so that an RCT may be implemented. Thus, using alternative research designs might improve the feasibility of clinical trials in people with SCI. Furthermore, better facilitation of the training equipment might be a way to make these trials more feasible; for example, if people have the possibility to exercise at home, they do not have to come to a rehabilitation center for each training session, which saves considerable travel time and effort. However, since in total there were only three hybrid cycles available in the rehabilitation centers and there was no money available to buy more cycles, it was impossible to facilitate all participants. For the handcycle group, this would have been easier since more handcycles were available in the rehabilitation centers and most participants had their own handcycle. In that case, participants should only have been provided with an ergotrainer, which is relatively affordable. Besides the difficulty of facilitating the training equipment, exercising at home might bring along some additional problems. For instance, if people are instructed to train alone, it is more difficult for the researcher to control whether all participants correctly perform the exercise protocol. Furthermore, many people in the hybrid cycle group would need help with properly attaching the electrodes over the muscle groups, making transfers from their wheelchair to the hybrid cycle and vice versa, positioning the legs in the foot pedals and controlling the electrical stimulation. Considering the above-mentioned issues regarding exercising at home, in the current RCT, it was chosen to train the participants in the rehabilitation center. In this way, trainers were able to properly standardize the

training protocol and help participants throughout the exercise sessions. Finally, offering the opportunity to exercise in the evenings and weekends might be another way to make these interventions more feasible for people with long-term SCI. This would especially be ideal for people with a full-time job who want to participate but are not able to train during office hours.

The graded exercise test

To be able to compare the effects on fitness with the other two ALLRISC intervention studies (described in chapter 1), exercise capacity was assessed during a graded exercise test in a manual wheelchair on a motor-driven treadmill [26]. In the other ALLRISC exercise intervention study, a 16-wk low-intensity wheelchair exercise program was performed [42]; thus, exercise testing was specific to the training sessions. However, this was not the case in the current RCT where a hybrid cycle or handcycle training program was performed.

At the start of this study, it has been considered to also include an incremental exercise test in the specific training set-up (either a hybrid cycle or handcycle) to examine potential positive effect on fitness. Valent et al. [27] described a standardized protocol to measure peak exercise capacity during a discontinuous graded peak exercise test in the handcycle on a motor-driven treadmill. However, in the literature there is a lack of good standardized hybrid cycle exercise testing protocols. In one study, an ergotrainer (Tacx, Technische Industrie Tacx B.V., Wassenaar, the Netherlands) was used to increase the workload every min with steps of 10 W, and after 10 min with 20 W [5]. We have extensively tested this protocol with our own Tacx ergotrainers and concluded that it was not possible to gradually increase the power output with this device. We have also tried to perform a hybrid cycle exercise test on the treadmill, following the handcycle protocol of Valent et al [27]. However, the main problem with hybrid cycling on a treadmill was that when the electrical stimulation was increased, the cycle speed became higher than the speed of the treadmill belt (which was kept constant during testing), sometimes resulting in risky situations where the front wheel of the cycle hit the front of the treadmill.

Besides the difficulty of performing a well-standardized hybrid cycle incremental test, another, more ethical reason for not including an additional exercise test was that we did not want to overload the participants with measurements. The people participating in the current RCT already had to come to the rehabilitation center 36 times (32 training sessions and four measurement days) and to the hospital twice (for vascular or DXA measurements). Since two different incremental exercise tests have to be performed on separate days, with at least 72 hours of relative rest in between the tests to provide sufficient recovery time, a second exercise test would have meant that the participants had to come to the rehabilitation center another four times and that the total duration of the RCT was increased with about two weeks.

The training protocol

In the current RCT, an interval training protocol (exercise blocks alternated with absolute rest blocks) was used since previous studies suggested that these protocols are very convenient to prevent early muscle fatigue and soreness during training [28,29]. Furthermore, this type of

protocol was expected to allow more people with a tetraplegia to complete the training program. During the 16-wk training period, total cycle time was gradually increased from 18 to 32 min and resting time between the exercise blocks was decreased from 2 to 1 min. Each session consisted of a short warm-up and cool-down period, including handcycling only. In practice, this training protocol turned out to be very suitable since all participants were able to complete the training sessions. Besides temporary muscle soreness due to exercise, no serious adverse events (e.g. severe musculoskeletal complaints) were reported as a consequence of the 16-wk training program. Occasionally, participants indicated that the muscle soreness (mostly occurring in the shoulders) was a limiting factor during training. In that case slight adjustments to the protocol were made (e.g. increasing the resting time between the exercise blocks) to be able to complete the total cycle time of that training session. Sometimes, an extra resting day was advised by the trainer to allow the participant to fully recover from the training session.

The current training program was largely based on the American College of Sports Medicine's guidelines for aerobic training programs in people with disabilities (i.e. frequency 3 x 30 min, duration 8-12 weeks, intensity 70% HRR, [30]). Initially, the intention was to train three times a week, following these guidelines; however, to increase the chance of including a sufficient number of participants and decrease the chance of drop outs and non-compliance, a training frequency of two times a week was considered to be more feasible in this physically inactive population with long-term SCI. In hindsight, considering the difficulties with the inclusion and the high drop-out rate in the current RCT, we believe this was a good choice. Based on previous studies [5-6,23,24], a training period of 16 weeks was considered to be sufficient to detect substantial effects on fitness, physical activity and health. However, for some outcome measures (e.g. knee BMD [21]), a longer training period might have been necessary to find significant and clinically relevant changes. Nevertheless, similar to a higher training frequency, a longer period of training might have resulted in even more difficulties with inclusion and a higher drop-out rate and non-compliance [31,32].

To ensure that the imposed exercise intensity of 65-75% HRR was maintained throughout the exercise program, heart rate was continuously monitored during training. The RPE, serving as a supplementary measure of exercise intensity, had to be 4-7 on a 10-point scale [33] and was assessed after each exercise block. All participants were very well capable to train at the target exercise intensity during the program, and to control the intensity by making adjustments in cycle speed and gear setting. As described in chapter 2, the HRR calculation was based on the incremental exercise test in the wheelchair. During the first training session, the calculated heart rate range was used to impose the exercise intensity. However, in practice it sometimes appeared that this range did not match the imposed RPE; mostly, an underestimation was made. In these cases, the heart rate range was adjusted to the participant's subjectively experienced exercise intensity. Beforehand, we knew this could occur in people with tetraplegia [27], however, it also happened in those with paraplegia. A logical explanation for this is the fact that a wheelchair exercise test was used to calculate the heart rate range; during wheelchair propulsion, often lower peak physiological exercise responses (e.g. heart rate and VO_2) are achieved than during hybrid

cycling or handcycling [43]. Therefore, specific exercise testing might have been better to properly set the objective training intensity. In the preceding section on 'The graded exercise test', it is explained why we chose not to include an exercise test in the specific training set-up next to the wheelchair test. Besides heart rate and RPE, other indicators to monitor exercise intensity during hybrid cycling and handcycling could have been used, such as power output. Since the use of heart rate as an indicator of training intensity can be unreliable in people with tetraplegia, exercising at a certain percentage of PO_{peak} might have been more suitable than exercising at a certain percentage of HRR in this population [27]. However, at the start of the current RCT, there were no valid and reliable power meters (such as the SRM system (Schoberer Rad Messtechnik, Jülich, Welldorf, Germany) or PowerTap (CycleOps, Madison, WI, USA)) available in both rehabilitation centers. Moreover, as for heart rate, in case of using power output as an indicator of training intensity, specific exercise testing should have been performed to prevent under- or overestimation of PO_{peak}.

The people who were assigned to the hybrid cycle group immediately started the 16-wk hybrid cycle exercise protocol. However, a problem was that the lower-limb muscles of these people were relatively untrained at the beginning of the training program, often resulting in rapid lower-limb muscle fatigue during cycling. If the leg musculature becomes fatigued during hybrid cycling, voluntary arm activity takes over the entire propulsion and the legs will only move passively together with the arms. Since there were no power measurement systems available to separately measure the power output contributions of the legs, it remained unclear to what extent the legs contributed to the total power output (measured with the ergotrainer) during hybrid cycling. The effects of hybrid cycling might have been larger if strong lower-limb muscle contractions (i.e. large power output of the legs) were ensured over the entire exercise session and during the whole training program. For this purpose, first a conditioning phase for the paralyzed legs (e.g. FES-induced leg cycling or resistance training of the quadriceps muscles [41]) for the people in the hybrid cycle group could have been performed.

Clinical implications

Based on the current thesis and the existing literature [34,35], it can be stated that staying physically active is essential to prevent deconditioning in people with long-term SCI. In chapters 4, 5 and 7 it was demonstrated that both the hybrid cycle and handcycle are effective exercise modalities to improve aspects of fitness, physical activity and health in this vulnerable population. This finding was supported by several other studies on the effects of hybrid cycling [5,6,23,24] and handcycling [36-38] in people with SCI. The hypothesis that hybrid cycling would induce larger beneficial effects than handcycling alone due to the larger active muscle mass was not supported in this thesis; except for an increase in lean mass of the legs, there were no notable benefits of the added FES-induced leg exercise, promoting handcycling as a cheaper and more accessible exercise mode for improving fitness, physical activity and health in people with long-term SCI. However, in chapter 3 it was demonstrated that hybrid cycling induces higher metabolic and cardiorespiratory responses at equal subjective exercise intensity levels

than handcycling, suggesting that hybrid cycling is more suitable for fighting obesity and increasing cardiorespiratory fitness in people with long-term SCI. Moreover, the addition of FES-induced leg exercise to arm exercise alone has been shown to provide supplementary benefits on vascular [23,24] and musculoskeletal systems [16,39,40] in the lower extremities. Considering these potential greater benefits of hybrid exercise over arm exercise alone, people with SCI should implement hybrid exercise (e.g. cycling or rowing) next to their other physical activities (e.g. wheelchair propulsion or handcycling) in daily life.

However, in the Netherlands, hybrid exercise modalities are not yet commonly used in clinical rehabilitation and SCI aftercare. Many rehabilitation professionals and people with SCI are not completely familiar with the potential greater benefits of hybrid exercise over upper-body exercise alone. In only two of the eight Dutch rehabilitation centers with a specialized SCI unit there is a hybrid cycle available, and compared to the other mobility and exercise devices available in these centers (e.g. the handcycle), this cycle is not used very often. An important practical reason for this is that hybrid cycle exercise takes relatively much time due to the placements of the electrodes and the transfers that need to be made. Moreover, since the purchase of hybrid exercise modes is relatively expensive and not covered by the Dutch insurance companies, not everybody is in the position to acquire such a cycle, making it difficult for people with SCI to maintain hybrid exercise for the long term.

Therefore, alternative methods for hybrid exercise should be considered. As previously stated in this thesis, FES-induced leg exercise in people with SCI is essential to prevent lower-body deterioration, and should be introduced early during clinical rehabilitation and maintained throughout the lifespan of these people. However, it might be more convenient and feasible to use this technique separately from the conventional upper-body activities (e.g. handcycling and wheelchair sports). For example, a relatively easy and cheap way to activate the paralyzed lower-limb musculature is to use a custom-made FES shorts (Axiobionics, Ann Arbor, MI, USA), containing embedded surface electrodes with build-in leads that can be connected to a portable stimulator (NeuroPro, Axiobionics, Ann Arbor, MI, USA) [46]. These FES shorts can be worn under normal pants and the electrodes are automatically aligned over the gluteal and hamstring muscles when putting them on.

To conclude, clinical rehabilitation should focus on the prevention of deconditioning in people with SCI, and offer a model of lifetime follow-up rehabilitation in this population. In this context, FES-induced leg exercise (either hybrid exercise or leg exercise alone) plays a crucial role.

Main conclusions

- The metabolic and cardiorespiratory responses during hybrid cycling are higher than during handcycling when exercising at equal subjective exercise intensity levels.
- Both the 16-wk hybrid cycle and handcycle exercise intervention led to positive effects on aspects of fitness, physical activity and health.
- Except for an increase in lean mass of the legs, there were no notable additional benefits of the hybrid cycle intervention over the handcycle intervention.
- In future studies on the effects of hybrid exercise, first a conditioning phase of the paralyzed legs should be performed.
- Specific graded exercise testing should be used to properly set objective training intensity.
- To be able to include a sufficient number of participants and to prevent a high drop-out rate and non-compliance, future research should consider how to make exercise interventions more feasible and attractive for people with long-term SCI.
- FES-induced leg exercise should be introduced early during clinical rehabilitation and maintained throughout the lifespan of people with SCI.
- Clinical rehabilitation should focus on the prevention of deconditioning in people with SCI.
- Clinical rehabilitation should offer a model of lifetime follow-up rehabilitation for people with SCI.

REFERENCES

1. Hooker SP, Figoni SF, Rodgers MM, Glaser RM, Mathews T, Suryaprasad AG, et al. Metabolic and hemodynamic responses to concurrent voluntary arm crank and electrical stimulation leg cycle exercise in quadriplegics. J Rehabil Res Dev 1992;29(3):1-11.
2. Raymond J, Davis GM, Climstein M, Sutton JR. Cardiorespiratory responses to arm cranking and electrical stimulation leg cycling in people with paraplegia. Med Sci Sports Exerc 1999;31(6):822-8.
3. Raymond J, Davis GM, Fahey A, Climstein M, Sutton JR. Oxygen uptake and heart rate responses during arm vs combined arm/electrically stimulated leg exercise in people with paraplegia. Spinal Cord 1997;35(10):680-5.
4. Post MW, van Asbeck FW, van Dijk AJ, Schrijvers AJ. Services for spinal cord injured: availability and satisfaction. Spinal Cord 1997;35(2):109-15.
5. Heesterbeek PJC, Berkelmans HWA, Thijssen DHJ, van Kuppevelt HJM, Hopman MTE, Duysens J. Increased physical fitness after 4-week training on a hybrid FES-cycle in persons with spinal cord injury. Technology and Disability 2005;17(2):103-10.
6. Brurok B, Helgerud J, Karlsen T, Leivseth G, Hoff J. Effect of aerobic high-intensity hybrid training on stroke volume and peak oxygen consumption in men with spinal cord injury. *Am J Phys Med Rehabil* 2011;**90:**407-414.
7. Valent L, Dallmeijer AJ, Houdijk H, Slootman HJ, Post MW, Van der Woude LH. Influence of handcyling on physical capacity in the rehabilitation of persons with a spinal cord injury: a longitudinal cohort study. *Arch Phys Med Rehabil* 2008;**89:**1016-1022.
8. Nooijen CF, de Groot S, Postma K, Bergen MP, Stam HJ, Bussmann JB, et al. A more active lifestyle in persons with a recent spinal cord injury benefits physical fitness and health. *Spinal Cord* 2012;**50:**320-323.
9. Manns PJ, McCubbin JA, Williams DP. Fitness, inflammation and the metabolic syndrome in men with paraplegia. Arch Phys Med Rehabil 2005; 86: 1176-1181.
10. Gorgey AS, Mather KJ, Cupp HR, Gater DR. Effects of resistance training on adiposity and metabolism after spinal cord injury. Med Sci Sports Exerc 2012; 44: 165-174.
11. D'Oliveira GL, Figueiredo FA, Passos MC, Chain A, Bezerra FF, Koury JC. Physical exercise is associated with better fat mass distribution and lower insulin resistance in spinal cord injured individuals. J Spinal Cord Med 2014; 37: 79-84.
12. Jeon JY, Weiss CB, Steadward RD, Ryan E, Burnham RS, Bell G, et al. Improved glucose tolerance and insulin sensitivity after electrical stimulation-assisted cycling in people with spinal cord injury. Spinal Cord 2002; 40:110-117.
13. Mohr T, Dela F, Handberg A, Biering-Sørensen F, Galbo H, Kjaer M. Insulin action and long-term electrically induced training in individuals with spinal cord injury. Med Sci Sports Exerc 2001; 33: 1247-1252.
14. Griffin L, Decker MJ, Hwang JY, Wang B, Kitchen K, Ding Z, et al. Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury. J Electromyogr Kines 2009; 19: 614–622.
15. Carlson KF, Wilt TJ, Taylor BC, Goldish GD, Niewoehner CB, Shamliyan TA, et al. Effect of exercise on disorders of carbohydrate and lipid metabolism in adults with traumatic spinal cord injury: systematic review of the evidence. J Spinal Cord Med 2009; 32: 361-378.
16. Baldi JC Jr, Moraille R, Mysiw WJ (1998) Muscle atrophy is prevented in patients with acute spinal cord injury using functional electrical stimulation. Spinal Cord 36: 463–469.
17. Krause JS, Vines CL, Farley TL, Sniezek J, Coker J (2001) An exploratory study of pressure ulcers after spinal cord injury: relationship to protective behaviors and risk factors. Arch Phys Med Rehabil 82: 107-113.
18. Chen SC, Lai CH, Chan WP, Huang MH, Tsai HW, et al. (2005) Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. Disabil Rehabil 27: 1337–1341.
19. Bélanger M, Stein RB, Wheeler GD, Gordon T, Leduc B (2000) Electrical stimulation: can it increase muscle strength and reverse osteopenia in spinal cord injured individuals? Arch Phys Med Rehabil 81: 1090–1098.
20. Shields RK, Dudley-Javoroski S (2007) Musculoskeletal adaptations in chronic spinal cord injury: effects of long-term soleus electrical stimulation training. Neurorehabil Neural Repair 21: 169–179.
21. Biering-Sørensen F, Hansen B, Lee BS (2009) Non-pharmacological treatment and prevention of bone loss after spinal cord injury: a systematic review. Spinal Cord 47: 508-518.
22. Astorino TA, Harness ET, Witzke KA (2013) Effect of chronic activity-based therapy on bone mineral density and bone turnover in persons with spinal cord injury. Eur J Appl Physiol 113: 3027-3037.

23. Thijssen DH, Heesterbeek P, van Kuppevelt DJ, Duysens J, Hopman MT. Local vascular adaptations after hybrid training in spinal cord-injured subjects. Med Sci Sports Exerc 2005;37(7):1112-8.
24. Thijssen DH, Ellenkamp R, Smits P, Hopman MT. Rapid vascular adaptations to training and detraining in persons with spinal cord injury. Arch Phys Med Rehabil 2006;87(4):474-81.
25. Myers J, Lee M, Kiratli J. Cardiovascular disease in spinal cord injury: an overview of prevalence, risk, evaluation, and management. Am J Phys Med Rehabil 2007;86(2):142-52.
26. Dallmeijer AJ, Kilkens OJ, Post MW, de Groot S, Angenot EL, van Asbeck FW, et al. Handrim wheelchair propulsion capacity during rehabilitation of persons with spinal cord injury. J Rehabil Res Dev 2005;42(3 Suppl 1):55-63.
27. Valent LJ, Dallmeijer AJ, Houdijk H, Slootman J, Janssen TW, Hollander AP, et al. The individual relationship between heart rate and oxygen uptake in people with tetraplegia during exercise. Spinal Cord 2007;45(1):104-11.
28. Butcher SJ, Jones RL. The impact of exercise training intensity on change in physiological function in patients with chronic obstructive pulmonary disease. Sports Med 2006;36(4):307-25.
29. Tordi N, Gimenez M, Predine E, Rouillon JD. Effects of an interval training programme of the upper limbs on a wheelchair ergometer in able-bodied subjects. Int J Sports Med 1998;19(6):408-14.
30. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 6th ed. Baltimore, Md: Lippincott Williams & Wilkins;2000.
31. Davis G, Plyley MJ, Shephard RJ. Gains of cardiorespiratory fitness with arm-crank training in spinally disabled men. Can J Sport Sci 1991;16(1):64-72.
32. Hicks AL, Martin KA, Ditor DS, Latimer AE, Craven C, Bugaresti J, et al. Long-term exercise training in persons with spinal cord injury: effects on strength, arm ergometry performance and psychological well-being. Spinal Cord 2003;41(1):34-43.
33. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377-81.
34. Fernhall B, Heffernan K, Jae SY, Hedrick B. Health implications of physical activity in individuals with spinal cord injury: a literature review. J Health Hum Serv Adm 2008;30(4):468-502.
35. Nash, M. Exercise as a health-promoting activity following spinal cord injury. J Neurol Phys Ther 2005;29(2):87-103, 106.
36. Valent L, Dallmeijer AJ, Houdijk H, Slootman HJ, Post MW, Van der Woude LH. Influence of handcyling on physical capacity in the rehabilitation of persons with a spinal cord injury: a longitudinal cohort study. Arch Phys Med Rehabil 2008;89(6):1016-22.
37. Valent LJ, Dallmeijer AJ, Houdijk H, Slootman HJ, Janssen TW, Post MW, et al. Effects of hand cycle training on physical capacity in individuals with tetraplegia: a clinical trial. Phys Ther 2009;89(10):1051-60.
38. Valent L, Dallmeijer AJ, Houdijk H, Slootman HJ, Post MW, Van der Woude LH. Influence of handcyling on physical capacity in the rehabilitation of persons with a spinal cord injury: a longitudinal cohort study. Arch Phys Med Rehabil 2008;89(6):1016-22.
39. Sloan KE, Bremner LA, Byrne J, Day RE, Scull ER. Musculoskeletal effects of an electrical stimulation induced cycling programme in the spinal injured. Paraplegia 1994; 32: 407–415.
40. Chen SC, Lai CH, Chan WP, Huang MH, Tsai HW, Chen JJ. Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. Disabil Rehabil 2005;27(22):1337-41.
41. Arnold PB, McVey PP, Farrell WJ, Deurloo TM, Grasso AR. Functional electric stimulation: its efficacy and safety in improving pulmonary function and musculoskeletal fitness. Arch Phys Med Rehabil 1992;73(7):665-8.
42. Van der Scheer JW, de Groot S, Postema K, Veeger DH, van der Woude LH. Design of a randomized-controlled trial on low-intensity aerobic wheelchair exercise for inactive persons with chronic spinal cord injury. Disabil Rehabil 2013;35(13):1119-26.
43. Dallmeijer AJ, Zentgraaf ID, Zijp NI, van der Woude LH. Submaximal physical strain and peak performance in handcycling versus handrim wheelchair propulsion. Spinal Cord 2004;42(2):91-8.
44. Ashcroft RE. Current epistemological problems in evidence based medicine. J Med Ethics 2004;30(2):131-5.
45. West SG, Duan N, Pequegnat W, Gaist P, Des Jarlais DC, Holtgrave D, et al. Alternatives to the randomized controlled trial. Am J Public Health 2008;98(8):1359-66.
46. Smit CA, Legemate KJ, de Koning A, de Groot S, Stolwijk-Swüste JM, Janssen TW. Prolonged electrical stimulation-induced gluteal and hamstring muscle activation and sitting pressure in spinal cord injury: effect of duty cycle. J Rehabil Res Dev 2013;50(7):1035-46.