Physical Fitness, Ambulation and Physical Activity in Ambulatory Children and Adolescents with Spina Bifida

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Physical Fitness, Ambulation and Physical Activity in Ambulatory Children and Adolescents with Spina Bifida

Fysieke Fitheid, Loopfunctie en Fysieke Activiteit bij lopende kinderen en adolescenten met Spina Bifida
(met een samenvatting in het Nederlands)

PROEFSCHRIFT
ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. J.C. Stoof, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 17 december 2010 des middags te 4.15 uur.

door

Janke Frederike de Groot
geboren op 24 februari 1971 te Enschede

Promotoren: Prof. dr. P.J.M. Helders
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Voor mijn oma

en kinderen met Spina Bifida

Contents

General Introduction

Chapter 1

J.F. de Groot

Physical activity, physical fitness in healthy adults and children.

Many studies have shown the association between levels of physical activity (PA) and physical fitness (PF) and cardiovascular and overall mortality (1-3). Bouchard and Shephard (4) have described the relationship between physical activity, physical fitness and health in their model of health related fitness, with physical activity and physical fitness and general health being dependent on each other, while at the same time genetics and environment playing an important role in this interaction (see Fig. 1).

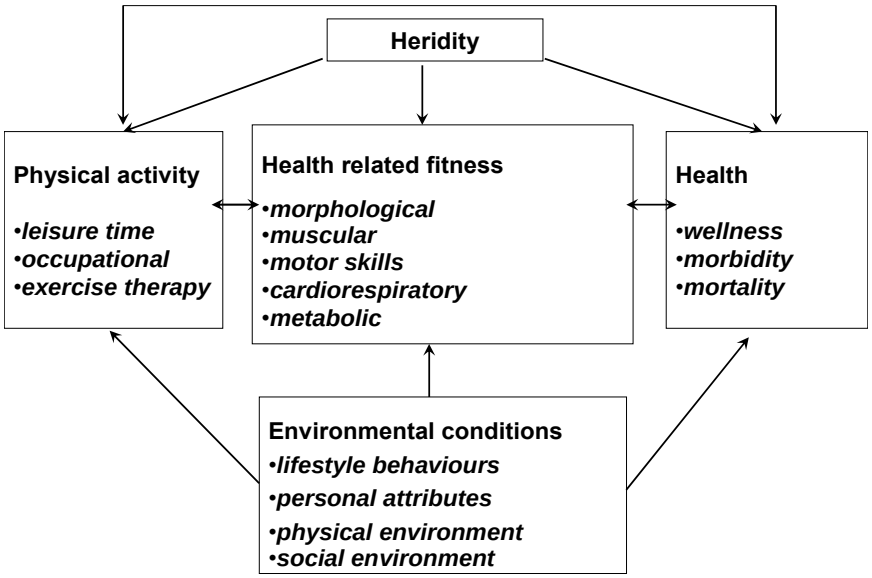

Fig. 1 Model of health-related fitness according to Bouchard and Shephard (4).

Although the presumed relationship between levels of physical activity and fitness during youth and adolescence and physical activity and fitness in adulthood are not consistently found in several studies on this topic (5-7), there does seem to be a relationship between health status in youth and health status in adults. The European Youth Heart Study found children engaged in physical activities less than one hour a day at higher risk for cardiovascular risk factors than those who were more active (8). Other studies have looked at the relationship between body composition and fitness

in children, with a negative relationship between the two (9). Overall, it seems that children with higher fitness levels are healthier than those who are less fit. Knowing healthy children becoming healthy adults, there is a need to promote healthy activity and fitness levels in children.

Physical activity and physical fitness in children with chronic disease

While "healthy" children already are increasingly inactive compared to previous generations(10-12), children with disability are even at higher risk of developing a hypoactive lifestyle (13). Bar-Or has summarized this in his model of illness and hypoactivity (Fig. 2)

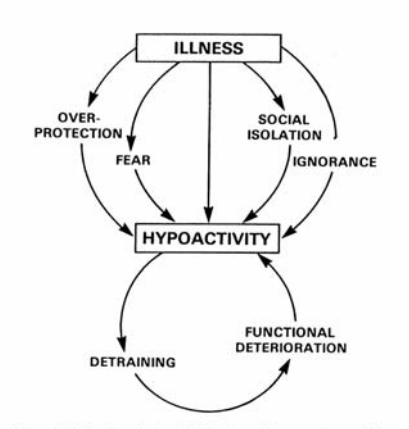

Fig. 2 Model of Chronic Illness, Hypoacitivity and Deconditioning by Bar-Or (13)

Recent studies in children with chronic disease and disability have shown these children to indeed be less active and less physically fit (14-18). Implementing exercise programs designed to improve physical fitness in children with chronic disease and disability has shown improvement not only in physical fitness, but also in activities of daily living participation (17, 19-21) and seem beneficial in both primary prevention of general health and secondary prevention(22).

Physical activity and physical fitness in children and adolescents with Spina Bifida

Spina Bifida (SB) is the most frequently seen congenital deformity of the neural tube, with an incidence ranging from 2-8 per 1000 live births worldwide (23). Due to advances in the medical approach, mortality rates have decreased in recent years and 60-80% of children with SB can now be expected to live to be adults (24-27). This requires a different approach in medical management of these patients from childhood through adolescence and adulthood not only focusing on the pathological aspects, but also at the (preventable) medical and social consequences of the disease (28).

There are several types of Spina Bifida, with varying impact on daily living: SB Occulta (closed type), Meningocele (MC) and Myelomeningocele (MMC), the latter two both open types of SB, with MMC being the most common and involved type of SB (26). This malformation of the spinal cord and often the brain can result in both motor and sensory impairment, incontinence for bowel and bladder and cognitive impairment. Schoenmakers et al. (29) looked at the disablement process in children with MMC and found mental status to be impaired in 41%, lower extremity strength reduced in 44-91% (depending on muscle group tested), contractures of the lower extremities to be present in 52%, ambulation level reduced in 80%, lower functional level in 55-76% and health- related quality of life (HRQoL) below the 50^{th} percentile in 63% of the patients. They also found a significant correlation ($r=0.5-0.72$, $p<0.001$) between muscle strength and ambulation and an association between HRQoL and ambulation, functional abilities, level of independence and mental status.

Simeonsson et al. (28) conclude in an extensive review the most frequently seen secondary consequences in children with SB are in the domain of body function of the ICF (44%) and activities and participation (52%). Secondary impairments include obesity, scoliosis, decubitus ulcers, urological problems and osteomyelitis, latex allergy (60%) and behavioral problems. There also seemed to be a negative interaction between greater body fat percentage and ambulation and activity levels. Adolescents with SB seem to be prone to be in a vicious cycle of mobility and functional impairment, a hypoactive lifestyle resulting in obesity, reduced health related quality of life and lower levels of physical fitness, in its turn influencing

functional ability and participation (30, 31). Interestingly, a recent study in a large population of children and adults with SB, showed that in adolescence, a lower lesion level was associated with an increased risk for obesity (32). This raises the interest for life-style interventions in this subgroup. With adolescents with SB being less active and less fit, the question is, whether this downwards vicious cycle can be prevented in childhood. An exercise program aimed to improve fitness in children with SB could reverse and prevent further deconditioning due to low levels of physical activity.

Despite existing literature on deconditioning, hypoactivity and decline in ambulatory status in adolescents with SB, little research has been done regarding exercise intervention in this group of children. A recent review (33) concludes that the limited available evidence does show improvements in strength after several types of exercise interventions. At the same time, much of the evidence was rated as low methodological quality. They conclude further research is needed regarding various strength-training interventions for children with myelomeningocele and the relationship between increased strength and improved activity and participation.

The *U*trecht *S*pina Bifida *A*nd *G*raded *E*xercise study

The *U*trecht *S*pina Bifida *A*nd *G*raded *E*xercise study (USAGE) will focus on children who are considered to be at least community ambulatory. About 20% of the lesions occur at the sacral level, enabling them to be, in most cases, community or normal ambulators according to Hoffer (34) and adapted by Schoenmakers (29). Despite high levels of functioning, these patients still experience difficulties in performing both dynamic motor skills and activities of daily living. In the adolescents years a large number of children seem to become wheelchair dependent as ambulation becomes too strenuous (35).

Fatigue and difficulties during daily activities put these children at risk for developing a hypoactive lifestyle and the consequential risk factors associated with poor levels of activity. At the same time, this fatigue may be explained by both a lower level of physical fitness and a higher cost of energy expenditure during daily activities (see Fig. 3).

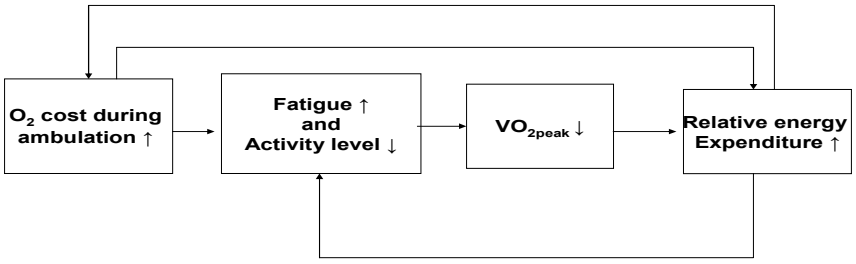

Fig 3. Possible cause of fatigue and reduced physical activity in children with SB.

In the literature this combination of reduced exercise capacity and higher cost of locomotion is referred as "diminished physiological reserve" (36).

Earlier studies have shown higher levels of energy expenditure during ambulation in patients with SB, which are associated with a pathological gait pattern due to muscle weakness in the lower extremities (37-46), compared to healthy children. Higher energy expenditure during gait may result in higher levels of fatigue while physically active. Obesity and poor levels of physical fitness could further impair ambulation and mobility in these children, an important predictor for future ambulation level. Looking at prognosis and development of SB, a 25-year cohort study found a decline in ambulation as the main mode of locomotion from 95% at age 0-5 to 46% at age 20-25 in patients with SB, despite stable or even improving motor exams in respectively 73% and 16% of the patients (24). They also found that ambulation level during teenage years was predictive of ambulation as the main mode of locomotion as young adults. Therefore especially this group of children could greatly benefit from a new approach to literally "keep them moving" and walking.

Since components of physical fitness are associated with efficiency of movement (13), it would be interesting to know whether peak oxygen uptake (VO_{2peak}) is related to energy cost during ambulation in children with SB. Both VO_{2peak} and

energy cost or efficiency of movement can be improved by training (47, 48), which will be the focus of the proposed intervention study.

In conclusion, the *U*trecht *S*pina Bifida *A*nd *G*raded *E*xercise study (USAGE) consist of the following three parts:

1. **Fitness and energy cost of locomotion in ambulatory children with SB: two exploratory studies.**

The aims of the first part are:

- To assess and relate several components of physical fitness, ambulation and physical activity in ambulatory children with SB. (Chapter 2)
- To interpret outcomes of peak oxygen uptake (VO_{2peak}) in children with SB and explore the relationship between VO_{2peak} and oxygen uptake (VO_2) during functional ambulation. (Chapter 3)

2. **Development of appropriate exercise testing for ambulatory children with Spina Bifida.**

The second part of the study consisted of:

- Determining reproducibility of energy expenditure measures during gait in ambulatory children with SB. (Chapter 4)
- Determining whether VO_{2peak} measured during an incremental treadmill test is a true reflection of VO_{2max} in ambulatory children with SB. (Chapter 5)
- Assessing both reliability and agreement of maximal and sub-maximal exercise parameters in ambulatory children with SB. (Chapter 6)

3. **Intervention aimed to improve ambulation and physical fitness in ambulatory children with Spina Bifida.**

Based on the results from the first two studies, the purpose of the intervention study was to evaluate the effects of an individualized treadmill training program aimed at improving both aerobic fitness and ambulation in ambulatory children and adolescents with SB.

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Muscle Strength, Aerobic Capacity and Physical Activity in Independent Ambulating Children with Lumbosacral Spina Bifida

Chapter 2

Schoenmakers MACG, de Groot, JF, Gorter, JM, Hillaert, JLM, Helders PJM, Takken, T. Disability and Rehabilitation 2009; 31(4): 259-66

Abstract

Purpose

This cross-sectional study investigates deficits and associations in muscle strength, 6-minute walking distance (6MWD), aerobic capacity (VO_{2peak}), and physical activity (PA) in independent ambulatory children with lumbosacral spina bifida

Method

Twenty-tree children participated (13 boys, 10 girls). Mean age (SD): 10.4 (± 3.1) years. Muscle strength (manual muscle testing and hand-held dynamometry), 6MWD, VO_{2peak} (maximal exercise test on a treadmill), and PA (quantity and energy expenditure (EE)), were measured and compared with aged-matched reference values.

Results

Strength of upper and lower extremity muscles, and VO_{2peak} were significantly lower compared to reference values. Mean Z-scores ranged from -1.2 to -2.9 for muscle strength, and from -1.7 to - 4.1 for VO2peak. EE ranged from 73% to 84% of predicted EE. 6MWD was significantly associated with muscle strength of hip abductors and foot dorsal flexors. VO2peak was significantly associated with strength of hip flexors, hip abductors, knee extensors, foot dorsal flexors, and calf muscles.

Conclusions

These children have significantly reduced muscle strength, 6MWD, VO_{2peak} and lower levels of PA, compared to reference values. VO_{2peak} and 6MWD were significantly associated with muscle strength, especially with hip abductor and ankle muscles. Therefore, even in independent ambulating children training on endurance and muscle strength seems indicated.

INTRODUCTION

Over the last decade, few studies have reported on problems in young children with lumbosacral spina bifida (SB) [1-4]. There is increasing evidence that physical fitness in children with SB is impaired, even in those with lumbosacral lesions [2,3,4]. Several studies on aerobic capacity showed that oxygen cost of walking is significantly higher compared to healthy peers [2,3]. This is partly attributable to their altered gait pattern. Many compensatory movements are observed in the

frontal and sagittal plane, particularly caused by muscle weakness in lower extremities [2,4].

There is very weak evidence that exercise training can improve muscle strength and physical fitness in children with SB [5]. At the same time, studies on determinants of physical fitness are scarce. This information is important for designing proper exercise programs to improve physical fitness in children who will benefit most. Purposes of the present study were twofold. First, we investigated muscle strength, six minute walking distance (6MWD), aerobic capacity, and physical activity (PA) in two groups of ambulatory children with lumbosacral SB. We compared the outcome of children with myelomeningocele (MMC), who mostly have hydrocephalus and Chiairi II malformation, to those with lipomyelomeningocele (LMMC), where there is only involvement of the spinal cord. In addition, each group was compared with reference values of the normal population. Second, we investigated associations between muscle strength on the one hand and aerobic parameters and PA on the other.

METHODS

Participants

The study group consisted of 23 children diagnosed with MMC or LMMC, from the SB clinic of the University Children's Hospital. Participants included those with paralysis level L5 or below, Intelligence Quotient (IQ) > 80, aged 6-18 years and being able to ambulate 500 meters or more without crutches or parawalkers. Participants who had surgery less than six months prior to inclusion, and those with monoparesis or cerebral movement impairments were excluded, as were Non-Dutch speaking participants. Thirty-three subjects met the inclusion criteria, 23 of them were willing to participate (13 boys and 10 girls). Their general characteristics are presented in Table 1.

Table 1. Patient characteristics

	MMC (N = 16)	LMMC (N = 7)
Mean age (years) (± SD)	9.9 (± 3.2)	11.6 (± 2.7)
Ambulation		
- normal	10	7
- community	6	
Hydrocephalus		
- shunted	9	
- non-shunted	3	
- no hydrocephalus	4	7
Lesion level		
- L5-S1	7	3
- S1-S4	5	1
- No motor deficit	4	3

Abbreviations: MMC = myelomeningocele; LMMC = lipomyelomeningocele; SD = standard deviation

The parents of 10 patients refused to participate. There were no differences in terms of gender, mean age, or ambulation level between the MMC and LMMC group. All study procedures were approved by the University Medical Ethics Committee. Informed consent was obtained from the parents and the participants themselves when they were ≥ 12 years of age.

Measurements

All measurements were performed by the same experienced researchers for all participants. Data concerning the presence of shunted hydrocephalus, mental status (IQ), and lesion level, according to the ASIA criteria [6], were obtained from the medical records. Ambulation level was defined according to Hoffer [7]. The scoring was adapted for children with normal ambulatory skills. In Hoffer's description, participants with normal ambulatory skills are not distinguished from community walkers (walking outdoors with/without braces and possibly using a wheelchair for longer distance). This difference was considered clinically important, and we described participants who did not need a wheelchair at all, as 'normal

ambulant' (community ambulator = + Ankle-Foot-Orthosis (AFO), + wheelchair (WC); normal ambulator = +/- AFO, - WC).

Anthropometrics

Body weight and height, were measured to calculate Body Mass Index (BMI), and compared with reference values for healthy subjects matched for age and sex. Z-scores were calculated [8]. Body composition was assessed using the sum of 7 skin folds according to Pollack [9]. The measurements were taken at the biceps, triceps, supra-iliacal, mid-abdominal, subscapular, medial thigh, and calf, at the right side of the body.

Muscle strength

Muscle strength in upper and lower extremities was graded 0-5 according to the standard Manual Muscle Testing (MMT) as described by Hislop [10]. As intertester reliability of MMT is poor (range in coefficients: 0.11 - 0.58) [11], all tests were performed by the same examiner. As MMT appears to be less specific for grade ≥ 4 [11], in addition for muscles ≥ 4, Hand-Held Dynamometer (HHD) (Citec, type CT 3001, CIT Techniques, Groningen, The Netherlands) was used to quantify isometric maximal muscle strength (in Newton). The tests were performed according to Beenakker [12]. We tested: shoulder abductors, wrist extensors, hip and knee flexors, hip abductors, hip and knee extensors, ankle dorsal flexors, and grip strength. The plantar flexors were not measured using HHD, as reference values were not available. Muscle strength was compared with Dutch reference values for healthy subjects matched for age and sex, obtained from Beenakker [12]. HHD data were used for studying correlations, with the exception of plantar flexors. In these muscles only MMT data were available.

Six minute walking distance (6MWD)

The 6-minute walking test was performed on an 8-meter track in a straight corridor as described previously [13]. Participants were instructed to cover the largest possible distance in 6 minutes at a self-chosen walking speed. Encouragements were provided according to the ATS Guideline [14]. 6MWD and average walking

speed were measured. 6MWD was compared with reference values of the normal population [13,15].

Aerobic capacity

After the 6-minute walking test, subjects performed a maximal exercise test using a treadmill (Enmill, Enraf, Delft, The Netherlands). Between the 6-minute walking test and the maximal exercise test, there was a recovery period of at least 15 minutes. After this period, all participants were able to start walking without tiredness. It is known from the literature that children recover significantly faster than adults from an exercise bout [16]. For both tests, participants were allowed to use their orthosis or orthopaedic shoes. In order to accommodate children of varying abilities, two progressive exercise test protocols were used. Children, who were community ambulant, were tested with a starting speed of 2 km/hr that was gradually increased with a speed of 0.25 km/hr every minute. Children who were normal ambulant, were tested with a starting speed of 3 km/hr that was increased with 0.50 km/hr every minute. The protocols were continued until the participant voluntarily stopped due to exhaustion, despite verbal encouragement of the test leader. Maximal walk/run speed was recorded. During the maximal exercise test, physiologic responses were measured using a heart rate (HR) monitor (Polar) and calibrated mobile gas analysis system (Cortex Metamax B^3, Cortex Medical GmbH, Leipzig, Germany). The Cortex Metamax is a valid and reliable system for measuring ventilatory parameters during exercise [17].

Peak oxygen uptake (VO_{2peak}) was taken as the average value over the last 30 seconds during the maximal exercise test. Relative VO_{2peak} ($VO_{2peak/kg}$) was calculated as VO_{2peak} divided by body mass. Peak oxygen pulse was calculated as $VO_{2peak}/HR_{peak.}$ Predicted VO_{2peak} values were obtained from established values from age- and sex- matched Dutch reference values [18].

Physical activity

A diary was used to estimate daily PA, both the quantity of activities, and energy expenditure (EE) according to Bouchard [19]. The diary included static activities (sleeping, lying, or sitting) as well as dynamic activities (transfers, walking, running,

sporting, etc.). The quantity of PA was determined by mean daily hours of dynamic activities from the diary.

The term EE was used for the calculation of MET´s according to Bouchard [19]. In the record, every 15 minute period over 3 days, including a Saturday, was qualified in terms of energy costs on a 1 (= sleeping or resting in bed) to 9 scale (= high intensity sport activities or sport competition), corresponding to a range of 1.0 metabolic equivalent transformation (MET) to 7.8 METs and higher [19]. Approximate median energy cost for each of the nine categories in kcal/kg/15min was used to compute the EE for each individual. The measured total EE was compared with predicted values of healthy peers adjusted for height, sex and age [20].

An estimation of daily EE for any of the days of the activity record appears quite reproducible [19]; the intraclass reliability correlations range from 0.86 to 0.95. Mean Kcal energy expenditure for the 3 days was highly reliable with a correlation coefficient of 0.96 ($p<0.01$). It appears to be a reliable method in children ($r = 0.91$; $p < 0.01$ [18]) and has been used previously in children with MMC [20].

The diaries were filled out at the end of the day by the participants themselves, assisted by their parents.

Statistical analysis

Associations between muscle strength on the one hand, and 6MWD, aerobic parameters and PA on the other, were tested with Pearson's correlations. Alpha level was set at $p < 0.05$ for all analyses. T-tests were used to test differences between both groups (MMC vs. LMMC) and the normal reference values. If scores were skewed, nonparametric tests Mann-Whitney U-test were used (skin folds measurements, VO_{2peak}, grip strength, knee flexor and dorsal flexor strength). Statistical analyses were performed using SPSS for Windows (version 12.0, SPSS Inc, Chicago, Ill).

RESULTS

Anthropometrics

Results are shown in table 2. In both groups, body height was significantly lower compared to reference values (MMC p = 0.03; LMMC p = 0.008). BMI was only significantly higher in MMC group (p = 0.03) compared to healthy peers.

Table 2. Anthropometric values

	N	MEAN (SD) SB PATIENTS	MEAN (SD) CONTROLS	Z-SCORE (SD)	P VALUE
Height (m)					
-MMC	16	1.37 (0.19)	1.45 (6.59)	-0.01 (0.01)	0.03*
-LMMC	7	1.47 (0.18)		-0.01 (0.01)	0.008**
Weight (kg)					
-MMC	16	35.7 (12.4)	36.2 (5.1)	0.5 (2.1)	0.32
-LMMC	7	41.7 (13.5)		0.1 (0.9)	0.74
BMI (kg/m^2)					
-MMC	16	18.1 (2.93)	16.6 (1.54)	1.5 (2.9)	0.03*
-LMMC	7	18.7 (3.1)		0.9 (1.4)	0.15
Sum of 7 skin folds	12	89.8 (38.5)	81.7 (31.2)	0.1 (1.6)	0.78
-MMC	6	96.3 (57.0)		0.3 (1.8)	0.67
-LMMC					

Abbreviations: SD = standard deviation; m = meters; MMC = myelomeningocele; LMMC = lipomyelomeningocele; * = P value < 0.05, ** = P value < 0.01; kg= kilogram.

Muscle strength

We found no significant differences between participants in the MMC vs. LMMC group. Therefore, data are presented for the total group. As can be appreciated from table 3, the MMT indicated that in > 25% of participants, muscle strength in

the hip abductors and the plantar flexors were < 3. Moreover, < 50% of the participants had fully functioning hip extensors (grade 5).

Table 3. Muscle strength measured with manual muscle testing. The values indicates the number of participants (%) with a certain grade (0-5).

	MUSCLE GRADE					
MUSCLE GROUP	0	1	2	3	4	5
Hip flexors	-	-	-	-	2 (8.7)	21 (91.3)
Hip abductors	-	-	1 (4.3)	5 (21.7)	1 (4.3)	16 (69.6)
Hip extensors	-	-	3 (13)	1 (4.3)	8 (34.8)	11 (47.8)
Knee extensors	-	-	-	-	1 (4.3)	22 (95.7)
Knee flexors	-	-	-	-	4 (17.4)	19 (82.6)
Dorsal flexors	-	-	1 (4.3)	4 (17.4)	3 (13)	15 (65.2)
Plantar flexors	3 (13)	1 (4.3)	1 (4.3)	1 (4.3)	3 (13)	14 (60.9)

Z-scores of muscle strength measured with HHD [figure 1] were significantly reduced compared to reference values (all P values < 0.01) in lower as well as in upper extremities (mean range: -1.2 to -2.9). Even in the participants without paralysis when measured with MMT (grade 5), strength was significantly reduced in all muscle groups compared to healthy peers (mean range: –1.4 to -3.0).

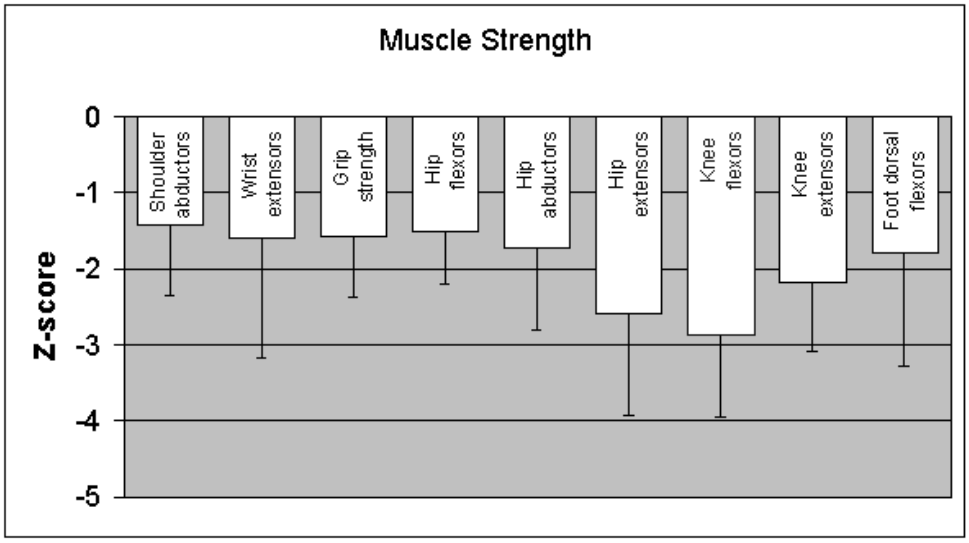

Figure 1. Mean Z-scores (SD) of upper and lower extremity muscle strength.

Six minute walking distance

The mean 6MWD was 353 metre (SD ± 108) in the MMC group, compared to 424 metre (SD ± 65) in the LMMC group (p = 0.07), and was significantly lower compared to reference values of healthy peers (664 metre SD ± 65.3; p = 0.03)

Aerobic capacity

VO_{2peak}, $VO_{2peak/kg}$ and HR_{peak} in children with MMC and LMMC were significantly reduced compared to healthy peers (all P values < 0.05) [figure 2], but not different between the MMC vs. LMMC group.

Maximal treadmill walk/run speed was significantly lower in the MMC group compared to the LMMC group, 6.3 (SD ± 2.1) vs. 8.4 (SD ± 1.7) respectively (p = 0.03).

Even in the seven participants without paralysis (4MMC, 3LMMC), aerobic capacity was impaired. Mean Z-score for VO_{2peak} was: -2.0 (SD ± 0.8), Z-score for $VO_{2peak/kg}$: -2.7 (SD ± 1.4), and their HR_{peak} was reduced as well (Z-score -3.5 (SD ± 2.3)).

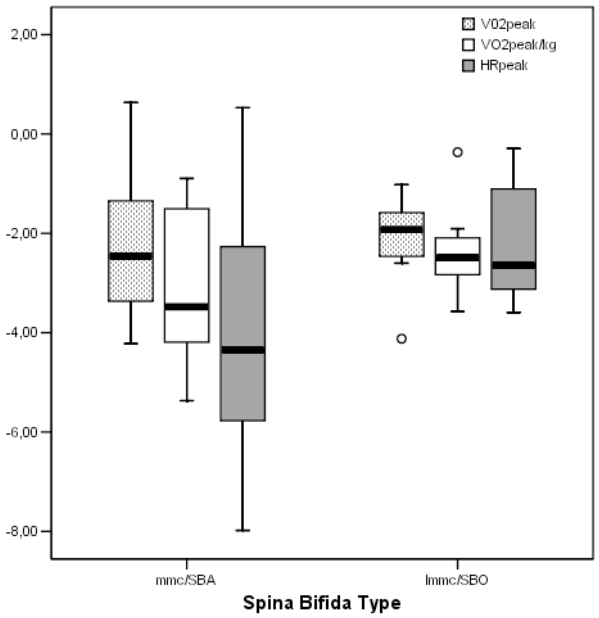

Figure 2. Z-scores for maximal exercise capacity (VO_{2peak}, VO_{2peak}/kg and HR_{peak}) in subjects with MMC and LMMC
Abbreviations: MMC = myelomeningocele; SBA = spina bifida aperta; LMMC = lipomyelomeningocele; SBO = spina bifida occulta; o = outlier

Physical activity

There were no significant differences between the LMMC and MMC group in terms of PA. The mean daily hours of dynamic activities was 2.8 for the total group. Fifty-seven percent used an active mode of transportation to school (35% bicycle, 22% walked). All others used an inactive mode of transportation (car or taxi).

Mean EE was significant lower in both groups compared to predicted normal EE; 5953 KJoule/day (SD ± 1626) in the MMC group (p = 0.009) (is 73% ± SD 10 of predicted EE), and 7226 KJoule/day (SD ± 2260) in the LMMC group (p = 0.03) (is 84% ± SD 13% of predicted EE).

Correlations between muscle strength, 6MWD, aerobic capacity and PA

The correlations are presented in table 4 and 5. The 6MWD was significantly associated with muscle strength of hip abductors (0.47, p = 0.04) and foot dorsal flexors (0.55, p = 0.02), whereas peak treadmill walking/running speed (V_{peak})

showed significant associations with the strength of plantar flexor muscles (0.59, p = 0.01). VO_{2peak} was significantly associated with muscle strength of hip flexors (r = 0.50, p = 0.02), hip abductors (r = 0.51, p = 0.03), knee extensors (r = 0.48, p = 0.03), foot dorsal flexors (r = 0.48, p = 0.048), as well as with calf muscles (r = 0.52, p = 0.049). $VO_{2peak/kg}$ was significantly associated with strength of plantar flexor muscles (r = 0.44, p = 0.045). Neither aerobic capacity, nor muscle strength were significantly correlated with PA.

Table 4. Correlations (P value) between muscle strength (hand–held dynamometry), 6-minute walking distance, and aerobic capacity

MUSCLE STRENGTH							
	Z-score Hip flexors	Z-score Hip abductors	Z-score Hip extensors	Z-score Knee extensors	Z-score Knee flexors	Z-score Dorsal flexors	Plantar flexors (MMT)
6MWD	0.36 (0.10)	0.47* (0.04)	0.05 (0.92)	0.15 (0.52)	0.37 (0.09)	0.55* (0.02)	0.40 (0.09)
Aerobic capacity V_{peak}	0.24 (0.34)	0.16 (0.57)	0.04 (0.86)	0.09 (0.71)	0.34 (0.17)	0.38 (0.19)	0.59** (0.01)
Z-score VO_{2peak}	0.50* (0.02)	0.51* (0.03)	0.24 (0.24)	0.48* (0.03)	0.42 (0.06)	0.48* (0.048)	0.52* (0.049)
-Z-score VO_{2peak}/kg	0.25 (0.27)	0.33 (0.17)	0.02 (0.95)	0.7 (0.77)	0.34 (0.14)	0.31 (0.22)	0.44** (0.045)

Abbreviations: MMT = Manual Muscle Testing; 6MWD = 6-minute walking distance; Vpeak = maximum treadmill walk/running speed ; * = P value < 0.05, ** = P value < 0.01. All correlations are expressed in Pearson correlation coefficients.

Table 5. Correlations (P value) between muscle strength (hand–held dynamometry) and physical activity

	MUSCLE STRENGTH						
PHYSICAL ACTIVITY	Z-score Hip flexors	Z-score Hip abductors	Z-score Hip extensors	Z-score Knee extensors	Z-score Knee flexors	Z-score Dorsal flexors	Plantar flexors (MMT)
Quantity	0.31 (0.90)	-.13 (0.59)	-.40 (0.10)	-.03 (0.92)	-.25 (0.31)	-.15 (0.56)	-.001 (0.99)
Energy Expenditure	-.09 (0.74)	-.02 (0.94)	-.34 (0.20)	-.02 (0.92)	-.25 (0.31)	-.15 (0.60)	-.06 (0.80)

Abbreviations: MMT = Manual Muscle Testing; * = P value < 0.05, ** = P value < 0.01. All correlations are expressed in Pearson correlation coefficients.

DISCUSSION

Our study shows that independent ambulating children with SB have significantly reduced muscle strength, 6MWD, aerobic capacity and lower levels of PA, compared to reference values. 6MWD and aerobic capacity were significantly associated with muscle strength, especially with hip abductor and ankle muscles.

In 26% of the participants the strength of hip abductor and calf muscles was below grade 4, resulting in a waddling or crouched gait, that might be energy consuming [3,4]. The reduced muscle strength in the lower extremities is in line with previous research [1,2,4]. Compared to healthy peers, we found significantly reduced strength in all lower extremity muscles, even in MMT grade 5. We observed significantly reduced muscle strength in the upper extremities. It is known that, in children with SB, the loss of muscle function below the actual level of the lesion directly affects motor performance [21]. This may impair daily functioning and

influence general activity levels. The strength of intact, functional muscle groups may, according to our data, is indirectly affected in this population as well. It might be due to deconditioning or to a certain defect in the neural drive of upper extremity muscles.

In all our participants maximal aerobic capacity was impaired, even in participants without paralysis. Since its relationship with muscle strength, aerobic capacity might be related to functional muscle mass of the patient. This has been previously suggested by Agre et al. [22]. They emphasised the importance of HHD measurements and recommended further studies to investigate the role of muscle mass in ambulatory children with SB [22].

Van den Berg-Emons et al [23] found that adolescents and young adults with MMC (particularly non-ambulatory) were considerably hypoactive when compared to healthy peers. This was also observed in 13-20 years old patients using the doubly–labelled water method [23]. Moreover, levels of objectively measured PA seemed to be significantly related to ambulation level and fitness [23]. In contrast to Van den Berg-Emons [23], we found no significant associations between PA with any of the measured physical fitness parameters. This might be explained by the fact that the ambulation level and the quantity of PA were homogenous within our participants.

Questions can be raised regarding measurement of VO_{2peak} and PA (quantity and EE) in this study, as protocols to measure VO_{2peak} and PA are not available for children with SB. Our results regarding PA (quantity and EE) should be interpreted with caution. Although an estimation of daily EE, from the activity record according to Bouchard [19], appears to be a reliable method in children [19] and has been used previously in children with MMC [20], we might have underestimated the EE as the 'waddling' gait, as well as other PA which might be more energy consuming compared to healthy subjects.

There are no valid and reliable instruments for measuring PA and EE in children with SB, except for the very expensive doubly-labelled water method as previously used [24]. In future studies, accelerometers [25, 26] in combination with heart-rate monitoring [27] and indirect calorimetry should be used, to estimate the intensity of daily activities more precisely.

We found aerobic capacity to be strongly related with muscle strength. Nonetheless, PA, quantity as well as EE, showed no correlations with physical fitness parameters. There is weak evidence that exercise training can improve fitness and strength in children with SB [5]. To our knowledge only one study in a heterogeneous group of 8 participants exercising for 1 hour/week for 10 weeks showed improvements in muscle strength, exercise capacity, and self-concept [5]. Moreover, a low initial fitness level might provide a 'large room for improvement' for children with a chronic condition. Since there is a lack of clinical evidence, a rigorous designed exercise intervention trial in children with SB seems indicated.

It is our recommendation that prior to doing future research on improving physical fitness valid and reliable protocols for these children should be developed to measure cardio- respiratory fitness and PA.

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Limiting Factors in Peak Oxygen Uptake and the Relationship with Functional Ambulation in Ambulating Children with Spina Bifida

Chapter 3

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ABSTRACT

Objectives: To interpret outcomes of peak oxygen uptake (VO_{2peak}) in children with SB and explore the relationship between VO_{2peak} and functional ambulation.

Design: Retrospective cross-sectional study.

Setting: Wilhelmina's Children's Hospital Utrecht, the Netherlands.

Participants: Twenty-three ambulating children with SB.

Methods: VO_{2peak} was measured during a graded treadmill-test. Eschenbacher's and Maninna's algorithm was used to determine limiting factors in reaching low VO_{2peak} values. Energy expenditure during locomotion (both O_2 rate and O_2 cost) and percentage of VO_{2peak} and HR_{peak} were determined during a 6-minute walking test (6MWT). Differences between community and normal ambulators were analyzed.

Results: VO_{2peak}, VO_{2peak}/kg, HR_{peak}, RER_{peak} and VE_{peak} were significantly lower compared to reference values, with significant differences between normal and community ambulators. Limiting factors according to the algorithm were mostly “muscular and/or deconditioning” (47%) and ventilatory “gasexchange” (35%). Distance walked during 6MWT was 48.5% of predicted distance. Both O_2 rate and O_2 cost were high with significant differences between normal and community ambulators (17.6 vs 21.9 ml/kg/min and 0.27 vs 0.43 ml/kg/m). Also $\%HR_{peak}$ and $\%VO_{2peak}$ were significantly higher in community ambulators when compared to normal ambulators (resp. 97.6 vs 75% and 90.2 vs. 55.9%).

Conclusion: VO_{2peak} seems to be mostly limited by deconditioning and/or muscular components and possible ventilatory factors. For both peak values and functional ambulation, community ambulators were significantly more impaired than normal ambulators. High energy expenditure, $\%VO_{2peak}$ and $\%HR_{peak}$ reflect high level of strain during ambulation in the community ambulators. Future exercise testing in children with SB should include assessment of ventilatory reserve. Exercise training in ambulatory children should focus on increasing both VO_{2peak} and muscular endurance, as well as decreasing energy cost of locomotion.

INTRODUCTION

Spina bifida (SB) is the most frequently seen congenital deformity of the neural tube, with an incidence ranging from 1.4-3.6 of every 1000 in the Netherlands (1). The severity of these deficits is largely determined by both the type and level of lesion of the SB. In 80% of children with the more serious open type of SB (Spina Bifida Aperta), hydrocephalus and a Chiari II malformation – a malformation in the brainstem- are present (2). The level of lesion, classified according to the ASIA guidelines (3) determines which muscles are being (partly) innervated. Besides this medical classification, children are functionally classified using the Hoffer classification (4), recently adapted by Schoenmakers et al. (5), presented in table 1. About 20% of the lesions occur at the sacral level, enabling them to be, in most cases, community or normal ambulators. Despite high levels of functioning, these patients still experience difficulties in performing both dynamic motor skills and activities of daily living (6). This could be an important factor in inducing a cycle of less ability resulting in less activity, further reducing physical fitness and ambulation. In adolescence a large number of children seem to become wheelchair dependent as ambulation becomes too strenuous (7). Studies indeed have shown children and young adults with SB to be less active with reduced levels of physical fitness compared to their healthy peers (8;9;9;10). Based on these results, Van den Berg-Emons (9) concluded that programs aimed at regular physical exercise and daily physical activity should be started in childhood to prevent further decline in physical fitness and daily functioning.

Table 1. Ambulation level by Hoffer et al, adapted by Schoenmakers et al. (Schoenmakers et al. 2005)

LEVEL OF AMBULATION	Description
Normal Ambulation	Independent and unrestricted ambulation without use of assisted devices
Community ambulation	Independent outdoor ambulation with or without use of braces and/or assisted devices; using wheelchair for longer distances
Household ambulation	Using braces or assisted devices for indoor ambulation; using wheelchair for outdoor locomotion
Non-functional ambulation	Walking only in therapeutic situations
Non-ambulation	Wheelchair dependent

At the same time, small studies have shown higher levels of energy expenditure during ambulation in patients with SB, a finding that is associated with a pathological gait pattern (11-13). Energy expenditure refers to both O_2 rate (ml O_2/kg/min), an indicator of strain or effort and O_2 cost (ml O_2/kg/meter) (14). Higher energy expenditure during ambulation may result in higher levels of fatigue while physically active. This combination of reduced exercise capacity and higher cost of locomotion is referred to as “diminished physiological fitness reserve” (15) .

In our SB clinic, 23 ambulatory children with SB were seen for sports and lifestyle advice. Results showed low levels of overall muscle strength, exercise capacity and daily physical activity (16). While designing an exercise program specifically aimed at improving both endurance and ambulation in ambulatory children with SB, the following questions were raised:

(1) Which factors (cardiovascular, pulmonary or muscular) are limiting VO_{2peak} in ambulatory children with SB?

(2) Since components of physical fitness are associated with efficiency of movement (17), is VO_{2peak} related to oxygen expenditure during ambulation in children with SB?

METHODS

Subjects

The study group consisted of a 23 ambulatory children with SB visiting the SB clinic of the University Children’s Hospital in Utrecht (The Netherlands) for lifestyle and sports advice in 2004. Study procedures were approved by the University Medical Ethics Committee.

Children were included when they were (1) at least community ambulatory (see table 1), (2) able to follow instructions regarding testing and (3) between 6 and 18 years of age. Parents and children signed informed consent prior to testing.

Exclusion criteria were medical events that might interfere with the outcomes of the testing and medical status that did not allow maximum exercise testing.

Study design

Retrospective cross-sectional study, using outcomes of incremental exercise testing and the six-minute walking test (6MWT).

Demographics

Data concerning medical history were obtained from medical records. These data included type of SB, level of lesion, use of orthotics, ambulation level, age and sex.

Body mass index (BMI)

BMI was calculated as weight (kg)/(length (m) ^{2}). This index has proven to be a reliable and valid tool to estimate children's nutritional status, e.g. whether they are over- or underweight (18;19). Weight was measured using an electronic scale. Height was measured while standing using a wall-mounted centimeter.

Peak oxygen uptake (VO_{2peak})

In exercise testing, $VO_{2\ peak}$ is considered to be the single best indicator of aerobic exercise capacity, which is often referred to as aerobic fitness. Gas exchange analysis during an incremental ergometry test to the point of volitional termination due to exhaustion is considered the gold standard to measure VO_{2peak} (20). Earlier studies employing exercise testing in healthy children show it is possible to test VO_{2peak} in healthy children (21-25). In this study, VO_{2peak} was measured using a treadmill test (EnMill, Enraf, Delft, The Netherlands), since all children would be able to perform this test and reference values are available for both young children and adolescents. In previous studies, treadmill protocols have been used to test VO_{2peak} in children with disability (10;26;27), including children with Spina Bifida (10;28). In order to accommodate children with different ambulatory abilities, two progressive exercise test protocols were used. Children considered community ambulators were tested with a starting speed of 2 km/hr, which was gradually increased by 0.25 km/hr every minute. Children classified as normal ambulators were started at a speed of 3 km/hr, with the speed being increased 0.50 km/hr every minute. The protocols were continued until the patient stopped due to exhaustion, despite verbal encouragement of the test leader. During the incremental exercise test, physiologic responses were measured using a heart rate

(HR) monitor (Polar) and calibrated mobile gas analysis system (Cortex Metamax B^3, Cortex Medical GmbH, Leipzig, Germany). The Cortex Metamax is a valid and reliable system for measuring gas-exchange parameters during exercise (29;30).

Functional ambulation

Functional ambulation was measured during a six-minute walking test (6MWT). The test was performed on an eight-meter track in a straight corridor and gas exchange parameters were measured continuously with a portable Cortex gas analysis system (Cortex Metamax B^3, Cortex Medical GmbH, Leipzig, Germany). Patients were instructed to cover the largest possible distance in 6 minutes at a self-selected walking speed. The test and encouragements during the test were performed in accordance with the ATS guidelines (31).

Data analysis

Peak oxygen uptake

Peak exercise parameters were calculated as the average value over the last 30 seconds during the exercise test. Normalized VO_{2peak} was calculated as VO_{2peak}/kg. Predicted peak values were obtained from established values from age- and sex-matched historical Dutch controls (32). For comparison with healthy children Z-scores were calculated for VO_{2peak}, VO_{2peak}/kg, HR_{peak} RER_{peak} and VE_{peak}. Standard deviation scores > 2 SD below or above normal were considered to be significantly different from the norm values.

Data were evaluated using the algorithm from Eschenbacher and Maninna (33). This algorithm has been developed for the interpretation of outcomes of exercise testing in adults. For this purpose it uses cut-off points routinely measured during exercise testing in order to make a distinction between cardiac, pulmonary or "other" limitations (deconditioning and/or musculoskeletal factors) to explain exercise capacity. The following parameters were measured and used in the algorithm: VO_{2peak}, VCO_{2peak}, VE_{peak}, VE_{peak}/VCO_{2peak}, anaerobic threshold (AT) and heart rate response (HRR) expressed as $(HR_{peak}-HR_{rest})/(VO2_{peak}-VO2_{rest})$. Whereas the original algorithm uses adult cut-off points, in this study values were

adapted to the pediatric population, based on earlier work from our laboratory regarding maximum exercise testing parameters in healthy children (34).
In this algorithm, VE_{peak}/VCO_{2peak} is a general indicator of the efficiency of the both the lungs and gas exchange; high values (VE_{peak}/VCO_{2peak} >36) suggest gas exchange difficulties. Since FEV_1 was not measured and no known pulmonary problems were present, it was assumed that ventilatory reserve in all children was normal. HRR refers to the increase in HR in relation to the increase in VO_2. An excessive increase in HR (> [-6.25 x age] + 150) might reflect either cardiac disease or deconditioning. In our patients no known cardiac history was present and therefore increased HRR was considered an indicator of deconditioning rather than cardiac disease. AT occurring at less then 40% VO_{2peak} was considered an indicator of poor circulatory or "pump" limitation. When no ventilatory or cardiac limitations were present, patients were considered to be limited by "other limitations".

Functional ambulation

The following functional parameters were measured based on the 6MWT: (1) Six-minute walking distance (6MWD) and percentage of predicted 6MWD. Predicted 6MWD was calculated using the formula of Li and Yin et al. (35), based on heart rate increase and sex (see equation 1 and 2);(2) O_2 rate as uptake per minute (ml/kg/min).

Equation 1. Boys $554.16 + ((HR_{6min} - HR_{rest}) \times 1.76) + (\text{height (cm)} \times 1.23)$
Equation 2. Girls $526.79 + ((HR_{6min} - HR_{rest}) \times 1.66) + (\text{height (cm)} \times 0.62)$

Steady state was taken as the average value over the period during which oxygen uptake changed less than 5% (14) ; (3) Subsequently, the following parameters were derived: Speed (meter/min), calculated as 6MWD/6; O_2 cost (ml/kg/meter), calculated as O2 rate/speed (12) ; individual strain ($O_2 rate_{steady\ state}/VO_{2peak}$ x 100% and maximum HR_{6mwt}/HR_{peak} x 100%)

For all measurements, t-tests were used to test differences between normal and community ambulators after testing for normal distribution and equality of means. When this was not the case (VO_{2peak}), Mann-Whitney U-test were used. For the

correlation between VO_{2peak} and O_2 expenditure, a Spearman Rho was calculated. Significance level was set at $p<0.05$. Statistical analyses were performed using SPSS for Windows (version 15.0, SPSS Inc, Chicago, Ill.).

RESULTS

Population

The study population consisted of 23 children (13 boys/11 girls, age 6 – 17) with either SB aperta (n = 16) or SB occulta (n = 7). Children's age, height, weight and BMI are described in table 2. The level of lesion, classified according to the ASIA guidelines (3) and the ambulation level are presented in table 3.

Table 2. Subjects characteristics.

	Mean (SD)	Z scores (SD) compared to reference values
Age (years)	10.4 (3.1)	
Height (meters)	1.4 (0.18)	-009
Weight (kg)	37.5 (12.7)	.4
BMI (kg/m^2)	18.4 (2.9)	1.4

Table 3. Level of lesion and functional ambulation level

	Number (%)
Level of lesion	
L5-S1	10 (43.5)
S1-S4	6 (26.1)
No motor loss	7 (30.4)
Ambulation level	
Normal ambulator	17 (74)
Community ambulator	6 (26)
Use of orthotics	13 (56)

Peak oxygen uptake and other peak parameters

Out of 23 children, 21 performed the treadmill test without any significant problems. Two did not participate due to anxiety (n=1) or pain during ambulation (n=1). VO_{2peak}, VO_{2peak}/kg , HR_{peak}, VE_{peak}, VCO_{2peak} and RER_{peak} and their Z-scores are presented in Table 4.

Table 4. Descriptives of exercise testing in 21 children with SB.

	Mean (SD) All children	Z score (SD)	Mean (SD) NA	Z scores (SD)	Mean (SD) CA	Z scores (SD)
VO_{2peak} (l/min)	1.28 (.57)	-2.2#	1.39 (.58)	-1.9	.85 (.24)	-3.6#*
VO_{2peak}/kg (ml/kg/min)	33.14	-2,9#	34.77	-2.5#	26.2*	-4.5#*
HR_{peak} (beats/min)	172.2 (21.2)	-3.4#	175.5 (20.8)	-3.0#	158.5 (19.1)	-5.0#*
$V'E_{peak}$ (l/min)	45.6 (19.1)	-2.4#	49.3 (19.3)*	-2.0	30.0 (7.0)	-3.8#*
VCO_{2peak} (l/min)	1.30 (.63)	NA	1.42 (.65)	NA	.82 (.24)*	NA
RER_{peak} (VCO_2/VO_2)	1.00 (.13)	-2.1#	1.01 (.14)	-2.0	.97 (.2)	-2.4#

Legend: * = p<0.05 between normal and community ambulators; # = Z-scores > -2SD; NA = normal ambulator; CA = community ambulator; all Z-scores are in SD compared to reference values

One tailed t-test showed a significant difference between the normal and community ambulators for Z-scores of VO_{2peak}, VO_{2peak}/kg, HR_{peak}, VE_{peak} scores and outcomes of VCO_{2peak} and VO_{2peak}/kg. Normal ambulators showed higher scores for both ventilation, VO_{2peak} and VCO_{2peak}. Ventilatory equivalents for both carbon dioxide and oxygen (VE_{peak}/VCO_{2peak} and VE_{peak}/VO_{2peak}) did not differ, but were high in both groups.

Limiting factors using Eschenbacher's and Mannina's algorithm.

Eighty-five percent of complete test data (n=20) scored below 90% of predicted VO_{2peak}, indicating lower levels of fitness than expected.

Table 5. Cut-off points in the algorithm by Eschenbacher and Maninna as measured in 21 children with SB.

	Mean	Range	Used cut off points	Indicative for	% reaching critical values
VO_{2peak} pred (%)	79.6	51 – 120	< 90%	Low VO_{2peak}	(85%)
VE/VCO_{2peak}	36.6	27.6 - 52.7	> 36	Ventilatory limitations	(35%)
HRR	88.5	-.33 - 182.7	> (-6.25 x age) + 150	Deconditioning and/or muscular limitations	(47%)
AT%	72.3	35.8 - 98.86	< 44	Cardiovascular limitations	(6%)

Note: VE/VCO_2, HRR and AT% are being shown for those VO_{2peak} pred < 90% (n=18)
Legend: HRR = heart rate reserve; AT = anaerobic threshold.

Looking at the limiting factors, 47% showed signs of "other limitation" e.g. muscular deficiency and/or deconditioning, as indicated by high heart rate response (HRR). Thirty-five percent showed possible signs of insufficient gas exchange at the pulmonary level, as indicated by VE_{peak}/VCO_{2peak} > 36.

Functional ambulation

Ambulation parameters from 22 children were analyzed. Results are shown in Table 6 and Figures 1 and 2.

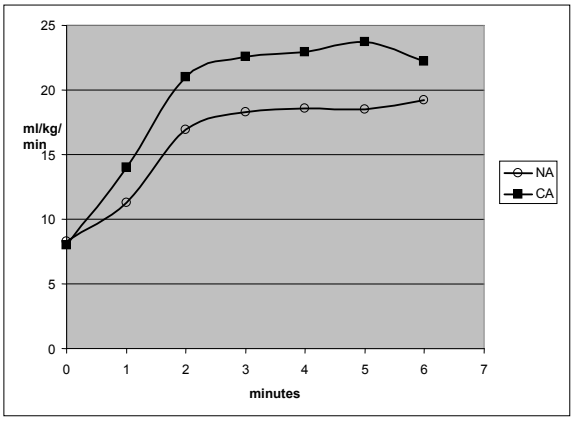

Figure 1. O_2 rate during 6MWT comparing normal and community ambulators

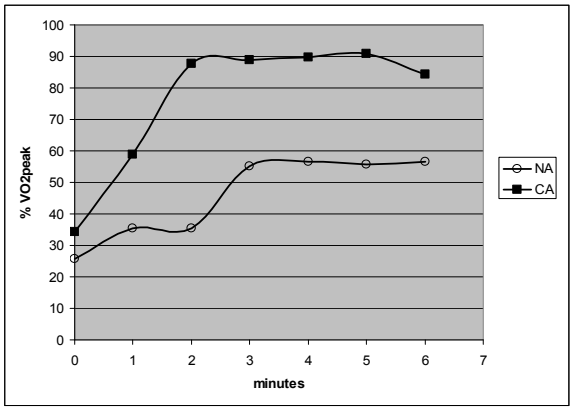

Figure 2. $\%VO_{2peak}$ during 6MWT comparing normal and community ambulators

A steady state was reached in 20 children after the second or third minute of walking in both groups. A difference between normal and community ambulators is clear throughout the 6MWT, with significant differences starting during minute 2. Average distance walked was 391.4 (± 61) meters, which was 48.5% of predicted distance. Significant differences were seen between the community and normal ambulators regarding distance ($p < 0.01$), % predicted distance ($p < 0.05$), speed ($p < 0.01$), oxygen rate ($p < 0.05$), oxygen cost ($p < 0.0005$), maximum HR reached during 6MWT ($p < 0.015$), $\%VO_{2peak}$ ($p < 0.0001$) and $\%HR_{peak}$ ($p < 0.04$). Figure 1 and 2 show O_2 rate and $\%VO_2$ during the 6MWT.

Percentage VO_{2peak} during the 6MWT averaged 63.1% (± 20%), with significant differences between normal and community ambulators (55.9% vs 90.2%). Similar differences were seen for $\%HR_{peak}$, respectively 75.0 versus 97.6% for normal versus community ambulators.

Table 6. **Outcomes of 6MWT.**

	Mean (SD) All children	Mean (SD) Normal ambulators	Mean (SD) Community ambulators
6MWD (meters)	391.4 (61)	408.5 (57.2)	333.4 (30.6)*
Predicted distance (%)	48.5 (8.3)	50.2 (8.3)	41.1 (2.7)*
Mean O_2 rate (ml/kg/minute)	18.5 (3.9)	17.6 (3.3)	21.9 (4.8)*
O_2 rate $_{steady\ state}$ (ml/kg/minute)	20.0 (3.9)	19.3 (3.5)	22.9 (4.3)
$HR_{max6MWT}$	134 (18)	129 (15)	150 (14)*
O_2 cost (ml/kg/meter)	0.3 (0.09)	0.27 (0.06)	0.43 (0.07)*
% VO_{2peak} **	63.1 (20)	55.9 (14.3)	90.2 (7.6)*
$\%HR_{peak}$	80 (14.8)	75 (11.6)	97.6 (11.6)*
Speed (km/hr)	3.9 (.6)	4.1 (.6)	3.3 (.3)*

Legend: * = $p<0.05$ between normal and community ambulators;**measured during steady state

Both O_2 rate and O_2 cost were high with significant differences between normal and community ambulators (17.6 vs 21.9 ml/kg/min and 0.27 vs 0.43 ml/kg/m). The community ambulators walked more slowly and thus covered less distance, while performing the task at a much higher percentage of their maximum capacity and at the same time requiring more energy during locomotion.

Correlation between VO_{2peak} and oxygen utilization during ambulation

Both O_2 rate and O_2 cost during 6MWT correlated negatively with VO_{2peak} (respectively r_{sp}= -0.56 ($p < 0.001$) and r_{sp}= -0.76 ($p < 0.001$)), indicating lower energy expenditure during locomotion in children reaching higher VO_{2peak}.

DISCUSSION

Peak oxygen uptake

The first purpose of the study was to determine why ambulatory children with SB showed significantly reduced levels of VO_{2peak} compared to healthy peers. Despite subjective signs of peak effort, the treadmill testing resulted in both low HR_{peak} and RER_{peak} values, calling into question the true maximal character of the testing procedures. Currently we are using a protocol of Rossiter et al. (36) using a supra-maximal step (105-110% of last reached speed) to determine whether the regular protocol yields true maximum values or whether a different approach in exercise testing should be used in children with SB. At the same time the low HR_{peak} seems to be in line with other studies regarding exercise testing in children with SB (10;28) with HR_{peak} ranging from 130-185 beats per minute. In one of these studies (10) HR_{peak} seems negatively related to level of lesion. Another explanation for low HR_{peak} could be that exercise capacity in children with SB is not limited by the cardiovascular system, but by muscular components.

Using the algorithm (33), limiting factors in exercise capacity in ambulatory children with SB indeed seem to be mostly “deconditioning and/or muscular” components. Muscular limitations can partly be explained by the disease itself. Lower muscle mass in children with SB results in lower VO_{2peak}. VO_{2peak}/kg was even more reduced. This is likely a result of the different body composition in these children with less active muscle mass and increased fat mass (37). In contrast with the muscular consequences of the disease, atrophy and muscular inefficiency as a result of disuse and sedentary lifestyle can be expected to improve through a training program. In the studied population, not only was exercise capacity reduced, they also showed lower strength above the lesion level and a sedentary lifestyle (16). In combination with a high HRR, the muscular limitations identified in this study seem partly due to deconditioning. Exercise programs aimed at

improving physical fitness in ambulatory children with SB are scarce, but they do show significant improvements in both strength and endurance (38-40).
In this study high ventilatory equivalents were found for both VCO_2 and VO_2, which could be an indicator of ventilatory limitations. These findings are consistent with one other study reporting on pulmonary dysfunction due to restrictive lung disease and respiratory muscle weakness in children with SB during exercise (28).
Another possible explanation for these high ventilatory equivalents might be the presence of a Chiari II malformation, often present in children with SB. This malformation affects the brain stem and is known to influence both O_2 and CO_2 peripheral chemoreceptor function in children with SB (41;42). Future studies should include assessment of ventilatory reserve during exercise, so that a distinction can be been made between the different causes of pulmonary limitations, e.g. diffusion type versus gas exchange versus mechanical limitations.

Functional ambulation

Our second purpose was to determine the relationship between VO_{2peak} and functional ambulation. The 6MWT is a submaximal test of functional exercise capacity (35). One of the main outcomes is the distance walked. In our study only half of the predicted distance was reached. A likely reason for reduced 6MWD is reduced muscle strength resulting in decreased motor control and an altered gait pattern leading to high energy expenditure (12;43). In this study, both O_2 rate and O_2 cost were indeed high compared to values for healthy children, which range in the literature from 12-18 ml/kg/min and 0.18-0.27 ml/kg/m. In the literature values for O_2 rate and O_2 cost during ambulation in children with SB range from 17.5 -19 ml/kg/min and from 0.28-0.47ml/kg/m (43;44). The O_2 rate in our study was higher, while the cost ranged from 0.27 ml/kg/min in normal ambulators to 0.43 ml/kg/min in community ambulators. These other studies used different protocols regarding both mode of testing (treadmill versus level ground), walking speed (self-selected versus imposed) and preparation of the subjects, factors hinderomg comparison between the studies. Therefore we are using new protocols, proposed in recent literature (14;45) in our current study.
Another interesting result from this study is the individual level of strain during locomotion. Community ambulators showed a much higher HR during the 6MWT

than normal ambulators. Studies in healthy children show HR reached during the 6MWT to be around 134 beats per minute, which is similar to the normal ambulators (46;47). Looking at the intensity of ambulation, community ambulators performed this task at a very high level of individual strain (91% VO_{2peak} and 97.6% HR_{peak}). Studies in healthy children reach 65%-70% of HR_{peak} during the 6 MWT (48). One explanation for this could be the low HR_{peak} reached during the exercise test. But as mentioned above the community ambulators reached a high HR during the 6MWT. In combination with high oxygen utilization, the effort of walking remains high.

Correlation between VO_{2peak} and oxygen utilization during ambulation

VO_{2peak} values were related to oxygen utilization during locomotion. This indicates lower levels of peak oxygen uptake are associated with both higher oxygen rate and oxygen cost during locomotion. Rate is indicator of strain or effort, which might explain the level of fatigue during locomotion. Reybrouck et al observed similar trends in treadmill testing when comparing children with chronic fatigue with healthy peers, concluding that high individual strain was associated with early fatigue (49).

Energy cost is an indicator of efficiency (14). From the literature it is known that energy cost of locomotion in people with disabilities can be improved by training (50;51), so future research should also look at the effects of training to reduce the energy cost during locomotion in ambulatory children with SB.

Limitations of the study

Questions could be raised with regards to use of a treadmill protocol. Other studies (52-54) have used upper extremity ergometry. An advantage of arm ergometry in this population could be that the muscles tested are less involved in the disease process. In this way the outcomes of the test might more closely reflect cardiorespiratory limitations in exercise testing. On the other hand, upper extremity ergometry has been known to result in lower VO_{2peak} values, due to the smaller muscle mass being involved in testing (55). In this study a treadmill protocol was chosen for several reasons. First, for all children, ambulation was the main mode of transportation. In this case it is recommended to use a treadmill for maximum

exercise testing, due to the specificity of testing (56). Secondly, we were interested in comparing outcomes from the peak exercise test to other ambulation parameters. If we had used arm ergometry, these comparisons would be hard to interpret due to the differences in physiological responses between arm ergometry and treadmill testing. In this study the 6MWT was performed using an eight meter track. Looking at the studies establishing reference values (35;47;57) for the 6MWD in children, a 20 meter track seems to result in a longer 6MWD. In this study however, the children were walking with a significantly lower speed as compared to healthy children reducing the importance of the shorter distance between the turning points. Despite this shorter track a steady state of O_2 utilization was reached by all, but two children. Currently we are working with the more commonly used 20 meter track.

CONCLUSION

Lower levels of VO_{2peak} in ambulatory children with SB seem to be related to muscular and /or deconditioning components rather than cardiopulmonary deficiencies. Future exercise testing in ambulatory children with SB should include evaluation of the ventilatory reserve to better determine possible ventilatory limitations.

Both O_2 rate and O_2 cost during locomotion are high in ambulatory children with SB, even in those considered to be normal ambulators. Oxygen utilization correlated negatively with VO_{2peak}. Overall, community ambulators showed significantly worse outcomes than normal ambulators. At the same time, the normal ambulators only walked half of the predicted distance at high O_2 rate and O_2 cost. Future training programs for ambulatory children with SB should focus on improving VO_{2peak} and muscular endurance, as well as decreasing energy expenditure during locomotion to increase physiological reserve.

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Reproducibility of Energy Cost of Locomotion in Ambulatory Children with Spina Bifida

Chapter 4

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Abstract

Objectives: Many ambulatory children with Spina Bifida (SB) experience functional decline in ambulation despite stable or even improving motor exams. Improving or maintaining low energy cost of locomotion during childhood and throughout the teenage years, could be an important goal for children and adolescents with SB. Purpose of this study was to determine reproducibility of energy expenditure measures during gait in ambulatory children with SB.

Design: Reproducibility study.

Setting: Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands.

Participants: Fourteen ambulatory children (6 boys/ 8 girls) with SB. Mean age was 10.8 years (± 3.4).

Methods: Net and gross energy expenditure measures during locomotion were determined during a six-minute walking test. These measures consisted of energy consumption (ECS), expressed in J/kg/min, and energy cost (EC), expressed in J/kg/m. For reliability, the intra-class coefficient (ICC) was determined. For agreement, the smallest detectable difference (SDD) was calculated.

Results: ICCs vary from 0.86 to 0.96 for both EC and ECS. The SDD ranges from 18-24 % for gross measures, up to over 30% for net values.

Conclusion: Reproducibility of energy expenditure during ambulation in children with SB should be considered carefully when using these measures in the evaluation of gait. High reliability of energy expenditure measurements makes these measurements appropriate to use as discriminative tools in children with SB, while agreement of only gross EC seems acceptable to use as an evaluative tool in children with SB. Overall, measures of reliability and agreement seem higher in young children when compared to adolescents. Further research is recommended to determine clinically relevant changes in energy expenditure in children with SB.

INTRODUCTION

Spina bifida (SB) is the most frequent congenital deformity of the neural tube, with an incidence of approximately 1 per 1000 live births (1, 2). Depending on both the type and level of lesion of the SB, patients experience a variety of deficits in cognition, motor function, sensory function and bowel and bladder function (3). Besides medical classification according to type, lesion level and presence of hydrocephalus, children are functionally classified using the adapted Hoffer classification (4). In this classification community ambulatory children are distinguished from normal ambulatory children, based on the use of a wheelchair or other devices of locomotion for longer distances.

About 20% of the lesions occur at the sacral level, enabling them to be, in most cases, community or normal ambulatory. Looking at prognosis and development of SB, a 25-year cohort study found a decline in ambulation as the main mode of locomotion from 95% at age 0-5 to 46% at age 20-25 in patients with SB, despite stable or even improving motor exams in respectively 73% and 16% of the patients (5). At the same time, ambulation level during teenage years seemed predictive of ambulation as the main mode of locomotion as young adults. Thus, improving or maintaining efficient ambulation during childhood and throughout the teenage years, may be an important goal for ambulatory children and adolescents with SB. Earlier studies have shown higher levels of energy expenditure during ambulation in patients with SB (6-15), compared to healthy children. These studies, however, are hard to interpret and compare, as different protocols were used regarding both mode of testing (treadmill versus level ground), walking speed (self-selected versus imposed), calculation of energy cost, and preparation of the subjects (see Appendix 1).

Moreover, they often do not report true energy expenditure in caloric units or Joules, but rather oxygen expenditure (VO_2). Since substrate utilization (fatty acids versus carbohydrates) per liter oxygen results in different amounts of energy expenditure, this is an important distinction. For these reasons, new methodology has been proposed in recent literature to evaluate energy expenditure during gait (16-18). These changes include (1) use of energetic outcomes versus oxygen utilization and (2) net versus gross outcomes.

Studies in different populations have shown improvement in energy expenditure, again measured in different ways, after training (19, 20) or orthopedic interventions (13). In order to use energy expenditure during locomotion as an outcome measure in the rehabilitation process of children and adolescents with SB, information is needed regarding reproducibility of energy expenditure in this population. In the literature regarding reproducibility of energy expenditure measures in children with CP, new methodology has been proposed (16, 18, 21). For energy expenditure measures in children with SB, this new methodology has not yet been applied. Furthermore, information regarding the reproducibility of energy expenditure measures in children with SB is lacking. Therefore, the purpose of this study was to determine the reproducibility of both gross and net energy expenditure during gait in ambulatory children and adolescents with SB.

METHODS

Study population

This study was part of a larger study (The *U*trecht *S*pina Bifida *A*nd *G*raded *E*xercise (USAGE) study) regarding exercise and functional capacity testing in ambulatory children with SB. Study procedures took place at the department of pediatric physical therapy and exercise physiology of the Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands 2007 and 2008. All study procedures were approved by the University Medical Ethics Committee.

Children were included when they were (1) at least community ambulatory, (2) able to follow instructions regarding testing and (3) between 6 and 18 years of age. Parents and children signed informed-consent forms prior to testing. Exclusion criteria were medical events that might interfere with the outcomes of the testing and/or medical status that did not allow maximum exercise testing.

Measurements

Demographics

Data concerning medical history were obtained from medical records. These data included type of SB, motor level of lesion, use of orthotics, ambulation level, age, pubertal staging and sex.

Energy expenditure

During rest and ambulation, physiologic responses were measured using a heart rate (HR) monitor (Polar) and calibrated mobile gas analysis system (Cortex Metamax B^3, Cortex Medical GmbH, Leipzig, Germany) for breath-by-breath analysis. All measurements and calibration were performed according to the manufacturer's instructions and guidelines. The mask was checked for possible leakage throughout the test. The Cortex Metamax is a valid and reliable system for measuring gas-exchange parameters during exercise (22, 23).

Test protocol

Each test consisted of a resting measurement and measurements during ambulation. Resting measurements were recorded while participants were seated in a chair for five minutes. Energy expenditure during locomotion was measured during a six-minute walking test (6MWT). The test was performed on a twenty-meter track in a straight corridor. Patients were instructed to cover the largest possible distance in six minutes at a self-selected walking speed. The test and encouragements during the test were performed in accordance with the American Thoracic Society guidelines (24). The distance walked was recorded to calculate speed. Re-test took place two weeks later, with the children being tested during the same time of day.

Energy expenditure analysis

Steady state (SS) normalized oxygen consumption (VO_2/kg/min) was calculated as the average value over the period during which oxygen consumption changed 5% or less. For this purpose, VO_2 was plotted for visual inspection (see Figure 1).

Within the period of least differences, a SS of two minutes was determined. Respiratory exchange ratio (RER) was calculated as VCO_2/VO_2 during steady state. Speed (m/min) was calculated as distance (m)/6 (min). Subsequently the following parameters were derived: Resting energy consumption (ECS_{rest}), gross energy consumption (ECS_{gross}). Net energy consumption (ECS_{net}) was calculated as the difference between ECS_{gross} and ECS_{rest}. ECS was expressed in J/kg/min, using VO_2 and RER in the following equation: J/kg/min = (4.960 x RER during steady state + 16.040) x VO_2/kg (25) . Furthermore gross energy cost (EC_{gross}) and net energy cost (EC_{net}), expressed in J/kg/m, were calculated, dividing respectively ECS_{gross} and ECS_{net} by speed.

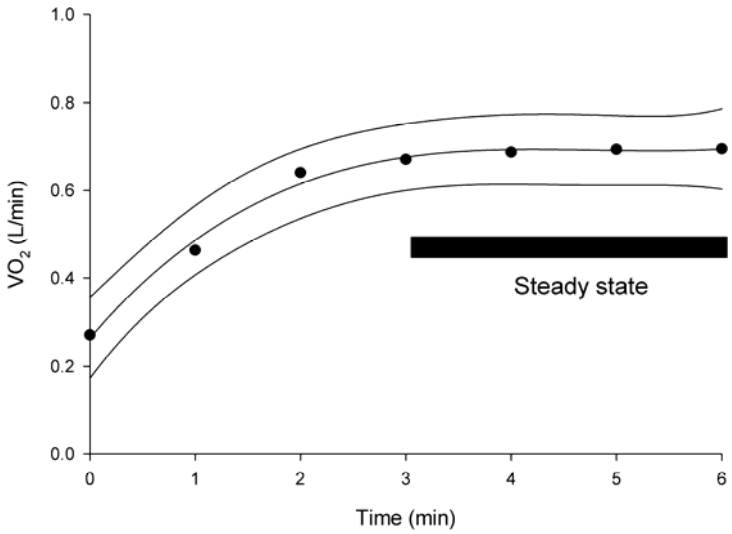

Figure 1. Example of steady state determination during six-minute walk test.

Statistical Analysis

For initial analyses, data were checked for normality and heteroscedasticity, the latter referring to the degree of variability depending on the outcome of the measurement. Heteroscedasticity was defined as a correlation coefficient between the differences of test–retest and the mean of the observations greater than 0.3 (26). At the same time, a visual interpretation of Bland and Altman plots was

performed to check for heteroscedasticity. All data were distributed normally and heteroscedasticity was not present.

T-tests were performed for test and retest data, with significance level set at $p < 0.05$. Reproducibility encompasses both reliability and agreement (27). For reliability, the intra-class correlation$_{consistency}$ (ICC) was calculated using the following formula: variance$_{patient}^2$ / variance$_{patient}^2$ + variance$_{residual}^2$ (27). An ICC of 0.8 or higher was considered good (28).

For agreement, the Standard Error of Measurement (SEM) and the Smallest Detectable Difference (SDD) were calculated, using the following equations: SEM = SD * $\sqrt{}$ 1- ICC$_{consistency}$ and SDD = 1.96 * $\sqrt{}$ 2 * SEM. SDD was also expressed as a percentage of the mean score (27, 28). Secondary analysis included (1) t-tests between normal and ambulatory children and between prepubertal children and pubertal adolescents and (2) recalculation of ICC and SDD for the pubertal groups. Statistical analyses were performed using SPSS for Windows (version 15.0, SPSS Inc, Chicago, Ill.).

RESULTS

Population

The study population consisted of 14 ambulatory children (6 boys/ 8 girls) with SB. Mean age was 10.8 years (± 3.4), height 1.0 m (± 0.2) and weight 38.4 kg (± 18.7). The motor level of lesion (classified according to the American Spine Injury Association guidelines (29)), and the ambulation level are presented in Table 1.

Table 1. Level of lesion, ambulation level and anthropometrics of participants

	Number (%)
Level of lesion	
L3-L4	1 (7)
L4-L5	10 (72)
S1-S4	1 (7)
No motor loss	2 (14)
Ambulation level	
Normal ambulatory	8 (57)
Community ambulatory	6 (43)
Anthropometrics	Mean (SD)
Height (meters)	1.0 (0.2)
Weight (kg)	38.4 (18.7)
BMI (kg/m^2)	18.6 (3.0)
Z-scores BMI	+1.1 (1.2)

Energy expenditure during ambulation

All children completed the six-minute walking test and retest without difficulties. Results include data from all children. Outcomes from both test and retest can be found in Table 2. T-tests showed no significant differences between test and retest for any of the outcome measures ($p < 0.05$ for all measures).

Table 2. Mean energy expenditure outcomes during test and retest

	Test (SD)	Retest (SD)	Difference (Test-retest)
Speed (m/min)	70.0 (13.8)	70.4 (14.8)	-0.4
ECS rest (J/kg/min)	162.9 (62.1)	160.5 (70.5)	2.4
ECS gross (J/kg/min)	441.6 (99.6)	465.1 (107.4)	-23.4
EC gross (J/kg/m)	6.5 (1.8)	6.8 (2.2)	-0.3
ECS net (J/kg/min)	278.7 (94.9)	304.4 (93)	-25.8
EC net (J/kg/m)	4.0 (1.4)	4.4 (1.6)	-0.4

Legend: ECS = energy consumption; EC = energy cost

Reproducibility of energy expenditure during ambulation

Reproducibility measures for speed and both gross and net energy expediture can be found in Table 3. ICCs vary from 0.86 and 0.88 for net EC and ECS to 0.96 for resting ECS. ICC for speed is 0.97. The SDD for speed is 6.8 m/min. SDDs for ECS range from 36.8 to 89.4 kJ/kg/min and from 1.5 to 1.7 kJ/m for EC.

Table 3. Reproducibility data for speed and energy expenditure in children with SB

	ICC	Pearson	SEM	SDD	SDD%
Speed	0.97	0.97	2.5	6.8	9.7
ECS rest	0.96	0.96	13.3	36.8	22.8
ECS gross	0.91	0.91	31.0	86.1	18.9
EC gross	0.91	0.92	0.6	1.7	24.8
ECS net	0.88	0.88	32.3	89.4	30.5
EC net	0.86	0.86	0.6	1.5	37.0

Legend: ECS = energy consumption; EC = energy cost

To gain more insight in the clinical value of the SDDs, unpaired t-tests were performed to analyze differences between community (n=6) and normal ambulators (n=8). Only gross EC and speed differed significantly among the groups. The difference in speed was 20.8 m/min ($p = 0.01$) while the difference in gross EC was 2.4 J/kg/m ($p = 0.02$), with normal ambulatory children walking faster at a lower cost.

Table 4. Differences between normal and community ambulatory children

	Nomal ambulatory (SD)	**Community ambulatory (SD)**	**Difference**	**P value**
Speed (m/min)	77.9 (8.4)	57.1(12.5)	20.8	0.01*
ECS rest	148.7 (39.9)	179.1 (91.4)	30.4	0.41
ECS gross	443.2 (56.9)	467.0 (147.3)	23.8	0.68
EC gross	5.7 (0.6)	8.1 (2.4)	2.4	0.02*
ECS net	294.5 (64.9)	287.8 (125.1)	6.6	0.89
EC net	3.7 (0.7)	4.9 (2.04)	1.2	0.13

Legend: * significant differences between normal and community ambulatory children; ECS = energy consumption; EC = energy cost

Looking at pubertal groups, only ECS_{rest} differed significantly among the pubertal versus prepubertal children (120 J/kg/min (SD 26.4) versus 193.1 J/kg/min (SD 71)). In this population, all prepubertal children were younger than twelve years of age and those in later stages of puberty older than twelve years of age. Further analysis showed higher ICCs and lower %SDD for all energy expenditure measures in the younger children compared to the adolescents (see Table 5).

Table 5. Reproducibility data for speed and energy expenditure in children with SB younger versus older than 12 years of age

	ICC <12	ICC >12	SDD% <12	SDD% >12
ECS rest	0.97	0.73	17.7	31.7
ECS gross	0.98	0,7	14.9	27.6
EC gross	0.93	0.85	11.0	38.0
ECS net	0.93	0.7	27.6	36.9
EC net	0.92	0.85	25.5	33.3

Legend: ECS = energy consumption; EC = energy cost; <12 = younger than twelve years of age; >12 = older than 12 years of age

DISCUSSION

The purpose of this study was to determine the two aspects of reproducibility (reliability and agreement) of both gross and net energy expenditure during gait in ambulatory children and adolescents with SB. Reliability of all energy expenditure measurements and speed in ambulatory children with SB can be considered good to excellent, with ICCs varying from 0.86 for net EC to 0.97 for speed. This means measurement of energy expenditure during gait can correctly distinguish higher scores from lower scores. These ICCs are comparable with those reported in the literature, ranging from 0.82 – 0.99 in children with CP and from 0.59-0.89 in healthy children (18).

For clinicians, agreement of the measurements is more of interest, because they look to determine meaningful improvements in a single patient. From the results of this study, we can conclude that improvements of 86.1 J/kg/min (19%) and 1.7 J/m (25%) are needed for respectively ECS_{gross} and EC_{gross} to interpret a change as

true improvement. For net energy expenditure, improvements even need to exceed 30%, while the SDD for speed remained below 10% or 6.8 m/min. Again, these outcomes are comparable to the existing literature regarding agreement for energy expenditure in children with ambulatory difficulties, except for a much lower SDD reported for EC_{gross} (18). In healthy children, Thomas et al. (21) have shown the coefficient of variation (CV) for gross ECS and EC in healthy children to be around 9-10%, while variability in net measures increased to 14-15%. To deal with the moderate agreement of energy expenditure in patients with ambulatory difficulties, modifications have been proposed to improve reproducibility of energy expenditure of locomotion (16). While these methodological changes might improve scientific outcomes, questions remain regarding the practical implications of needing several repetitions of these expensive and "high-tech" measurements for four weeks in a row, to establish a baseline measurement in the clinical setting. Schwartz et al. (30) have shown a reduction in variation of energy expenditure in healthy adults and adolescents by calculating a non-dimensional speed, using leg length. In our current randomized clinical trial, we are using this simple modification for the assessment of net non-dimensional consumption and cost.

Another important issue, when looking at the SDD, is its relation to clinical relevant change (CRC). What we don't know is how ECS and/or EC relate to improvement or deterioration in functional status of patients with ambulatory difficulties and this should be a topic of future intervention research. Secondary analysis in our group showed significant differences of 2.4 J/kg/m for gross EC between normal and community ambulation levels. In light of these findings, an SDD of 1.7 J/kg/m for gross EC seems acceptable to use as a clinical marker. In a longitudinal study of Thomas et al., including children with both thoracic and lumbar lesions, gross oxygen cost – not energy cost - was more than 100% higher in children who became non ambulatory, compared to those who remained ambulatory in a three year period (9). Recalculating the data from the children with lumbar and sacral lesions only, it is interesting to see a 30% difference in gross oxygen cost between the future walkers and non-walkers at the beginning of the three year period. It seems that in this context as well, the SDD of 24.8% of gross EC might be small enough to mark clinically important differences.

As in other studies, gross measurements seem less variable than net measurements. This is probably due to the high variability in measuring resting ECS. Net values are particularly important when interested in follow-up over a period of years, as growth and maturation change oxygen utilization and speed of walking (31-33), where gross values can be used in shorter follow-up (16).
Because our resting energy values were high compared to those mentioned in the literature (18, 34), we tested differences of resting as well as gross and net energy expenditure between children younger than twelve years of age and those older than twelve years of age, coinciding with prepubertal versus pubertal staging. One interesting finding from this analysis was a much higher agreement of both net and gross energy expenditure measures in children under twelve years of age compared to the older children. Looking at these results, changes of 15% and 11% in, respectively, gross ECS and EC can be detected in young children. The adolescents still showed a larger intra-variability. This is an interesting finding in itself because it raises the question of whether this increased variability of energy cost might be an indicator or marker of (future) decline in ambulatory function often seen during the adolescent years. Considering the small sample size of both groups, these results should be interpreted with caution, but yield for future research looking into these differences.

Limitations of the study

The large variability and poor reproducibility of resting ECS, makes further discussion about net values unnecessary, except that these measures need further improvements. Our protocol consisted of five minutes of sitting in a chair, without talking or moving around, with children refraining from eating or drinking at least one hour before measurements. The mean resting ECS in this study is higher than reported by Littlewood et al. (34). They reported a resting metabolism of approximately 120 J/kg/min in children with SB, measured with a fasting protocol and lying down for 10 minutes. Despite their strict protocol, a large inter-subject variability was reported in children with SB, which is in line with the findings in our study. Higher resting values are most likely due to our protocol and the younger age group included in our study. Measures to increase reproducibility could include lying down, longer familiarization with the equipment and a longer fasting period.

Again, while of interest for scientific purposes, these measures are harder to implement in the daily clinical practice.

Further questions could be raised regarding the use of the six-minute walking test (6MWT) for measuring steady state energy expenditure. In healthy populations, encouragement to cover the largest possible distance could result in discontinuous fast speed, not appropriate for determining steady state. Ambulatory children with SB are limited in their speed by decreased coordination and motor control. In this study, a constant walking velocity throughout the 6MWT was observed, consistent with other gait studies including pathologic gait patterns (31).

Finally, increased variability in EC compared to variability in ECS contrasts with results in other studies (16, 18, 21), where EC shows less variability than ECS. This could be due to a fast and uncomfortable walking velocity or leakage from the mask. Looking at the secondary analysis though, this only seems to be the case for the older children, limiting the role of the procedures used in this study.

CONCLUSION

Reproducibility of energy expenditure during ambulation in ambulatory children with SB should be considered carefully, when using these measures in the assessment or evaluation for this population. Reliability of energy expenditure measurements in ambulatory children with SB is good to excellent, supporting the use of these measures for discriminative purposes in this population. Agreement for gross energy cost seems acceptable to use in the clinical evaluation of energy expenditure in children with SB, with a SDD of 1.7 J/kg/m. Overall, measures of reliability and agreement are superior in younger children compared to adolescents. While the concept of measuring energy expenditure during ambulation is a promising concept, future research should focus on (1) how changes in energy consumption and/or energy cost relate to improvement or deterioration in functional status of patients with ambulatory difficulties and (2) the possible increased variability of measurements of ECS in adolescents with SB.

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Appendix 1. Overview of protocols to measure energy expenditure in children with SB.

Authors	Subjects (n)	Age in years	Test Protocol	Outcome measures *
De Groot et al. 2008	23	6-18	Walking a six-minute walk test in a straight corridor	Gross oxygen expenditure
Bartonek et al. 2002	8	5-14	Walking as far as possible	$HR_{walk} – HR_{rest}$
Bartonek et al. 2001	53	3-11	Walking as far as possible	$(HR_{walk} – HR_{rest})$/Speed
Bare et al. 2001	14	7-12	Treadmill walking at four different velocities: 75% - 100% - 150% of self selected speed and velocity of an aged matched healthy peer	Gross oxygen expenditure
Thomas et al. 2001	23		Walking on an oval track at self selected speed	Gross oxygen expenditure
Duffy et al. 2000	12	6-16	Walking 10m laps in the gait lab until steady state was reached	Gross oxygen expenditure
Duffy et al. 1996	21	5-12	Walking 10m laps in the gait lab at a self selected speed	Gross oxygen expenditure
Williams et al. 1983	15	5 -12	Walking outside on a 60.5m oval level track at a faster velocity than their own choice	Gross oxygen expenditure
Evans and Tew 1981	22	10-16	Walking at their customary walking speed over a standardized flat, tiled floor course	Gross energy expenditure (Kcal/min and Kcal/m), not normalized for body mass

* Gross oxygen expenditure includes both oxygen consumption (ml/kg/min) and oxygen cost (ml/kg/m)

Treadmill testing in ambulatory children with Spina Bifida: does peak oxygen uptake reflect maximum oxygen uptake?

Chapter 5

de Groot JF, Takken T, de Graaff S, Gooskens RH, Helders PJ, Vanhees L.
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ABSTRACT

Objectives: To determine whether VO_{2peak} measured during an incremental treadmill test is a true reflection of VO_{2max} in ambulatory children with SB.

Design: Cross-sectional study.

Setting: Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands.

Participants: Twenty ambulating children with SB.

Methods: VO_{2peak} was measured during a graded treadmill exercise test. Validity of VO_{2peak} was evaluated by using (1) Rowland's guidelines for maximum exercise testing in healthy children and (2) differences between VO_{2peak} and VO_2 during a supra-maximal protocol ($VO_{2supramaximal}$).

Results: VO_{2peak} and normalized VO_{2peak} averaged respectively 1.23 ± 0.6 l/min and 34.1 ± 8.3 ml/kg/min. Fourteen (70%) children met at least two out of three of Rowland's criteria, while one child failed to meet any. While there were no significant differences between VO_{2peak} and $VO_{2supramaximal}$, five children did still improve during supra-maximal testing.

Conclusion: VO_{2peak} measured during an incremental treadmill test seems to reflect true VO_{2max} in ambulatory children with SB, validating the use of a treadmill test for these children. When maximum effort needs confirmation, adding a supra-maximal step is an easy and well tolerated method in children with disability.

INTRODUCTION

Due to advances in medical science, many children with chronic disease live a longer and healthier life than they used to in earlier days. This requires a different approach in the medical management of these patients, from childhood through adolescence and on into adulthood. An approach, that focuses not only on the pathological aspects, but also on the (preventable) medical, functional and social consequences of the disease and lifestyle issues. As a result of this shift, exercise testing and training in children with chronic disease, like Spina Bifida (SB), has become an emerging interest within the field of pediatric exercise physiology (1).

SB is the most frequent congenital deformity of the neural tube, with an incidence of 0.4-1.0 per 1000 births (2-4). Depending on both the type and level of lesion of the SB, patients experience a variety of deficits in cognition, motor function, sensory function and bowel and bladder function (5). Besides medical classification according to type, lesion level and presence of hydrochephalus, children are functionally classified as “normal” or “community” ambulatory using the adapted Hoffer classification (6);(7)[1].

About 20% of the lesions occur at the sacral level, enabling them to be, in most cases, community or normal ambulatory. Despite high levels of functioning, these patients still experience difficulties in performing both dynamic motor skills and activities of daily living (8). This could be an important factor in inducing a cycle of less ability resulting in less activity, further reducing physical fitness and ambulation. Studies have indeed shown children and young adults with SB to be less active and with reduced levels of physical fitness compared to their healthy peers (9-12).

In exercise testing, maximum oxygen uptake (VO_{2max}) is considered to be the single best indicator of aerobic exercise capacity, which is often referred to as aerobic fitness (13). Gas exchange analysis during an incremental ergometry test to the point of volitional termination due to exhaustion is considered the gold standard to measure VO_{2max} (14). In the literature there is much debate about peak oxygen uptake (VO_{2peak}) versus VO_{2max}[2]. Where VO_{2peak} is the highest attained VO_2 during a single test, VO_{2max} is considered the maximal *possible* attainable level of

[1] See Appendix 1 for definitions of ambulation level

[2] See appendix 2 for definition

oxygen utilization by both the cardio- respiratory and neuromuscular system, resulting in a VO_2 plateau at the end of testing despite an increase in workload (15;16). Common methods of exercise testing in children are an incremental cycle or a treadmill test (1). In patients with spinal cord injury, arm ergometry has been used (17-18). An advantage of using arm ergometry with this population could be that the muscles tested are less involved in the disease process. In this way the outcomes of the test might more closely reflect cardiorespiratory limitations in exercise testing. On the other hand, upper extremity ergometry has been known to result in lower VO_{2peak} values, due to the smaller muscle mass involved in testing (19). Besides, for this group of children, ambulation is the main mode of transportation. In this case, it is recommended to use a treadmill for maximum exercise testing, due to the specificity of testing (20). To evaluate whether an exercise test in children yields "true" maximum values, Rowland has set out guidelines regarding heart rate (HR), respiratory exchange ratio (RER)[3] and the presence of a VO_2 plateau in the last minutes of testing (1). Since the presence of a plateau is much disputed in both adult and pediatric exercise testing (13), supra-maximal protocols have been used to evaluate whether the added step will yield higher VO_2, like the one-session protocol form Rossiter et al.(16). When the supra-maximal step does not increase VO_2, VO_{2peak} is considered to be a valid indicator of VO_{2max}.

In earlier studies, we have reported reduced VO_{2peak} values, using a treadmill exercise test in ambulatory children with SB (22). Lower VO_{2peak} in this study seemed to be due to reduced muscle mass, deconditioning and possible ventilatory limitations. At the same time, both low HR_{peak} and RER_{peak} in both our study and the literature (11;22), raised questions regarding the true maximal character of VO_{2peak} values obtained from this mode of testing.

While earlier studies employing treadmill exercise testing in healthy children show it is possible to validly test VO_{2peak} in healthy children (23-27), no research is available on validity of VO_{2peak} testing in ambulatory children with SB. The purpose of this study, therefore, is to determine whether VO_{2peak}, measured during a graded treadmill exercise test reflects VO_{2max} in ambulatory children with SB.

[3] See Appendix 2 for definition

METHODS

Patients

This study was part of a larger study regarding exercise and functional capacity testing in ambulatory children diagnosed with SB (The USAGE study). Study procedures took place at the Child development and exercise center at Wilhelmina Children's Hospital in 2007 and 2008. All study procedures were approved by the University Medical Ethics Committee.

Children were included when they were (1) at least community ambulatory, (2) able to follow instructions regarding testing and (3) between 6 and 18 years of age. Parents and children signed informed consent prior to testing. Exclusion criteria were medical events that might interfere with the outcomes of the testing and/or medical status that did not allow maximum exercise testing. The power calculation was performed assuming an alpha of 0.05 and power of 80%. Based on a population mean and standard deviation of 33.14 and 7.6 for VO_{2peak}/kg/min (22), and assuming a correlation of 0.9, a sample size of 18 children was sufficient to detect differences during the supra-maximal step of 110% (28).
The study population consisted of 20 ambulatory children (9 boys/11 girls) with SB. The level of lesion (classified according to the ASIA guidelines (29)), the ambulation level, the 6MWD, age and the anthropometrics are presented in Table 1.

Demographics

Data concerning medical history were obtained from medical records. These data included type of SB, level of lesion, ambulation level, age and sex.

Body mass index (BMI)

BMI was calculated as weight (kg)/height (m) ^{2}. This index has proven to be a reliable and valid tool to estimate children's nutritional status, e.g. whether they are over- or underweight (30;31). Weight was measured using an electronic scale. Height was measured while standing using a wall-mounted centimeter.

Table 1. Level of lesion and functional ambulation level in all children, normal ambulatory children and community ambulatory children with SB

	All children (n=20) Number (%)	Normal ambulatory children (n=10) Number (%)	Community ambulatory children (n = 10) Number (%)
Level of lesion			
L3-L4	2 (10)	0 (0)	2 (20)
L4-L5	7 (35)	1 (10)	6 (60)
L5-S1	6 (30)	4 (40)	2 (20)
S2 and below	1 (5)	1 (10)	0 (0)
No motor loss	4 (20)	4 (40)	0 (0)
6MWT			
> 400 meters	13 (65)	9(90)	3 (30)
Mean distance walked in meters (SD)	418 (95)	473 (45.5)	357 (100)*
Anthropometrics	Mean (SD)	Mean (SD)	Mean (SD)
Age	10.3 (4.9)	9.9 (3.2)	11.1 (4.1)
Height (m)	1.36 (0.21)	1.38 (0.19)	1.32 (0.24)
Weight (kg)	37.1 (18.7)	35.9 (15.0)	38.2 (21.5)
BMI (kg/m^2)	18.9 (3.9)	17.8 (2.8)	20.1 (4.7)

Legend: * = p<0.05 for differences between normal and community ambulatory 6MWT = Six-minute walking test

Peak and supra-maximal oxygen uptake (VO_{2peak} and $VO_{2supramaximal}$)

In this study, VO_{2peak} was measured using a graded treadmill test (EnMill, Enraf, Delft, The Netherlands), since all children would be able to perform this test and reference values are available for both young children and adolescents. In previous studies, treadmill protocols have been used to test VO_{2peak} in children with disability (11;32;33), including children with SB (11;22). In order to accommodate children with different ambulatory abilities, two progressive exercise test protocols were used. Children ambulating <400 meters during a six-minute walking test (6MWT), were tested with a starting speed of 2 km/h, which was gradually increased by 0.25 km/h every minute, with a set grade of 2%. Children ambulating >400 meters during the 6MWT, were started at a speed of 3 km/h, with the speed being

increased 0.50 km/h every minute, with a set grade of 2%. The cut-off point of 400 meters was chosen, based on earlier testing in our lab (21;22). The highest quartile of the 6MWT in the children classified as community ambulatory, starting at 400 meters, was overlapping with the lowest quartile in normal ambulatory children. Children were allowed to use the handrails to maintain balance. The protocols were continued until the patient stopped due to exhaustion, despite verbal encouragement from the test leader. After a resting period of 4 minutes, patients were tested for a maximum of three minutes at 105-110% of their maximum reached speed. This type of supra-maximal testing has been described earlier in healthy adults by Rossiter et al. (16). During the incremental exercise test, physiologic responses, including breath-by-breath gas analysis, were measured using a heart rate (HR) monitor (Polar accurex, Polar-Nederland BV, Almere, the Netherlands) and calibrated mobile gas analysis system (Cortex Metamax B^3, Cortex Medical GmbH, Leipzig, Germany). The Cortex Metamax is a valid and reliable system for measuring gas-exchange parameters during exercise (34;35).

Ambulatory ability

Ambulatory ability was measured during the 6MWT. The test was performed on a twenty-meter track in a straight corridor. Patients were instructed to cover the largest possible distance in 6 minutes at a self-selected walking speed. The test and encouragements during the test were performed in accordance with the American Thoracic Society (ATS) guidelines (36). Six-minute walking distance (6MWD) was recorded in meters. This test was performed prior to the treadmill test and was followed by a 15-minute recovery period.

DATA ANALYSIS

Peak oxygen uptake

Both peak and supra-maximal exercise parameters were calculated as the average value over the last 30 seconds during the exercise test. Normalized VO_2 was calculated as VO_{2peak}/kg or $VO_{2supramaximal}$/kg and expressed as ml/kg/min. Two-tailed t-tests were used to test differences between community and normal ambulatory children, after testing for normal distribution and equality of means. Significance level was set at $p<0.05$.

To evaluate validity of maximum exercise testing in children with SB, data were analyzed using the following methods:

Rowland's criteria

Rowland has established criteria for maximum exercise testing in healthy children (37). These criteria are subdivided in subjective and objective criteria, where every child has to meet the first and at least two of the latter for the test to be considered of maximal effort and character (see Table 2). VO_2 plateau was determined by the difference of normalized VO_{2peak} and VO_2 uptake in the last 30 seconds of the minute prior to the last minute. When the difference was 2.1 ml/kg/min or less, the child was considered to have reached a plateau (38).

Table 2. Rowland's criteria to evaluate VO_{2peak} in healthy children.

Subjective criteria:
• Signs of intense effort (unsteady walking, running of biking; sweating; facial flushing; clear unwillingness to continue despite encouragement)
Objective criteria:
• Heart rate (HR) > 95% x (210-age)
• Respiratory Exchange Rate (RER) > 1.00
• VO_2 plateau in the last minute

Supra-maximal protocol

Two-tailed paired t-tests were used to test differences between normalized VO_{2peak} and $VO_{2supramaximal}$ after testing for normal distribution and equality of means. Significance level was set at $p<0.05$. Statistical analyses were performed using SPSS for Windows (version 15.0, SPSS Inc, Chicago, Ill.). Clinically relevant differences between normalized VO_{2peak} and $VO_{2supramaximal}$ were defined as those for a plateau of > 2.1 ml/kg/min, as mentioned above.

RESULTS

Exercise testing

Twenty children completed a graded treadmill exercise test, followed by a supra-maximal step of three minutes. The supra-maximal protocol was well tolerated. Only one child (number 17) was not able to maintain the full three minutes of supra-maximal testing and had to stop after two minutes. VO_{2peak}, HR_{peak}, peak ventilation ($V'E_{peak}$), peak exhaled carbon-dioxide (VCO_{2peak}) and peak respiratory exchange ratio (RER_{peak}) are described in Table 3[4]. VO_{2peak} and VO_{2peak}/kg averaged, respectively, 1.23 (0.6) l/min and 34.1 (8.3) ml/kg/min.

Table 3. Descriptives of exercise testing in 20 children with SB.

	Mean (SD) All children	Mean (SD) Normal ambulatory	Mean (SD) Community ambulatory
VO_{2peak} (l/min)	1.23 (.6)	1.43 (.6)	1.02(.5)
VO_{2peak}/kg (ml/kg/min)	34.1 (8.3)	39.4 (5.7)	28.7 (7.0)*
HR_{peak} (beats/min)	183.8 (19.9)	184.7 (20.4)	182.3 (20.3)
RER_{peak} (VCO_2/VO_2)	1.07 (.1)	1.09 (.1)	1.05 (.1)
$V'E_{peak}$ (l/min)	45.1 (22.2)	51.4 (20.9)	38.9 (22.6)
VCO_{2peak} (l/min)	1.34 (.71)	1.57 (.7)	1.11 (.7)
Duration of testing (min)	9.0 (4.0)	10.4 (2.9)	9.3 (5.0)

Legend: * = p<0.05 for differences between normal and community ambulatory children; V'E = Ventilation; VCO_2 = Exhaled carbon-dioxide

Rowland's criteria

All children met signs of the subjective criteria. Sixty-five percent reached a VO_2 plateau during the last minute of exercise testing. The criteria for HR_{peak} were met by 65% children, whereas 80% reached a RER_{peak} > 1.00. Seven children met all three criteria, eight met two, four met one and one child failed to meet any of them (see Table 4 and 5). Seventy-five percent reached at least two out of three criteria.

[4] See Appendix 2 for definitions of terms

Table 4. Rowland's criteria during steep ramp exercise testing

	All children Number (%)	Normal ambulatory Number (%)	Community ambulatory Number (%)
Subjective signs	20 (100)	10 (100)	10 (100)
HR_{peak} > 95% (210-age)	13 (65)	7 (70)	6 (60)
RER_{peak}> 1.00	16 (80)	9 (90)	7 (70)
VO_2 plateau	13 (65)	7 (70)	6 (60)

Supra-maximal step

No significant differences were seen between the regular test and the supra-maximal protocol (VO_{2peak} versus $VO_{2supramaximal}$: 34.1 versus 34.8 ml/kg/min (p = 0.274)). Individual differences are presented in Table 5. An example of VO_{2peak} and $VO_{2supramaximal}$ testing is shown in Figure 1.

Looking at the individual values, five children showed clinically relevant differences between normalized VO_{2peak} and $VO_{2supramaximal}$. These children increased their VO_2 uptake more than 2.1 ml/kg/min during supra-maximal testing. The other children were not able to increase VO_2 during supra-maximal testing, with ten children not even able to reach previous peak values despite an increase in speed.

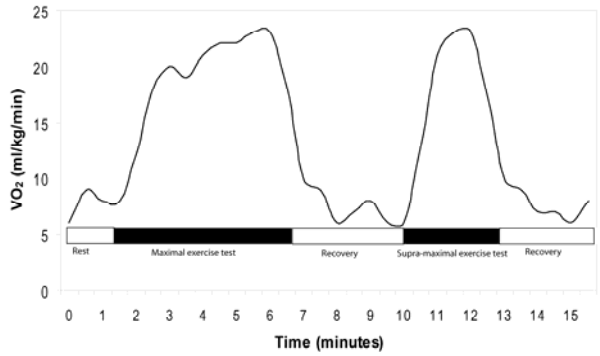

Figure 1. Example of maximal and supramaximal testing

Table 5. Individual differences in normalized VO_{2peak} and $VO_{2supra\text{-}maximal}$ and Rowland's criteria

Patient and ambulatory status	$VO_{2supramax}$/kg - VO_{2peak}/kg (ml/kg/min)	HR_{peak}	RER_{peak}	VO_2 peak – VO_2 last minute (ml/kg/min)	Rowland's criteria (out of 3)
1 CA	-0.49	143##	0.97##	3.11##	0
2 NA	-2.92	201	1.18	1.02	3
3 NA	8.21*	159#	1.17	5.62#	1
4 CA	3.09*	189	0.92#	1.98	2
5 NA	1.79	177#	1.04	1.55	2
6 NA	0.04	192	1.03	0.61	3
7 NA	2.27*	140#	1.02	1.82	1
8 CA	3.65*	200	1.06	1.61	3
9 NA	-0.18	202	1.05	0.38	3
10 CA	-0.18	188#	1.19	1.1	2
11 NA	-1.86	195	1.14	2.29#	2
12 CA	0.85	210	1.29	-0.32	3
13 CA	-3.28	192	1.00	2.28#	2
14 CA	-1.46	191	1.27	1.54	3
15 CA	1.32	159#	1.00	3.68#	1
16 CA	4.88*	165#	1.02	0.55	2
17 CA	-1.06	185	0.84#	4.99#	1
18 NA	1.79	198	1.30	2.35#	2
19 NA	-1.30	195	0.92#	1.32	2
20 NA	-1.11	188	1.06	0.27	3

Legend: NA = Normal ambulatory; CA = Community ambulatory; * = >+ 2.1 ml/kg/min in supra-maximal test; # = not reaching HR > 95%x (210-age), or RER > 1.00 or VO_2 plateau; ## = not reaching both HR > 180, RER >0.99 and VO_2 plateau

Of the five children who did not meet at least two out of three of the objective criteria as set out by Rowland, two continued to improve during supra-maximal testing. The child who failed to meet any of the criteria (patient 1), did not show improvement in VO_2 during the added step. Of those who were able to increase VO_2 uptake during supra-maximal testing, one child had met all three criteria (patient 8), three had met two out of three criteria (patients 4, 7 and 16) and one (patient 3) had met only one of Rowland's criteria for maximal exercise testing.

Three children did not meet the HR_{peak} criteria (patients 3, 7 and 16), one child reached an RER < 1.00 (patient 4) and one child did not reach a VO_2 plateau in the last minute of exercise testing. Of those reaching low HR_{peak}, 42% showed higher $VO_{2supramaximal}$. Of those reaching a low RER_{peak}, only 25% still improved during the supra-maximal step. Despite the fact that fewer community ambulatory children reached a RER_{peak} > 1.00 or a VO_2 plateau, this difference did not result in significant differences between VO_{2peak} and $VO_{2supramaximal}$ within the two groups. Of the seven children not reaching a VO_2 plateau, only one still improved during the added step. Furthermore, three of those still improving were community ambulatory, while two were normal ambulatory. During the last minute of the supra-maximal test, four out of five did reach a VO_2 plateau.

DISCUSSION

The purpose of this study was to determine whether VO_{2peak} measured during a graded treadmill exercise test reflects VO_{2max} in ambulatory children with SB.

Rowland's criteria

In the current study, the percentage of children meeting one of Rowland's criteria is much higher compared to our earlier data. Seventy-five percent met at least two out of three criteria and only one child failed to meet any. This is much more in line with earlier research with healthy children, that shows that VO_{2peak} in children is a valid indicator of VO_{2max} (24). Gulmans et al. tested 158 healthy children aged 12-18, with 100% reaching the maximum criteria. The criteria used in this study were somewhat different from those used in our study and included invasive testing, but were still based on guidelines set out by Rowland. In a large Danish study (26), 84% met at least two our of three of Rowland's objective criteria, which is similar to the findings in this study. In the literature, the presence of a plateau in pediatric exercise testing is much disputed. Even though often considered the true criteria for maximal exercise testing, a literature review found 21-95%, with an average of 55% of healthy children, to reach a plateau during exercise testing (13). In our study 70% reached a plateau, but interestingly, reaching a plateau was not predictive of improvement during supra-maximal testing. Four out of five children reaching higher $VO_{2supramaximal}$, did meet criteria for a VO_2 plateau during initial

testing, but only one out of seven not reaching a VO_2 plateau improved during the added step.

Supra-maximal step

Besides Rowland's criteria, we used a protocol described by Rossiter et al. (16) to determine whether true VO_{2max} had been reached during a graded treadmill exercise test. We did this by adding an extra step of 105-110% of the maximum achieved speed. In this study, we found no significant differences between VO_{2peak} and $VO_{2supramaximal}$ in either normal or community ambulatory children. These results are in line with other studies using supra-maximal protocols. Rowland (15) was unable to elicit an increase in VO_2 during supra-maximal testing in 9 healthy children. Rossiter et al. (16) concluded that, when subjects seem to give their maximum effort (Rowland's subjective criterion), VO_{2peak} most likely reflects VO_{2max}. At the individual level, though, five children still continued to improve during the supra-maximal test. Eighty percent did meet a plateau during supra-maximal testing, which implies a maximal measure of VO_2 during this added step. Besides meeting less than two out of three criteria, low HR_{peak} in particular, seems to be an indication that an individual may not have reached a true VO_{2max}.

The current study differed in two ways from our earlier study (21;22). First, the population of the current study included more "community ambulators" and children with a higher level of lesion (thus more muscular deficits). Despite these differences, HR_{peak} and RER_{peak} reached in this study were higher than in our previous study, without reaching higher VO_{2peak} though. Secondary analysis found no correlation between HR_{peak} and level of lesion. This is contrary to a study from Agre et al. (11). This difference could partly be explained by the fact that in children with a higher lesion level performed the treadmill test in a wheelchair, which was less strenuous than walking. At the same time, a discontinuous and less progressive testing protocol was used. Still, compared to studies involving healthy children, HR_{peak} was much lower in our population (183.4 versus 196-199 (26) or 199-200 (39)). This is likely due to the fact that VO_{2peak} in ambulatory children is not determined by cardiac limitations, but rather by deconditioning and/or muscular deficiencies and possible ventilatory limitations (22).

Secondly, we defined “ambulatory ability” in a different way. In the current study, actual performance during a 6MWT was used instead of functional classification in the decision about which treadmill-protocol to use. This change in protocol has improved peak outcomes for this population.

Limitations of the study

In the context of the USAGE study, only community or normal ambulatory children with SB were included. In future studies, it would be interesting to develop exercise testing for children who are considered “household ambulatory” as well. Questions could be raised about a possible practice effect and familiarization to the test procedures, involving both the treadmill test and the 6MWT. In a current study, we are looking into reproducibility of exercise testing ambulatory children with SB. Another question could be raised regarding the frequent use of medication in children with SB. It is unclear how these medications might interfere with the oxygen uptake, utilization and transport system in the body, as well as central and peripheral fatigue. Again, in our current study, we are monitoring medication use during exercise testing.

CONCLUSION

A graded treadmill exercise test is an appropriate method to measure VO_{2peak} in both normal and community ambulatory children with SB. When choosing a treadmill protocol, it is important to use actual performance and not functional classification as a decisive factor. Not RER_{peak}, but rather HR_{peak} at less than predicted levels, might be an indication of sub-maximal effort. When the true character of the maximum testing is in doubt, a supra-maximal step of 110% is an easy and well tolerated method in ambulatory children with SB for the confirmation and further interpretation of maximum exercise testing.

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Appendix 1. Adapted Hoffer classification (6;7)

LEVEL OF AMBULATION	Description
Normal Ambulation	Independent and unrestricted ambulation without use of assisted devices
Community ambulation	Independent outdoor ambulation with or without use of braces and/or assisted devices; using wheelchair for longer distances
Household ambulation	Using braces or assisted devices for indoor ambulation; using wheelchair for outdoor locomotion
Non-functional ambulation	Walking only in therapeutic situations
Non-ambulation	Wheelchair dependent

Appendix 2. Explanation of terminology*

VO_2	**Oxygen uptake (l/min). Determined by cardiac output (HR X Stoke volume) and the arterial-mixed venous oxygen content differences (= the Fick fomula).**
VO_{2peak}	The highest attained oxygen uptake (VO_2) during a *single* test without the necessity of flattening of VO_2 curve.
VO_{2max}	The maximal *possible* attainable level of oxygen utilization by both the cardio- respiratory and neuromuscular system, characterized by a flattening of the VO_2 curve despite an increase in work load. This is often determined in more than one test session. In healthy people, $V0_{2peak}$ and VO_{2max} are interchangeable.
VCO_2	Carbon dioxide output (l/min)
RER	Respiratory Exchange Ratio; calculated as VCO_2/VO_2
V'E	Minute ventilation (l/min)
HR	Heart rate (beats/min)

*** Based on: Wasserman K. et al. *Principles of Exercise Testing and Interpretation.* Lippincott Williams & Wilkins, Philadelphia, PA. Fourth Ed. 2005.**

Reproducibility of Maximal and Submaximal Exercise Testing in Normal and Community Ambulatory Children with Spina Bifida: which is best for the evaluation and application of exercise training?

Chapter 6

De Groot JF, Takken T, Gooskens R, Schoenmakers MAGC, Wubbels M, Vanhees L, Helders PJM. Accepted for publication in Physical Therapy.

ABSTRACT

Background: With emerging interest in exercise and lifestyle interventions for children with Spina Bifida, there is a need for appropriate measurements of exercise testing.

Objectives: To assess both reliability and agreement of maximal and sub-maximal exercise parameters in normal and community ambulatory children with SB.

Design: A reproducibility study, including 23 ambulatory children with SB at the Wilhelmina Children's Hospital., University Medical Center, The Netherlands.

Methods: Maximal exercise outcomes were measured using a graded treadmill-test. Peak parameters (VO_{2peak}, HR_{peak}, Heart rate response (HRR) and Oxygen Pulse (O_2-pulse)) were recorded. For submaximal parameters, HR and VO_2 at the ventilatory threshold (VT) and Oxygen Uptake Efficiency Slopes (OUES) were derived from the maximal parameters. Functional performance was measured as the six-minute walking distance and the maximal speed during the treadmill test.

After checking for normality and heteroscedasticity, paired T-tests, intra-class correlation (ICC) and smallest detectable difference (SDD) or the coefficient of variation (CV) were calculated.

Results: Performance measures showed good reliability and agreement. For maximal measures, acceptable ICCs were found for all parameters. For submaximal measures, only HR_{VT} showed an ICC < 0.8. Agreement showed CV < 10% for all measures, except for VO_{2VT}, HRR and OUES.

Limitations: Limitations of the study include missing data due to equipment failure. Furthermore, the outcomes are limited to normal and community ambulatory children with SB.

Conclusion: Both maximal and submaximal measures of exercise testing can be used for discriminative purposes in ambulatory children with SB. For evaluative purposes, HR measures are superior to VO_2 measures, while taking into account the individual variation of 5 to 8%. SDD for $speed_{peak}$ and 6MWD were 0.5 km/h and 36.3 meters. HRR, O_2-pulse and OUES are not recommended in the evaluation of exercise testing in this population.

INTRODUCTION

Spina Bifida (SB) is the most frequently seen congenital deformity of the neural tube, with an incidence ranging from 2-8 per 10000 live births worldwide (1). As a result of the neural tube deformity, patients experience a variety of deficits in cognition, motor function, sensory function and bowel and bladder function (2).

The severity of these deficits is largely determined by both the type and level of lesion of the SB. In 80% of children with the more serious open type of SB (Spina Bifida Aperta), hydrochephalus and a Chiari II malformation – a malformation in the brainstem- is present (3). Due to advances in the medical approach, mortality rates have decreased in recent years and 60-80% of children with SB can now be expected to live to be adults (4-7). This requires a different approach in medical management of these patients from childhood through adolescence into adulthood, with attention not only to the pathological aspects, but also to the (preventable) medical, functional and social consequences of SB. Several studies have shown children and adolescents and young adults with SB to be less active, resulting in obesity, reduced health-related quality of life and significantly reduced levels of physical fitness when compared to healthy peers (8-14). Ambulatory children with SB do not only perform poorer then their healthy peers, also compared to children with other chronic conditions (15, 16) they show lower levels of aerobic fitness and performance during a six-minute walk test (17). Besides, a relationship was found between aerobic capacity and energy expenditure during ambulation (18). This emerging interest in physical fitness, physical activity and implementation of lifestyle and exercise programs in children, adolescents and young adults with SB (7), emphasizes the need to develop appropriate protocols to monitor change in these areas. For evaluation of intervention programs, information is needed regarding validity and reliability of exercise testing in children with SB. Earlier, validity was analyzed of maximum exercise testing, using an adapted graded treadmill protocol (19). Conclusion was that the peak oxygen uptake values reflected maximum values using a treadmill protocol in ambulatory children with Spina Bifida. The purpose of this study was to analyze reproducibility of both maximal and sub-maximal outcomes of exercise testing in normal and community ambulatory children with SB. Since research labs and clinical settings differ in both

equipment and experience in exercise testing, both physiologic and performance parameters were analyzed in this study.

METHODS

Study design

The study was a reproducibility study of maximal and submaximal exercise measures, with retesting taking place two weeks later, at the same time of day by the same tester.

Subjects

The study group consisted of 23 ambulatory children with SB, type myelomeningocele (MMC), known at the SB outpatient clinic of Wilhelmina Children's Hospital , University Medical Center, The Netherlands. Study procedures took place at the Child Development & Exercise Center. All study procedures were approved by the University Medical Ethics Committee.

Children were included when they were (1) at least community ambulatory, (2) able to follow instructions regarding testing and (3) between 6 and 18 years of age. Parents and children signed informed-consent forms prior to testing. Exclusion criteria were medical events that might interfere with the outcomes of the testing and/or medical status that did not allow maximum exercise testing.

Measurements

Demographics

Data concerning medical history were obtained from medical records. These data included type of SB, motor level of lesion, use of orthotics, ambulation level and sex.

Weight, height and BMI

Weight was measured using an electronic scale. Height was measured while standing using a wall-mounted centimeter. Body Mass Index (BMI in kg/m^2) was derived from weight and height. Z-scores were calculated from Dutch growth charts.

Maximal measures

In this study, maximal exercise testing was measured using a graded treadmill test (EnMill, Enraf, Delft, The Netherlands). In previous studies, treadmill protocols have been used to test VO_{2peak} in children with disability (20-22), including children with SB (19, 23, 24). In order to accommodate children with different ambulatory abilities, two progressive exercise test protocols were used. Children ambulating < 400 meters during a six-minute walking test (6MWT) were tested with a starting speed of 2 km/h, which was gradually increased by 0.25 km/h every minute, with a set grade of 2%. Children ambulating > 400 meters during the 6MWT were started at a speed of 3 km/h, with the speed being increased 0.50 km/h every minute, with a set grade of 2%. The cut-off point of 400 meters was chosen, based on earlier testing in our lab (25, 26). Children were allowed to minimally use the handrails for maintenance of balance only. The protocols were continued until the patient stopped due to exhaustion, despite verbal encouragement from the test leader. During the incremental exercise test, physiologic responses, including breath-by-breath gas analysis, were measured using a heart rate (HR) monitor (Polar accurex, Polar-Nederland BV, Almere, the Netherlands) and calibrated mobile gas analysis system (Cortex Metamax B^3, Cortex Medical GmbH, Leipzig, Germany). The Cortex Metamax is a valid and reliable system for measuring gas-exchange parameters during exercise (27, 28). Heart rate response (HRR**)** -not to be confused with heart rate reserve- and oxygen pulse (O_2 pulse) were derived from VO_2 and HR measures. HRR was chosen because it assumes a linear relationship between VO_2 and HR during exercise, independent of the patient's motivation or ending the test prematurely e.g. when a test is considered "symptom-limited". HRR was calculated as $(HR_{peak}\text{-}HR_{rest})/(VO_{2peak}\text{-}VO_{2rest})$ (29). O_2-pulse, used as an index of stroke volume, was calculated as VO_{2peak}/HR_{peak}(30). Besides physiologic responses, maximal walking or running speed was recorded.

Submaximal measures

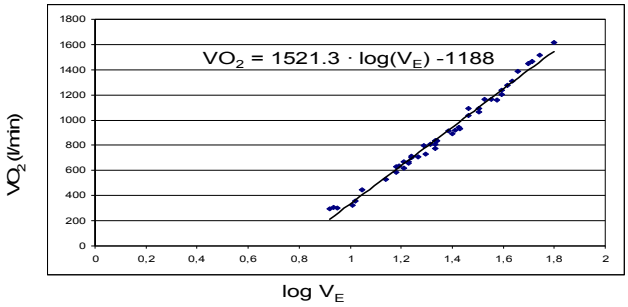
1. *Measures at the Ventilatory Threshold (VT)*

VO_2 and HR were determined at the VT. The VT was determined using the criteria of an increase in the ventilatory equivalent of oxygen (VE/VO_2) with no increase in

the ventilatory equivalent of carbon dioxide (VE/VCO_2), while respiratory exchange ratio (RER), defined as VCO_2 / VO_2 remained below 1.0 (31-33).

2. Oxygen Uptake Efficiency Slopes (OUES)

The OUES is considered a sub maximal measure, recently introduced by Baba et al. as an alternative to the VT, when VT cannot be determined and because of the questionable reliability of the VT when using different examiners (34). The OUES reflects efficiency of ventilation in relation to oxygen uptake; one of the underlying assumptions is the metabolic acidosis as a result of oxygen consumption in the muscle. The OUES is calculated by making use of the following regression equation: $VO_2 = a \cdot \log(V_E) + b$, in which the constant 'a' represents the rate of increase in VO_2 in response to an increase in V_E, called the OUES (see fig. 1).



In this example the Oxygen Uptake Efficiciency Slope (OUES) = 1521.3

Figure 1. Example of Oxygen Uptake Efficiency Slope

The slope is a constant slope throughout exercise testing. Therefore, it is considered an appropriate tool when maximal exercise testing is symptom-limited or not possible. A steeper slope, reflected by a higher OUES, represents a more efficient oxygen uptake (VO_2). For the determination of the maximal OUES, all data gained during the maximum exercise were used. Data from the first minute of exercise were excluded, since the breathing pattern of the first minute of exercise appears to be frequently unstable (30).

3. Six-minute walk test (6MWT)

The test was performed on a twenty-meter track in a straight corridor. Patients were instructed to cover the largest possible distance in six minutes at a self-selected walking speed. The test and encouragements during the test were performed in accordance with the American Thoracic Society guidelines (35). Next to HR in the last minute (HR_{6MWT}), the six-minute walking distance (6MWD) was recorded as performance outcome measure.

DATA ANALYSIS

For initial analyses, data were checked for normality and heteroscedasticity, the latter referring to the degree of variability, depending on the outcome of the measurement. Heteroscedasticity was defined as a correlation coefficient between the differences of test–retest and the mean of the observations greater than 0.3 (36). At the same time, a visual interpretation of Bland and Altman plots was performed to check for heteroscedasticity. After checking for normally distributed data, paired T-tests were performed for test and retest data, with significance level set at $p < 0.05$. Reproducibility encompasses both reliability and agreement (37). Subsequently, for reliability, the intra-class $correlation_{conistency}$ (ICC) was calculated using the following formula: $variance_{patient}^2$ / $variance_{patient}^2$ + $variance_{residual}^2$ (37). An ICC of 0.8 or higher was considered good (38).

For clinicians, agreement of the measurements is more of interest, because they look to determine meaningful improvements in a single patient. For agreement in normal distributed differences, the Standard Error of Measurement (SEM) and the Smallest Detectable Difference (SDD) were calculated, using the following equations: $SEM = SD * \sqrt{1 - ICC_{consistency}}$ and $SDD = 1.96 * \sqrt{2} * SEM$. (37, 38). For heteroscedastic data, the coefficient of variance (CV) was calculated as a measure for stability within individual results. When dealing with heteroscedastic data, log transformation is recommended (36, 39, 40). To examine the 95% confidence interval of the CV%, data was antilogged and expressed to the power of 1.96, using the available spreadsheet calculations by Hopkins. For data in exercise testing in children, CV's between 5-10% have been considered as acceptable inter-individual variation. Statistical analyses were performed using SPSS for Windows (version 15.0, SPSS Inc, Chicago, Ill.) or MS Excel, (Microsoft, Amsterdam, the

Netherlands). Performance measures were checked first, as a sign of stability of the test, before reproducibility of physiologic measures was further assessed.

RESULTS

Population

The study population consisted of 23 children (11 boys/12 girls), with a mean age of 10.7 years. Children's age, height, weight and BMI are described in Table 1. The level of lesion, classified according to the ASIA guidelines (41) and the ambulation level according to Hoffer adapted by Schoenmakers are presented in Table 1 as well.

Table 1. Level of lesion, ambulation level and anthropometrics

	Number (%)
Level of lesion	
L3-L4	2 (8.7)
L4-L5	10 (43.5)
L5 -S1	6 (26.1)
S2 and below	5 (21.7)
Ambulation level	
Normal ambulatory	10 (43.5)
Community ambulatory	13 (56.5)
Anthropometrics	Mean (SD)
Age	10.7 (3.5)
Height(meter)/ Z-scores	1.39 (0.2)/ -1.2 (1.6)
Weight (kg)/ Z-scores	38.6 (17.4)/ + 0.3 (1.3)
BMI (kg/m^2)/ Z-scores	19.0 (3.9)/ + 0.5 (1.1)

Children in the slow protocol (n=9) walked/ran for 10.7 (±1.4) minutes compared to 11.1 (±1.5) minutes for those in the faster protocol (n=10). When compared with healthy peers, average Z-values for VO_2/kg were - 2.5 (±1.6); there were no significant differences between the two protocols for neither Z-values nor time.

Performance measures

Outcomes of both test and retest can be found in Table 2. T-tests showed no significant differences for the performance tests. Reproducibility measures can be found in Table 3. ICC is high and agreement shows a SEM of 3% and 3.2% for respectively maximum speed during the treadmill test the 6MWD.

Table 2. Outcomes of Maximal and Submaximal Exercise parameters during test and retest

	N	Test (SD)	Retest (SD)	Difference	p-value
Performance measures					
$Speed_{peak}$ (km/h)	**19**	**6.4 (2.0)**	**6.6 (2.1)**	**-0.2**	**0.1**
6MWD	**19**	**406.8 (90.7)**	**408.0 (94.7)**	**-1.22**	**0.8**
Maximal measures					
VO_{2peak} (l/min)	18	1.37 (0.7)	1.27 (0.6)	0.1*	0.03
HR_{peak} (beat/min)	16	191 (12.4)	185 (21.1)	6.5*	0.04
HRR(beat/l)	14	111.7 (94.7)	111.3 (62.2)	0.39	1.0
Oxygen pulse (ml/beat)	16	7.1 (3.4)	6.7 (2.8)	0.37	0.2
Submaximal measures					
VO_{2VT} (L/min)	16	1.14 (0.6)	1.06 (0.4)	0.07	0.3
HR_{VT} (beat/min)	15	161 (13.0)	155 (8.1)	5.6	0.06
OUES	18	1402.2 (745.8)	1475.4 (692.0)	-73.2	0.50
HR_{6MWT} (beat/min)	13	149 (24.5)	149 (21.6)	0.02	1.0

Legend: SD = Standard deviation; 6MWD = Six-minute walking distance; VO_2 = Oxygen uptake; HR = Heart rate; HRR = Heart Rate Response; VT= Ventilatory Threshold; OUES= Oxygen uptake efficiency slope; * = significant difference ($p < 0.05$)

Maximal physiologic measures

Outcomes from both test and retest can be found in Table 2. T-tests showed significant, though not clinical relevant differences between test and retest for VO_{2peak} and HR_{peak}.. Reproducibility measures for maximum outcomes measures can be found in Table 3. ICC's for VO_{2peak}, HRR and O_2-pulse maximum speed were **> 0.8** (0.97-0.99) and moderate for HR_{peak}. CV for maximal measures ranged from 5.0% for HR_{peak} to 17.3% for HRR.

Table 3. Reproducibility data for Maximal and Submaximal Exercise Test parameters

	ICC	SEM	SDD	CV%	95% interval of CV%
Performance measures					
Speedmax (km/h)	**0.99**	**0.2**	**0.5**		
6MWD	**0.98**	**13.1**	**36.3**		
Maximal measures					
VO_{2peak} (l/min)	0.97			8.2	6.1 – 12.5
HR_{peak}	0.78			5.0	3.6 – 7.8
HRR	0.87			17.3	12.3 – 29.4
O_2-pulse	0.95			9.7	7.2 – 14.9
Submaximal measures					
VO_{2VT} (l/min)	0.89			13.2	9.6 - 21.1
HR_{VT}	0.53			4.6	3.3 – 7.3
OUES	0.8			24.3	17.9 – 38.9
HR_{6MWT}	0.94			5.4	3.2 – 7.5

Legend: ICC=intraclass coefficient; SEM=standard error of measurement; SDD=smallest detectable difference; CV= coefficient of variation; 6MWD = Six-minute walking distance; VO_2 = Oxygen uptake; HR = Heartrate; VT= Ventilatory Threshold; OUES= Oxygen uptake efficiency slope.

Submaximal physiologic measures

Outcomes from both test and re-test can be found in Table 2. T-tests showed no significant differences between test and retest for any of the submaximal outcome measures ($p > 0.05$ for all measures). Reproducibility measures for submaximal outcomes measures can be found in Table 3. ICCs varied from 0.53 for HR_{VT} to 0.94 for HR_{6MWT}. CV ranged from 4.6 for HR_{VT} up to 13.2 for VO_{2VT} and 24.3% for the OEUS.

DISCUSSION

The aim of this study was to determine both the reliability and agreement of maximal and submaximal exercise parameters in normal and community ambulatory children with SB.

Performance measures

Reliability regarding the performance tests were good, as reflected by the ICC's. Agreement was good as well, looking at the SEM and T-tests. These results are in agreement with reproducibility studies regarding the 6MWT (42-46) in both healthy children and children with chronic conditions, all reporting high ICC's (0.88 – 0.98), but with agreement varying from 43 meters in children with Cerebral Palsy (44), up to 139 meters in children with Cystic Fibrosis (45). Other studies do not directly report on maximal speed. Recalculating data from Verschuren et al. (47), they found an ICC of 0.99 and and SDD of 0.9 km/h. Stability of performance of the tests is an important criterion for further interpretation of the reproducibility of physiologic responses. As reproducibility is calculated based on the variance between the measurements (37), variance as a result of noise in the performance of the test can now be ruled out as a major source of noise in this study.

Maximal measures

For maximal measures, acceptable ICCs (ICC > 0.8) were found for all measures, with the exception of HR_{peak}, being just at the cut off point of moderate to good. High ICCs make a test appropriate to use for discriminative purposes.

As far as agreement, or individual variation between the test and re-test, only HRpeak and VO_{2peak} showed a CV < 10% and are thus most appropriate to use for evaluative purposes for maximum exercise testing of individual subjects. It is difficult to compare these outcomes to existing literature due to different ways of reporting on reproducibility, but a similar trend is seen in that CV for HR_{peak} is smaller than for VO_{2peak}. In healthy children, CV for VO_{2peak} ranges from 5.1 to 10% (48-50), which is in line with our own results. Johnston et al. have suggested that reliability for exercise testing should be determined for children with chronic disease as well. Takken et al. (51) have reported ICC >0.95 and CV <6% for VO_{2peak}, using a cycling test, for children with juvenile dermatomyositis, while reliability for VO_{2peak} was excellent for patients with juvenile arthritis as well (50).

CV or ICC for HR_{peak} are less commonly reported, but generally CV remains below 2.2% (48, 49), which is lower than the 5% in this population. One reason for these higher values could be the monitor we used to measure HR. In some children, the sideway movements of the upper body to compensate for weak hip musculature during gait, caused the monitor to slide down, resulting in obvious measurement error. Another reason could be the varying levels of fatigue which are clinically seen in these children, possibly resulting in varying heart rate during activity. The reliability of derived parameters, such as O_2-pulse and HRR, is not reported in previous literature. In this study, CV for these derived measures is 10% or higher and is thus not recommend for use in the individual evaluation and interpretation of exercise testing.

Submaximal measures

For submaximal outcome parameters, acceptable ICC were found for all measures, except for HR_{VT} (ICC = 0.53). Agreement was far superior in the HR measures compared to the VO_{VT} and OUES . This trend is in agreement with the results of the maximal parameters, where HR values show less intra-individual variation than VO_2 measures, consistent with the existing literature in healthy children (48). VO_{2VT} showed a large CV, indicating poor stability of the measurement, making it less appropriate as an individual marker. For the OUES slope, a large intra-variation was found as well. The OUES does not seem an appropriate replacement for VO_{VT} in this population, in contrast to some studies in adults (52). Regardless of reproducibility, the values of the OUES do seem significantly lower in children with SB compared to healthy peers (1402 versus 2254 to 2335 reported by Marinov et al. (53)).

Figure 2 shows the recommended measures to use in the evaluation of exercise capacity in ambulatory children with SB for both maximal and submaximal measures for use at group level as well as in individual patients**.** The CV% and SDD should be considered when evaluating true change from intra-individual variability. From the results of this study e.g. , we can conclude that improvements of 36 m or 6-12% are needed for respectively 6MWD and VO_{2peak} to interpret a change as true improvement.

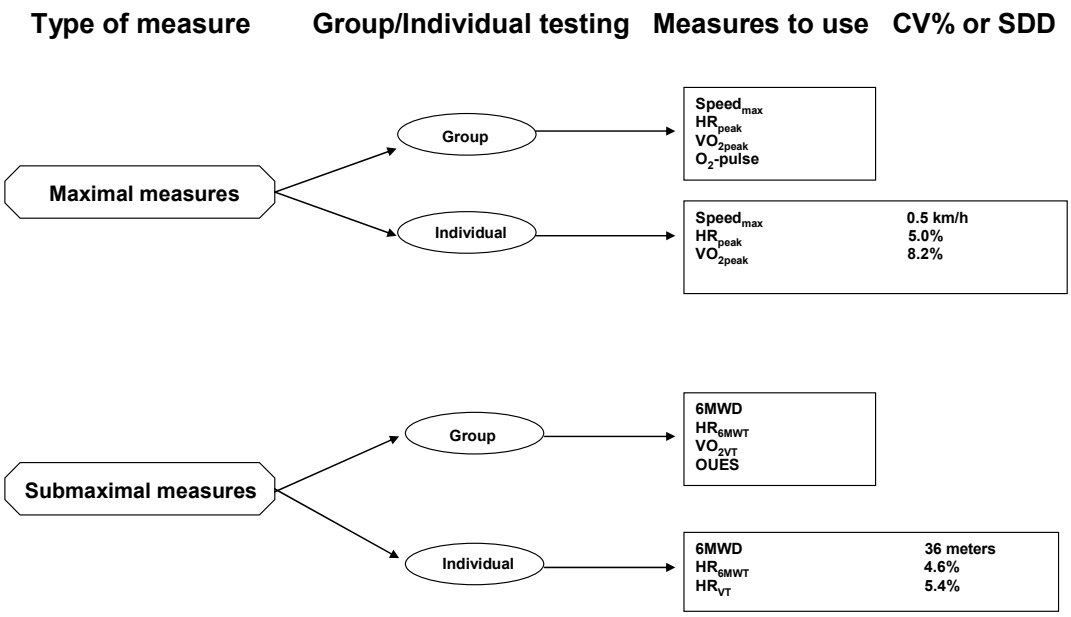


Figure 2. Appropriate measures to use in the evaluation of exercise capacity in ambulatory children with SB.

Limitations of the study

Limitations of this study include the missing data. While we started with 23 children, three were unable to perform the second test due to illness. Missing VO_2 data as a result of equipment failure compromised the results in four children. And while VT data could be useful in determining exercise intensity, a clear VT was not always identifiable. As stated earlier, HR monitoring was not possible in several cases, especially during the 6MWT. To reduce this problem, we recommend working with a more flexible band or a two-point ECG monitoring system. A second limitation concerns the group of children being tested. In the context of a larger study, only community or normal ambulatory children with SB were included. In future studies, it would be interesting to develop exercise testing for children who are considered

"household ambulatory". Despite limiting this study to normal and community ambulatory children with MMC only and leaving out the more asymmetric lesions, still a wide range of outcomes was reported. While for research purposes more homogeneity is preferred, these outcomes seem representative for this group of children. Other factors like cognitive status, obesity, different exposure to physical activity and spasticity seem important in the reported range of functional levels despite the level of lesion.

CONCLUSION

Looking at the physiological outcomes of this reliability study, HR measures and VO_{2peak} as well as performance outcomes (speed and 6MWD) can be used in the evaluation of exercise capacity at the maximal or submaximal level in ambulatory children with SB. In agreement with the existing literature, maximal measures are more reliable than those at the ventilatory threshold; and HR measures seem more reliable than oxygen measures, with functional outcomes – both treadmill speed and the 6MWD - being superior to all in detecting change. Whereas VO_2 measures give more insight in physiological processes, not every clinician working with these children has access to the knowledge, expertise or equipment to monitor these processes. In this case, functional outcome measures in combination with HR monitoring are useful tools in themselves to evaluate change or to assess exercise capacity in ambulatory children with SB. HRR, O_2-pulse and OUES are not recommended in the evaluation of exercise testing in this population.

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Randomized controlled study of home-based treadmill training for ambulatory children with Spina Bifida

Chapter 7

De Groot JF, Takken T, van Brussel M, Gooskens R, Schoenmakers MAGC, Versteeg C, Vanhees L*, Helders PJM*. Submitted to Neurorehabilitation and Neural Repair. *Shared last authorship

ABSTRACT

Context Many ambulatory children with Spina Bifida (SB) experience functional decline in ambulation despite stable level of the lesion. Improving or maintaining locomotion during childhood and throughout the teenage years, could be an important goal for children with SB.

Objective Purpose of this study was to evaluate the effects of a home-based treadmill training program on both ambulatory measures and aerobic fitness.

Design Randomized clinical trial, including 32 children.

Setting Wilhelmina Children Hospital, University Medical Center.

Interventions The intervention consisted of supervised treadmill training for twelve weeks at home. Patients exercised twice a week, with intensity set at 66% of HR_{peak}. Intervals of training consisted of 70 -140% of individual walking speed during initial exercise testing, with speeds increasing during the training period.

Main outcomes measures Ambulation was measured using the six-minute walk test (6MWT). Gross energy consumption (ECS_{gross}) and energy cost (EC_{gross}) were calculated. Maximal exercise capacity was measured using an incremental treadmill test. Both VO_{2peak} and $speed_{peak}$ were recorded as outcome parameters. For effect of training, T-tests or Mann-Whitney tests and effect sizes were calculated using Cohen's *d*. Mixed between-within subjects analysis of variance was used to analyze long-term effects of intervention, with eta for effect size.

Results After training, significant changes were seen between the groups for 6MWT ($p = 0.002$; $d = 1.08$), $speed_{peak}$ ($p = 0.001$; $d = 1.14$), VO_{2peak} ($p = 0.034$; $d = 0.78$) and ECS_{gross} ($p = 0.004$; $d = 1.01$). Long-term effects were recorded for 6MWT ($p = 0.003$; eta = 0.34), $speed_{peak}$ ($p = 0.003$; eta = 0.35) and ECS_{gross} ($p = 0.014$; eta = 0,29), but not for VO_{2peak}.

Conclusion A home-based, progressive treadmill training program for ambulatory children with SB has a large long-term effect on ambulation, with a moderate short-term effect on VO_{2peak}.

INTRODUCTION

Spina Bifida (SB) is the most frequently seen congenital deformity of the neural tube, with an incidence ranging from 2-8 per 1000 live births worldwide (1). As a result of the neural tube deformity, patients experience a variety of disturbances in cognition, motor function, sensory function and bowel and bladder function (2).

The severity of these disturbances is largely determined by both the type and level of lesion of the SB. Due to advances in the medical approach, mortality rates have decreased in recent years and 60-80% of children with SB can now be expected to live to be adults (3-6). Even children with lower lumbar lesions still experience difficulties in performing both dynamic motor skills and activities of daily living (7). In the adolescent years, a large number of children seem to become wheelchair dependent as ambulation becomes too strenuous (8). Looking at prognosis and development of SB a 25-year cohort study (3) found a decline in ambulation frequency as the main mode of locomotion from 95% at age 0-5 to 46% at age 20-25, despite stable or even improving motor lesions. Ambulation in adulthood correlated with lesion level, with 93% of patients with a sacral level ambulating, and respectively 91% and 57% of patients with L5 and L4 motor level being classified as ambulatory. At the same time, ambulation level during teenage years seemed predictive of ambulation as the main mode of locomotion as young adults. Therefore especially this group of children could greatly benefit from a new approach to literally “keep them moving” and walking. Earlier studies have shown higher levels of energy expenditure during ambulation in patients with SB, which are associated with a pathological gait pattern due to muscle weakness in the lower extremities (9;10). Higher energy expenditure during ambulation may result in higher levels of fatigue while physically active. Studies also have shown adolescents and young adults with SB to be less active and to have reduced levels of aerobic fitness, when compared with their healthy peers (11-13).

Fatigue and difficulties during daily activities put these children at risk for developing a hypoactive lifestyle and the consequential risk factors associated with poor levels of physical activity. At the same time, this fatigue may be explained by both a lower level of aerobic fitness and a higher cost of energy expenditure during daily activities. In the literature this combination of reduced exercise capacity and

higher cost of locomotion is referred as “diminished physiological fitness reserve” (14).

Earlier, our own results have shown VO_{2peak} and oxygen cost of locomotion to be associated, with higher VO_{2peak} being related to lower oxygen cost of locomotion (15) feeding into the hypothesis of “diminished physiological reserve” . Both VO_{2peak} and energy cost or efficiency of movement can be improved by training (16;17), which will be the focus of this intervention study.

While for ambulatory children with SB, only one small exercise study has been conducted with positive results on muscle strength and ambulation (18), in other children with chronic disorders, such programs have been implemented at a larger scale with positive effects on fitness and daily participation (19-21). Looking more specifically at programs aimed to improve ambulation, treadmill training has shown promising results in other pediatric populations (22), but with some hesitation due to methodological questions regarding study design and description of intensity and frequency of the intervention (23). From a motor learning point of view and specificity of training effects, treadmill training is a task specific training which allows for repetitive practice of gait cycles, important for motor learning and neural plasticity (24;25).

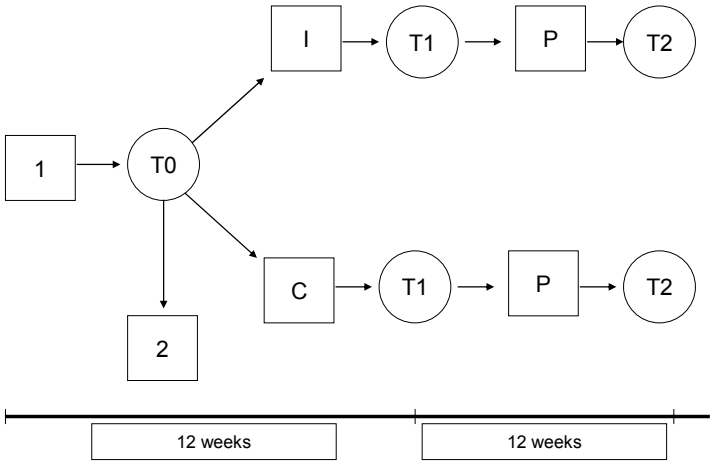
Therefore, the purpose of this study was to evaluate the effects of an individualized treadmill training program aimed at improving both aerobic fitness and ambulation in ambulatory children and adolescents with SB.

METHODS

Study design

A randomized clinical trial (RCT) with one arm receiving training intervention on top of their regular care and a control group without training intervention, but still receiving regular care (see Figure 1).

Fig. 1 Flowchart of the RCT



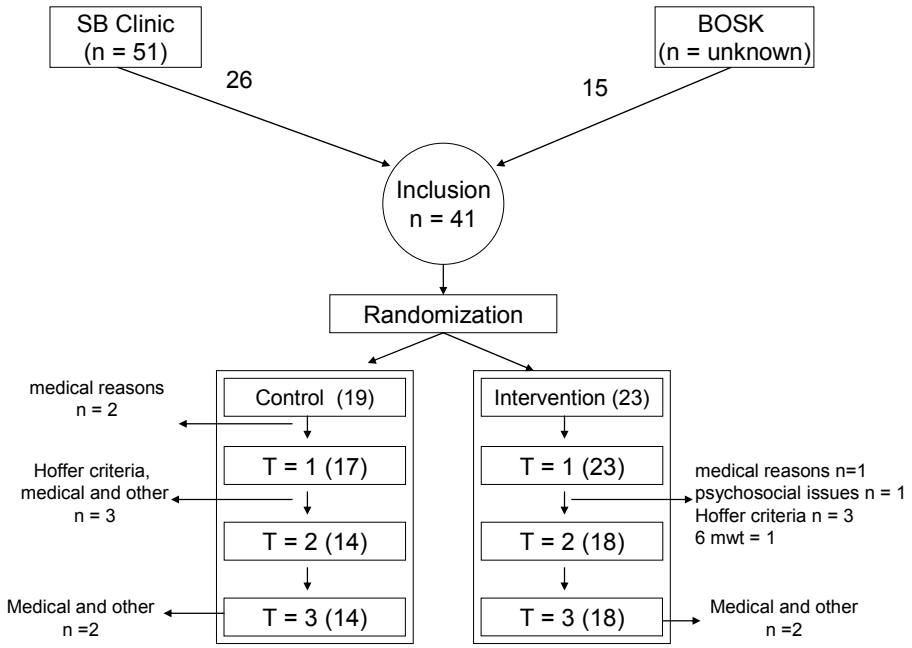
Legend: 1 = recruitment; 2= exclusion; T0, T1 and T2 = measurements; I = intervention; C= control; P = post-intervention period

The primary researcher and data entry assistants were blinded from group allocation. Participants were randomly allocated to the intervention or control group. Randomization was stratified according to age (older and younger than twelve years of age) and sex. For each stratum, random numbers 1 to 41 were assigned to the participants, which were put into envelopes; randomly it was determined that even numbers would enter the intervention group. Participants were assigned to the study by opening the envelopes. The different steps in the process were blindly administered by several research assistants. Due to logistics of transportation of the treadmill and assignment of therapist, the randomization happened prior to the first measurement. Participants were informed of their assignment after the first measurement.

Subjects

The study group consisted of 41 ambulatory children with SB, recruited both through the SB outpatient clinic of Wilhelmina Children's Hospital in Utrecht, The Netherlands and the parent organization for families with neurologic diseases (the BOSK). For inclusion and exclusion see Figure 2.

Fig. 2 Inclusion, exclusion and randomization of the USAGE study



Legend: SB = Spina Bifida; BOSK = Parent organization for families with neurological diseases.

Measurements were taken at the Child Development & Exercise Center at both the hospital and BIO research center, while supervised training took place at home. All study procedures were approved by the University Medical Ethics Committee. Children were included when they were (1) at least community ambulatory, (2) able to follow instructions regarding testing and training and (3) between 6 and 18 years of age. Parents and children signed informed-consent forms prior to testing.

Exclusion criteria were medical events that might interfere with the outcomes of the testing and/or medical status that did not allow maximum exercise testing.

Measurements

Demographics

Data concerning medical history were obtained from medical records and when not available through the parents. These data included type of SB, motor level of lesion, use of orthotics, ambulation level and sex.

Measures of Physical fitness

According to Bouchard et al., physical fitness consists of a combination of morphological, muscular and cardio-respiratory components, rather than one single measure (26). While aerobic fitness or peak oxygen uptake (VO_{2peak}) was the primary outcome measure in this domain, the following components were measured as well.

1. Weight, height and BMI

Weight was measured using an electronic scale. Height was measured while standing using a wall-mounted centimeter. Body Mass Index (BMI in kg/m^2) was derived from weight and height. Z-scores were calculated from Dutch growth charts.

2. Subcutaneous fat assessment

To assess fat percentage the sum of the seven following skin folds were used according to Pollock et al (27): triceps, biceps, subscapular, suprailliac, mid-abdominal, quadriceps and calf. Skinfold measurement provides an estimate of the total amount of subcutaneous fat. In adults several regression equations have been used to calculate fat percentage, but the validity of these equations in children (with SB) has not yet been established. Therefore in line with other research the sum of the skinfolds will be analyzed as an index for subcutaneous fat (28).

3. Muscular strength

Muscular strength refers to “the maximal force that can be generated by a specific muscle or muscle group”(29). Muscle strength was tested through use of a hand held dynamometer (HHD) as described by Beenhakker et al. (30). As an index for

upper muscle strength, handheld grip was recorded. Due to the recommendation to use HHD only in muscle groups scoring >3.5 in manual testing, many missing values were recorded in the lower extremity. For this reason, only quadriceps muscle strength was reported in this study for lower extremity strength.

4. Peak oxygen uptake (VO_{2peak})

In this study, maximal exercise testing was measured using a graded treadmill test (EnMill, Enraf, Delft, The Netherlands), using a protocol previously analyzed for validity and reproducibility in children with SB (31). In order to accommodate children with different ambulatory abilities, two progressive exercise test protocols were used. Children ambulating < 400 meters during a six-minute walking test (6MWT) were tested with a starting speed of 2 km/h, which was gradually increased by 0.25 km/h every minute, with a set grade of 2%. Children ambulating > 400 meters during the 6MWT were started at a speed of 3 km/h, with the speed being increased 0.50 km/h every minute, with a set grade of 2%. The cut-off point of 400 meters was chosen, based on earlier testing in our lab (15;31;32). Children were allowed to minimally use the handrails for maintenance of balance only. The protocols were continued until the patient stopped due to exhaustion, despite verbal encouragement from the test leader. During the incremental exercise test, physiologic responses, including breath-by-breath gas analysis, were measured using a heart rate (HR) monitor (Polar accurex, Polar-Nederland BV, Almere, the Netherlands) and calibrated mobile gas analysis system (Cortex Metamax B^3, Cortex Medical GmbH, Leipzig, Germany). The Cortex Metamax is a valid and reliable system for measuring gas-exchange parameters during exercise (33;34). Besides physiologic responses, maximal walking or running speed was recorded.

Measures of ambulation

1. Six-minute walk test (6MWT)

The test was performed on a thirteen-meter track in a straight corridor. Patients were instructed to cover the largest possible distance in six minutes at a self-selected walking speed. The test and encouragements during the test were performed in accordance with the American Thoracic Society guidelines (35). Next to HR in the last minute, the six-minute walking distance (6MWD) was recorded as primary outcome measure.

2. Energy cost of locomotion

Steady state (SS) normalized oxygen uptake (VO_2/kg/min) was calculated as the average value over the period during which oxygen consumption changed 5% or less, following the same methods as used in our reproducibility study (36). Within the period of least differences, a SS of two minutes was determined. Respiratory exchange ratio (RER) was calculated as VCO_2/VO_2 during steady state. Speed (m/min) was calculated as distance (m)/6 (min). Subsequently the following parameters were derived: Gross energy consumption (ECS_{gross}) and gross energy cost (EC_{gross}). ECS was expressed in J/kg/min, using SS VO_2 and RER in the following equation: J/kg/min = (4.960 x RER + 16.040) x VO_2/kg (37) . Furthermore gross energy cost (EC_{gross}) expressed in J/kg/m was calculated, dividing ECS_{gross} by speed. Reproducibilility of these energy measures was previously reported (36), with best outcomes for gross measures.

Measures of self-reported change and adherence to the program

After the intervention period, children and parents were asked to answer questions regarding change in both aerobic fitness and ambulation (see Appendix 1 for questions).

During the intervention period, a diary of daily physical activity was completed, including a diary of adherence to the exercise program for those in the intervention group. After the post-intervention follow up, children and parents from the intervention group were asked whether they had continued the treadmill program or any other type of physical activity.

Intervention

The intervention consisted of an individualized program taking into account HR_{peak} as well as the speed during the 6MWT to ensure an adequate intensity of training for both endurance and functional gait. The training consisted of intervals of different speeds, increasing throughout the 12 - week period based on fatigue, measured by the OMNI rating of perceived exertion scale and HR during exercise. In line with guidelines for exercise in children with chronic disease and/or disability, the child moved up to the next level (38) when fatigue reached 5 (on the 0-10 scale) or below and/or HR was below 66% of HR_{peak} For a full description of the program, see

Appendix 1. Children in the intervention group were instructed to exercise two times a week, next to their regular care. Children in the control group were instructed to maintain regular care and patterns of physical activity.

Post-intervention period

After the intervention period, patients were followed up to see if they were able to maintain possible effects of training on their own, by either continuing the treadmill program or by increasing daily physical activity. The treadmill remained at home during this post-intervention period. Children in both groups did not receive specific instructions during this period with regards to their daily physical activity.

Data analysis

Data were first checked whether they met assumptions for further statistical testing, including normality of data, normality of residuals and outliers. Missing values in the follow up measurements were filled in using the feed forward method.

Baseline data

Differences in baseline data between the intervention and control group were analyzed using unpaired T-tests and Mann-Whitney tests for not normally distributed data. Frequencies were compared, using the Chi-square test. To gain more insight about relations within baseline measures, Pearson or Spearman correlations were computed depending of type of data.

Efficacy of intervention

Differences between pre and post intervention period were calculated for both groups. These differences were compared between the groups, using unpaired T-tests or Mann-Whitney tests. For nominal data, the Chi-square test was used. Effect sizes were calculated using Cohen's d for significant differences. Cohen d less than .20 were considered small, d between .20 and .50 were considered medium, and effect sizes greater than .80 were considered large.

Maintenance of treatment effects

To test whether gains were maintained after treatment, paired T-tests were used for parameters that had showed improvement. Frequencies were used to describe the continuation of the program. Mixed between-within subjects analysis of variance was used to analyze long term effects of intervention. Effect sizes were calculated as

Partial Eta Squared (39), with eta less than 0.1 being considered small, eta = 0.6 moderate and eta > 0.14 as large effect. Significance for all tests was set at p=0.05. Statistical analyses were performed using statistical package SPSS version 17.

RESULTS

Baseline characteristics of both control and intervention group can be found in Table 1.

Table 1. Baseline characteristics

	Control	Intervention	P-value
Antropometrics			
Age	11.1 (2.6)	10.3 (2.9)	0.715
Boys:Girls	9:5	9:9	0.42#
Height	114.6 (16.1)	138.0 (19.7)	0.319
Weight	43.4 (18.6)	42.7 (22.5)	0.255
BMI	20.2 (5.1)	20.9 (5.7)	0.713
Sum of skinfolds	101.9 (56.6)	108.1 (58.2)	0.775
Ambulation			
Hoffer NA:CA	4:10	5:13	0.96#
6MWD	372.1 (116.5)	344.8 (125.3)	0.643
EC_{gross}	9.5 (6.9)	10.5 (6.4)	0.831
ECS_{gross}	487.4 (84.7)	460.2 (96.3)	0.427
Maximum test			
$VO2_{peak}$	33.4 (11.0)	32.3 (7.1)	0.185
HR_{peak}	174 (26)	169 (45)	0.669
RER_{peak}	0.97 (0.1)	0.96 (0.1)	0.769
$Speed_{peak}$	5.7 (1.9)	5.2 (2.0)	0.406
Muscle Strength			
Handgrip	86.4 (55.4)	73.9 (46.9)	0.495
Quadriceps	157.9 (51.0)	155.2 (62.8)	0.897
Fatigue and physical activity			
Total fatigue PEDS QL (%)	74.2 (16.2)	70.5 (16.4)	0.550
Self reported physical activity (min/week)	335.2 (176.2)	415.4 (171)	0.226

#Chi-square test; NA = normal ambulatory; CA = community ambulatory; 6MWD = six- minute walking distance; EC = energy cost; ECS = energy consumption

No significant differences were found at baseline between the control and intervention group. Presence of hydrocephalus and shunting were equally distributed between the groups as well as motor level and Chairi II Malformation,

with significance ranging from p = 0.14 to p = 0.95. Despite inclusion of normal and community ambulatory children only, the data do reflect a heterogeneous functional group as depicted by large SD's for 6 MWD, EC_{gross} and self reported physical activity. Secondary analysis for the group as a whole showed Z values for BMI to increase with age (r = 0.039 with p = 0.02) and level of lesion to be correlated with outcomes of 6MWT (r = 0.51 with p = 0.03) and normalized VO_{2peak} (r = 0.50 with p = 0.04).

Efficacy of intervention

Children in the intervention group reported a mean of 22.6 (± 6.2) completed training sessions, which resulted in 49.4 minutes (± 15) of treadmill ambulation per week, not including warming up or cooling down. Average training step (see Appendix 2) reached was 9.5 (± 3.2).

Table 2. Difference after intervention period (T1-T0)

	Control	Intervention	P-value	Effect size
Antropometrics	Mean (SD)	Mean (SD)		
Height	0.92 (1.1)**	1.2 (1.6)**	0.8#	
Weight	1.0 (1.9)	0.2 (1.6)	0.2	
BMI	-0.3 (0.9)	-0.1 (0.9)	0.1	
Sum of skinfolds	-2.4 (8.2)	-1.7 (17.5)	0.9	
Ambulation				
6MWD	-2.1 (27.8)	38.7 (34.6)**	0.002*	1.08
Percentage change 6MWD	-1.5 (10.1)	13.0 (12.4)**		
EC_{gross}	-0.8 (1.3)**	-0.3 (1.1)	0.2	
ECS_{gross}	-41.3 (63.7)**	49.1 (88.5)**	0.004*	1.01
Maximum test				
VO_{2peak}	-3.0 (7.5)	1.4 (3.7)	0.034*	0.78
Speed	-0.06 (0.6)	0.9 (0.8)**	0.001*	1.14
Muscle strength				
Handgrip (N)	-3.0 (7.6)	1.6 (9.9)	0.2	
Quadriceps (N)	-27.2 (27.2)**	-8.7 (71.7)	0.7#	
Fatigue and physical activity				
Total fatigue PEDS QL (%)	-0.4 (9.9)	7.8 (9.8)**	0.06	
Self reported physical activity (min/week)	-22.4 (145.3)	-8.3 (273.1)	0.66#	

* significant difference between groups; ** significant differences within groups; # non-parametric Mann-Whitney test; 6MWD = six- minute walking distance; EC = energy cost; ECS = energy consumption

No significant differences were recorded between groups with regards to anthropometric parameters and muscle strength (Table 2). Positive values can be interpreted as growth or improvements, with the exception for EC, in which negative values reflect improvement.

With respect to ambulation, there were significant differences between the two groups. After the intervention period, the children in the intervention group showed an improvement of 38.7 m during the 6MWT, while the children in the control group walked 2 m less compared to the first measurement.

The larger distance in the intervention group did not change gross energy cost of locomotion, while it did raise energy consumption per minute. EC was lowered significantly in the control group, but this difference falls within the measurement variability (36). The maximum graded exercise test showed significant differences between the groups in both VO_{2peak} and maximum speed. Effect sizes showed large effects for ambulation during both the 6MWT and treadmill test. It showed a moderate effect for VO_{2peak}. Because of the large SD's in the baseline measurements, secondary analyses were performed to analyze correlations between differences and baseline measurements. No correlations between baseline measures of ambulation or maximal exercise testing and differences after intervention were present. Differences after intervention regarding maximal speed, VO_{2peak} and 6MWD all correlated significantly with each other (p values between 0.03 – 0.04).

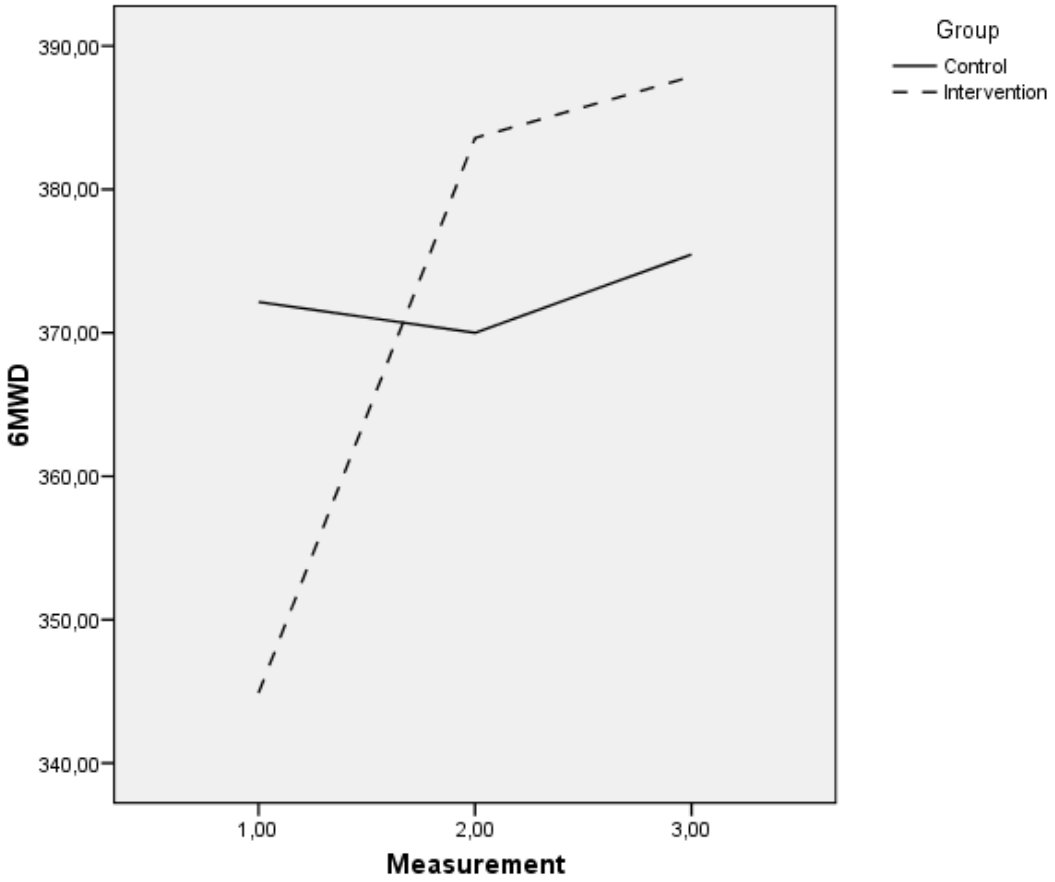
Self-perceived change showed significant differences between the groups, with 72% and 50% of parents of children in the intervention group reporting positive changes in endurance and respectively ambulation versus 5% ($p = 0.001$) and 0% ($p = 0.006$) in the control group. Qualitative changes were reported as well in terms like "now being able to join regular physical education classes at school", "nicer ambulation", "not wanting to use the wheelchair anymore for longer distances", "more initiative" and "easier to walk up and down stairs".

Maintenance of treatment effects

T-tests showed no significant changes between the post-intervention measurements and those taken three months after the last training regarding both

ambulation and aerobic fitness measures. This indicates that the gains from the intervention were not lost during the post-intervention period (see Fig. 3).

Fig. 3. Maintenance of Six-minutes walking distance (6MWD) at baseline, after intervention and three months after last training session



Mixed between-within subjects analysis of variance showed a large long term interaction effect of treatment for 6MWD ($p = 0.003$, ES = 0.34), maximal speed ($p = 0.003$, ES = 0.35) and ECS_{gross} ($p = 0.014$, ES = 0.29).

When asked whether the children in the intervention group had continued their program, 30% had continued using the treadmill, 27% had started some other type of activity (walking, biking, horseback riding or joining regular physical education

classes at school), while 39% reported no continuation or start up of new activities. Reasons for continuation were “just for fun”, “to further improve” or “my parents told me so”; reasons for not continuing were mostly “no time” or “no interest”, with one child being adapted with new orthotics making it impossible to continue.

DISCUSSION

The aim of this study was to evaluate the effects of an individualized treadmill training program aimed at improving both aerobic fitness and ambulation in ambulatory children and adolescents with SB.

While we did find large effect sizes for both over ground ambulation during the 6MWT and treadmill walking, these changes could not be related to our initial hypothesis of “diminished physiologic reserve”. While we did find moderate changes in VO_{2peak}, energy consumption during locomotion actually increased, keeping the physiologic reserve about the same.

The changes in ambulation are much in line with results from treadmill training in children with CP or adults with spinal cord injury, all reporting positive changes after treadmill training in ambulatory function.

While energy cost per meter did not change significantly, energy consumption did increase after intervention. At first, this seems like an unwanted change as it could indicate less efficiency during gait. Without changes in energy cost, the indicator of efficiency, it could also indicate more muscle mass being involved during ambulation resulting in faster ambulation. Unfortunately, without kinematic and electromyographic evaluation, this is hard to prove.

A recent study (40) looking at gait changes after treadmill training, concluded that improvements in speed were strongly correlating to kinematic changes and adaptations of muscle activation. Interestingly, maximal strength did not change after training, similar to our results. Increased muscle activation and changes in kinematic aspects of gait could be related to cerebral and/or spinal plasticity. De Bode et al. (41) have described changes in gait patterns related to physiological adaptations of the motor network in the brain after gait training in children post hemispherectomy. Other studies have looked at the possible role of plasticity at the spinal cord level in response to treadmill training (42-44) in both animal and human models. They conclude that “appropriate excitability level” of the

sensorimotor pathways can lead to restored function of the lumbosacral circuit of the spinal cord; this is the part were the “central pattern generator” circuits for locomotion are located. These studies raise exciting questions for future rehabilitation research in how to optimally stimulate these spinal cord pathways.

With regards to VO_{2peak}, there was a moderate effect size. Some other studies have reported larger increases in aerobic fitness (20;21), while some did not (45). One of the principles of training is the principle of overload of the target system (46). In the case of VO_{2peak}, the cardio-respiratory system needs to be trained a sufficient intensity for a sufficient period of time. Looking at the adherence diaries, children did comply to twice a week training for an average of 25 minutes per session, which could be considered a minimal time and frequency for training. As far as intensity though, Baquet et al. concluded in a review a target intensity of at least 80% of HR_{peak} when aiming to improve VO_{2peak} in children (47). In our study, in order to prevent overtraining and injuries to the musculoskeletal system, we have adhered to guidelines for children with chronic disease, in which training intensities at 60-70% of HR_{peak} are recommended (38). This may explain the smaller improvements in VO_{2peak}. During our training session, no injuries were reported, so it should be feasible to increase training intensity in the children with SB.

Yet, another principle of training is “specificity”, which refers to training the activity that needs improvement (46), in this case ambulation. While it would be tempting to increase the speed on the treadmill to running speed in order to increase the cardio-vascular load, it would decrease the specificity of training by altering the movement pattern from walking to running. It suggests that when implementing exercise training in ambulatory children with SB, one needs to choose which system will be target of training. This should be done based on the limiting factor in daily life (lack of aerobic fitness or walking pattern), or based on which system still shows room for improvement. Furthermore, the total intervention time (12 weeks) was relatively short. The study from Verschuren et al. has shown improvements to continue during an eight month trial in children with CP (21).

Looking at the self-reported patient outcome measures, the majority of parents and children in the intervention group did notice positive effects in activities of daily life compared to none in the control group. These changes could easily be described

as “placebo effect”, because the participants were not blinded. In this study though, these positive results are in line with the gains in ambulation and at the same time, and illustrate how positive laboratory changes are being perceived in daily life.

Looking at the possible washout effects, it is interesting to notice there were no significant differences between T1 (after training) and T2 (3 months after training), indicating children were able to maintain there functional gains for three months after training. This could be explained by the fact that close to 60% of the children had continued the treadmill training or had started some other type of sports. For some children, the training had made it possible to function at a higher level during sports, e.g. joining regular physical education classes at school or starting to play soccer. These findings do feed the theory of Bar-Or, in that reversing the downward spiral of detraining and deconditioning by improving function may indirectly lead to increased levels of activity and in the long run, possible increased levels of physical fitness.

Limitations of the study

The limitations of the study mainly involve the size of the study and the heterogeneity of the group. While heterogeneity is not ideal for research purposes, anyone working with this group of patients knows the many medical procedures these children undergo. We did not exclude the use of medication, but did look at possible effects of medication on outcome measurements. We did not find significant differences between those taking medication and those that did not.

Looking at baseline measures, measures of ambulation, maximal testing and muscle strength all show large variation within the groups. For this reason we did look at correlations between baseline measures and outcomes of training and no correlations were found.

Despite these limitations, this study still is one of the larger intervention studies available for children with SB, with many studies reporting outcomes on much smaller groups (48). Besides, this is the first RCT showing it is possible to improve ambulation in walking children with SB and that these improvements are maintained after the intervention period.

CONCLUSION

A home-based, progressive treadmill-training program for ambulatory children with SB has a large long-term effect on ambulation and a moderate short-term effect on VO_{2peak}.

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Appendix 1: Self-perceived improvement

Physical fitness/ambulation (of my child) is

1. *the same compared to the first measurement.*
2. *deteriorated since the first measurement; I notice this because…….*
3. *improved since the first measurement; I notice this because ……*
4. *I don't know*

Appendix 2: Training protocol

Step	Intervals	Repetitions	Total
Step 1	2 min at 70% $Speed_{6MWT}$ + 4 min at 100% $Speed_{6MWT}$	3	18 minutes
Step 2	**3** min at 70% $Speed_{6MWT}$ + 4 min at 100% $Speed_{6MWT}$	3	**21** minutes
Step 3	3 min at **70%** $Speed_{6MWT}$ + 4 min at **110%** $Speed_{6MWT}$	**4**	**28** minutes
Step 4	3 min at 80% $Speed_{6MWT}$ + 4 min at **120%** $Speed_{6MWT}$	4	28 minutes
Step 5	3 min at 80% $Speed_{6MWT}$ + **5** min at 120% $Speed_{6MWT}$	4	**32** minutes
Step 6	**4** min at 80% $Speed_{6MWT}$ + **6** min at 120% $Speed_{6MWT}$	**3**	**30** minutes
Step 7	4 min at **90%** $Speed_{6MWT}$ + 6 min at **130%** $Speed_{6MWT}$	3	30 minutes
Step 8	**3** min at 90% $Speed_{6MWT}$ + **7** min at 130% $Speed_{6MWT}$	3	30 minutes
Step 9	**2** min at 90% $Speed_{6MWT}$ + **8** min at 130% $Speed_{6MWT}$	3	30 minutes
Step 10	**3** min at **100%** $Speed_{6MWT}$ + **7** min at **140%** $Speed_{6MWT}$	3	30 minutes
Step 11	**2** min at 100% $Speed_{6MWT}$ + **8** min at 140% $Speed_{6MWT}$	3	30 minutes
Step 12	**1** min at 100% $Speed_{6MWT}$ + **9** min at 140% $Speed_{6MWT}$	3	30 minutes

General Discussion

Chapter 8

J.F. de Groot

DISCUSSION

In this chapter we will discuss the main results of the USAGE study. These results will be considered in the context of the study as a whole. For certain remaining questions, we have re-analyzed some data in order to further reflect on the relevance of the study.

The USAGE study was initiated based on several models in exercise physiology in which decreased physical activity levels were hypothetically related to reduced levels of fitness and function. We first described a general model of health-related fitness by Bouchard et al. (1) and then turned to a child-specific model of illness and hypoactivity by Bar-Or (2). We hypothesized that a physiologic explanation would account for the vicious downward cycle of deconditioning and decline in function and further diminished levels of physical activity. The theoretical model of diminished "physiologic reserve" served as a basis for physiologic measurements alongside functional measures throughout the USAGE study. In this model, VO_{2peak} and VO_2 during daily activities are related to each other, with the difference being considered as a reserve capacity. Existing literature has shown that both VO_{2peak} and efficiency of movement can be improved by exercise training, leading to the following hypothetical model for the USAGE study (see Fig 1.).

Fitness and energy cost of locomotion in ambulatory children with SB

Earlier studies have shown higher levels of energy expenditure during ambulation (3-12) and low VO_{2peak} (13) in children with SB, but correlations between these two separate physiologic constructs were not confirmed. Other studies have shown children and young adults with SB to be less active, with reduced levels of physical fitness compared to their healthy peers (13-15). Based on these results, Van den Berg-Emons (15) concluded that programs aimed at regular physical exercise and daily physical activity should be started in childhood to prevent further decline in physical fitness and daily functioning during adolescence and young adulthood.

In the first part of the USAGE study, we confirmed that ambulatory children with SB have significantly reduced muscle strength, six-minute walking distance (6MWD), aerobic capacity and levels of physical activity (PA), compared to reference values.

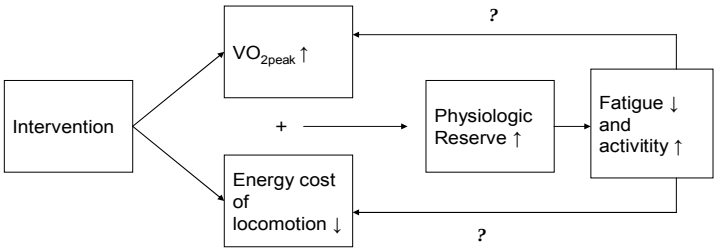

Fig. 1 Hypothetical model of training effect in children with SB on VO_{2peak}, energy cost of locomotion and physiologic reserve.

6MWD and aerobic capacity were significantly associated with muscle strength, especially with hip abductor and ankle muscles. Because lower levels of VO_{2peak} are not necessarily signs of poor cardiorespiratory fitness, but could be due to lower muscle mass or a symptom-limited test, data was re-analyzed to look for signs of deconditiong and possible relations with functional ambulation. Based on high heart rate response, generalized muscle weakness and low levels of PA, we concluded that VO_{2peak} seems to be mostly limited by deconditioning and/or muscular components, but also possibly by ventilatory factors. For both peak values and functional ambulation, community ambulators were significantly more impaired than normal ambulators. High energy expenditure, $\%VO_{2peak}$ and $\%HR_{peak}$ reflect high level of strain during ambulation in the community ambulators. We found aerobic capacity to be strongly related with muscle strength. Nonetheless, daily physical activity measured by diary, showed no correlations with physical fitness parameters. Questions can be raised about the use of subjective recall when using a diary. Preliminary data from the USAGE study suggest a moderate negative correlation ($r = -0.525$ with $p = 0.01$) between self-reported measures and objectively measured activity with an accelerometer, which is in line with other

studies. An accelerometer estimates accelerations produced by movement of a body segment or limb parts, which are then converted into “accelero-counts”. These counts are then used to predict physical activity energy expenditure, which is used to interpret the level of daily PA. Even using these objective measures, one may wonder about the validity of the predictions when dealing with patient groups with higher energy expenditure during ambulation, like children and adolescents with SB (16). For these reasons we are currently looking into data collected by accelerometry in children with SB.

Looking back at these studies, the question remains: what do these correlations between measures of fitness and ambulation mean? High VO_{2peak} and low energy cost of locomotion result in a large physiologic reserve. High VO_{2peak} and low energy cost probably also reflect outcomes of lower lesion levels and thus better muscular strength and ambulatory function to begin with. We analyzed our pooled data base from the different studies (n=70) to correct for level of lesion for correlations between VO_{2peak} and energy expenditure measures, which led to some some interesting findings. First, when comparing low, middle and higher level of motor lesion, we found significant differences in 6MWD and EC_{gross} when comparing the higher level lesions to the middle or lower lesions, but not for Z-values of VO_{2peak}/kg. So, while those with higher level of lesion walked a significantly shorter distance (316 compared to 406 and 429 m) at a much higher cost (9.9 compared to 6.3 and 6.2 J/kg/m), their level of aerobic capacity compared to healthy peers, expressed in Z-values, was not significantly different (-3.2 versus -2.6 and -2.2) from children with low levels of lesion. We will come back to these post-analyses in part three of the discussion.

Another question raised by on these first studies pertains to the methods of measuring VO_{2peak} and energy expenditure. Despite subjective signs of peak effort, the treadmill testing resulted in both low HR_{peak} and RER_{peak} values, causing doubt about the true maximal character of the testing procedures. These issues were further addressed in the second part of the USAGE study.

Development of appropriate exercise testing for ambulatory children with SB

This part of the study was designed for appropriate ways to evaluate effects of intervention. In light of the USAGE study, the main outcome measures to be evaluated were VO_{2peak}, ambulation and energy expenditure during walking. Other measures included anthropometric measures, measures of muscle strength and measures of physical activity, the latter still being evalutated.

Our first question regarding these measurements was derived from the earlier pilot study. Despite subjective signs of peak effort, the treadmill testing resulted in both low HR_{peak} and RER_{peak} values, calling into question the true maximal character of the testing procedures. Supra-maximal testing was used to evaluate the true maximal character of the adapted treadmill test. We concluded that HR_{peak} at less than predicted levels might be an indication of sub-maximal effort. When the true character of the maximum testing is in doubt, a supra-maximal step of 110% is an easy and well tolerated method in ambulatory children with SB for the confirmation and further interpretation of maximum exercise testing. Interestingly, in recent literature questions are being raised about the criteria for HR_{peak} and RER_{peak} for true maximal testing in healthy adults, with supra-maximal testing being proposed as a possible suitable verification criterion threshold for confirming true VO_{2peak} (17, 18).

The second question involved reproducibility of our outcome measures. While measurements of both the 6MWT, maximal exercise testing and energy expenditure showed high intra-class correlations (ICC), clinical use of some of these measures is limited by questionable levels of agreement. Despite stable performance measures, certain physiologic measures showed large inter-test variability and should be used with caution. Reliability of energy expenditure during gait had been described earlier in other patient groups. Outcomes of reliability of energy expenditure measures are comparable to those presented in the existing literature regarding agreement for energy expenditure in children with ambulatory difficulties (19), but agreement is much higher in healthy children (20). To deal with the moderate agreement of energy expenditure in patients with ambulatory difficulties, modifications have been proposed to improve reproducibility of energy expenditure of locomotion (21). While these methodological changes might improve scientific outcomes, uncertainty remains regarding the practical

implications of needing several repetitions of these expensive and “high-tech” measurements for four weeks in a row to establish a baseline measurement in the clinical setting. Schwartz et al. (22) have shown a reduction in variation of energy expenditure in healthy adults and adolescents with Cerebral Palsy, by calculating a non-dimensional speed. Using this method in our data, these adjustments did not reduce intra-individual variability. Further research is recommended to determine more reliable measures or methods of energy expenditure in ambulatory children with SB, possibly taking into account different age groups.

Based on the studies regarding exercise testing in ambulatory children with SB, we decided to use gross energy expenditure measures of locomotion for energy measures, VO_{2peak} and HR_{peak} as maximal exercise measures and both the 6MWT and the $speed_{peak}$ as functional outcomes of ambulation for the evalution and set-up of an exercise program.

Intervention aimed to improve ambulation and physical fitness

Our initial hypothesis was that increasing VO_{2peak} and reducing energy expenditure during ambulation would increase the “physiologic reserve” (see Fig. 2).

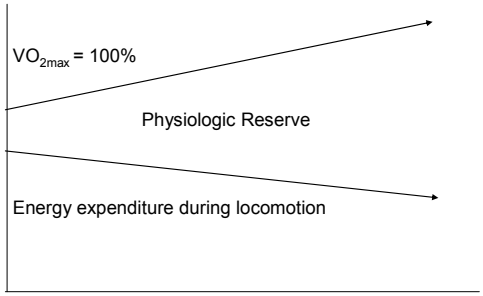

Fig. 2 Proposed effects of training in the USAGE study

This hypothesis was supported by negative correlations between oxygen expenditure during ambulation and VO_{2peak} in chapter 3 (11).

While we did find large effect sizes for both over-ground ambulation during the 6MWT and treadmill walking, these changes could not be related to our initial hypothesis of "diminished physiologic reserve". We did not find large changes in either VO_{2peak} or energy cost of locomotion. In our discussion we then hypothesized that the functional changes cannot be explained by an increase of the physiological reserve, but are more in line with theories of skill acquisition and neural plasticity (23-25)((26, 27).

Another explanation could be different constructs underlying energy expenditure and maximal exercise capacity. Another analyses of our full data set suggests that both both VO_{2peak} and energy exenditure are important factors for ambulatory function, but that they are not necessarily strongly related. When correcting for age and level of lesion and taking into account outcomes compared to healthy peers (Z-scores), the following model emerges:

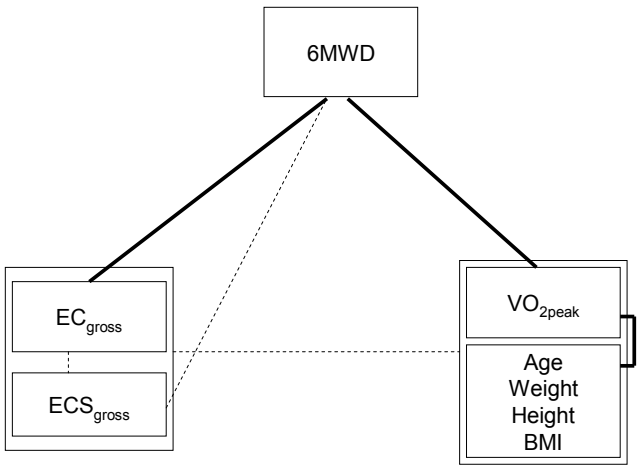

Fig. 3 Revised model of aerobic capacity, predicted 6MWD and Energy Expenditure

In this model significant correlations ($p < 0.05$) were found between predicted 6MWD, VO_{2peak} ($r = 0.5$) and energy cost ($r = -0.67$), while only small correlations between energy expenditure measures and VO_{2peak} ($r = 0.25$). VO_{2peak}, BMI, length and weight correlate moderately.These correlations are complex though, and are partly confounded by age, level of lesion and possible other factors and painting the need for further analysis. They do however, seem to imply different constructs for the relationship between strength, aerobic capacity and energy expenditure during ambulation, in opposition to our initial hypothesis. Looking at the *differences* after training (Fig. 4), differences in energy consumption are related ($r = 0.45$, $p < 0.05$) to differences in 6MWD, while differences in VO_{2peak} are related ($r = 0.6$, $p < 0.05$) to differences in $Speed_{peak}$. It seems to imply that functional improvements cannot be fully explained by exercise physiologic measures and theories and should be augmented by models of motor learning, skill acquisition and neural plasticity.

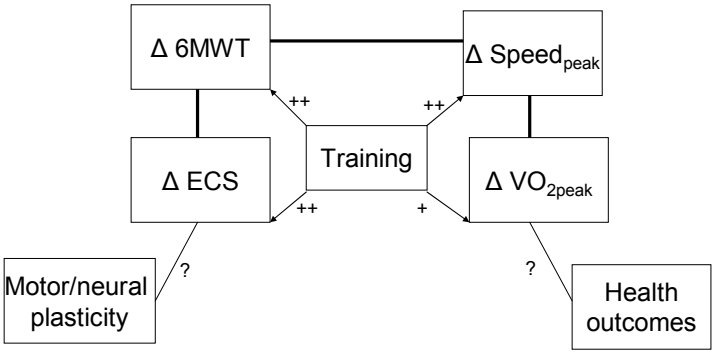

Fig. 4. Effect of training and correlations between differences after training in the USAGE study

As far as VO_{2peak} is concerned, there are still important reasons for improving VO_{2peak} in children with SB. Even though not directly related to changes in energy cost and the 6MWD, being able to utilize oxygen at a certain level, seems a precondition to any form of activity in daily life for an extended period of time.

Secondly, like in other children and adults, increasing physical fitness and reducing metabolic risk factors are important in the prevention of disease and optimal health. When aiming to improve cardiorespiratoy fitness though, intensity of training should be increased to 70-80% of HR_{peak}.

Limitations of the USAGE study

The main limitations of the different studies within the USAGE study concern sample size and heterogeneity. The small study sizes are partly due to drop out or missing measurements during the study, but also to the limited availability of children to participate. During the study, children could only be included if they did not have current medical issues and/or planned procedures during the course of the study that could interfere with the outcomes of the study. Children with SB are known to need frequent medical interventions or adjustments of orthotics. For regular care this should not be an obstacle for training, but for research purposes it obviously is. We did not exclude the use of medication, but did look at possible effects of medication on outcome measurements. We did not find significant differences regarding outcome measures between those taking certain types of medication and those that did not. While sample size is an issue, the USAGE study still is one of the larger randomized intervention studies available for ambulatory children with SB, with many studies reporting outcomes on much smaller groups (28, 29).

The second limitation involves the heterogeneity of the group. The baseline values show large variation in measures of ambulation, maximal testing and muscle strength. While not ideal, and possibly underestimating effects of treatment, this again is the reality of working with children with SB. Factors like cognitive status, presence of Chiari II malformation, hydrochephalus, obesity, use of different type of orthotics and spasticity seem important in the reported range of functional levels despite the same level of lesion. For this reason we did look at correlations between baseline measures and outcomes of training, but no correlations were found between these variables.

A last limitation concerns the way we have looked at some of the outcome measures throughout the USAGE study. We have limited ourselves to measures in exercise physiology to explain function (in this case ambulation). Looking back at

the results, the functional improvements without clear physiological changes do raise questions about other contributing systems (e.g. neurophysiologic models, models of motor learning, biomechanical models of ambulation or models of human behavior) possibly explaining the positive changes. Time, means and burdening of the patients played a role in the choices that were made. At the same time,

Future research

A couple of interesting points for future study emerge from the USAGE study.

1. While the control group was asked not to participate in extra physical activities, most of them did have regular weekly or bi-weekly physical therapy sessions, often aimed to improve muscle strength and components of ambulation. The control group did not show any improvements during the course of the trial. This may suggest that future research should focus on prescription of intensity and frequency of physical therapy interventions in relation to therapeutic goals for children with SB.

2. Related to this question, and in line with theories of motor learning and neural plasticity, future research looking into optimal intensity, frequency, time and amount of repetition would enhance our current knowledge for what is necessary for skill training and/or development in children with motor delay or reduced motor function. Research has even suggested that treadmill training of infants with motor delay is a promising way stimulate the development of walking (30, 31), so another subject of research could be the optimal developmental stages in early childhood to introduce functional training.

3. With the available evidence of decline in health-related fitness in adolescents and young adults with SB (32), further research is needed to optimize transition from childhood to young adulthood. A longitudinal study is advisable to look at ambulatory function and health- related fitness, including metabolic risk factors for cardiovascular disease, which are associated with low levels of physical activity. Several studies have reported high prevalence of metabolic risk factors in adolescences with SB (33, 34), so staying active remains an important goal for

children with SB. Parents during a BOSK meeting in 2009 did voice their motivation and interest to have their children participate in sports more, but find many obstacles along the way to do so. Such research should also include facilitators an inhibitors throughout childhood and adolescents for participation in sports activities.

Clinical bottomline

- Ambulatory children and adolescents with SB show signs of deconditioning and inactivity, which warrants early intervention to promote an active and healthy lifestyle.
- For the assessment and evaluation of functional ambulation and maximal capacity, the six-minute walk test the maximal treadmill test as described in chapter 5 and 6 are valid, reliable and easy-to-use measures of (functional) endurance and ambulation.
- When aiming to improve ambulation in children with SB, a treadmill program is effective, more so than the current usual care which is often aimed at components of ambulation.

A final point to consider

A final interesting point is raised by Kuo and Donelan (35). They state that while researchers and therapists are often interested in reducing energy cost of locomotion in order to keep patients ambulatory, individuals may have their own interest in walking the way they do or not do. Consider the examples of wearing high heels, walking too fast or the emerging trend of using "fit flops". In these cases not energy cost of locomotion, but fashion, a concern for being on time or even the desire to *increase* energy cost during ambulation (in order to lose weight), respectively, plays an important role in the way one walks. The same can be argued for our patient population. While researchers and therapists may advise treadmill training or the use of orthotics to stay ambulatory, the individual patient may still choose to use a wheelchair for locomotion purposes, in order to save energy for participation in school, sports or social activities. That said, this seems the right time to quote an adult patient with SB who attended a recent BOSK meeting: *"I used to walk and even play soccer. Due to social circumstances I chose*

to use the wheelchair more and more and I should warn you (parents): once in the wheelchair, my level of fitness plummeted and I cannot get it back up to my old level". This suggests the importance of including the patient in the goal setting for both the research and individual therapy, and underscores the value of staying ambulatory (when possible) for an active lifestyle in children with Spina Bifida.

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Summary

Chapter 1 describes the relevance of the USAGE study, starting with a general introduction of physical activity, health-related fitness and the importance of raising fit and healthy children. Children with chronic disease or child-onset disability, like Spina Bifida (SB), are at increased risk of being inactive. Earlier studies in adolescents and young adults, have found correlations between an inactive lifestyle and lower levels of aerobic fitness. A second important issue raised in this chapter is that of raised levels of energy cost of locomotion. With ambulation levels decreasing during the teenage years in many ambulatory children with SB, reducing energy cost of locomotion could be beneficial for this group of children. The two factors are combined in the hypothesis of "diminished physiologic reserve". The USAGE study builds on this hypothesis positing that improving aerobic fitness, and/or decreasing energy cost of locomotion, will make walking easier for ambulatory children with SB.

Chapter 2 is a cross-sectional study, investigating deficits and associations in muscle strength, 6-minute walking distance (6MWD), aerobic capacity (VO_{2peak}), and physical activity (PA) in independent ambulatory children with lumbosacral spina bifida. Results show that these children have significantly reduced muscle strength, 6MWD, VO_{2peak} and lower levels of PA, compared to reference values. VO_{2peak} and 6MWD were significantly associated with muscle strength, especially with hip abductor and ankle muscles. Therefore, even in independent ambulating children, training to improve endurance and muscle strength seems indicated.

In **Chapter 3** the findings from Chapter 2 are further analyzed and interpreted. Looking more closely at the outcomes of exercise testing, endurance (VO_{2peak}) seems to be mostly limited by deconditioning and/or muscular components and possible ventilatory factors. For VO_{2peak} and functional ambulation, community ambulators were significantly more impaired than normal ambulators. High energy expenditure, both absolute and relatieve ($\%VO_{2peak}$ and $\%HR_{peak}$), reflect high levels of strain during ambulation in both community and normal ambulatory children with SB. Exercise training in these ambulatory children should focus on increasing both VO_{2peak} as well as decreasing energy cost of locomotion.

Chapter 4 studies the reproducibility of energy expenditure measures during gait in ambulatory children with SB. Earlier studies had shown higher levels of energy expenditure during ambulation in patients with SB, compared to healthy children. These studies, however, are hard to interpret and compare, as different protocols were used regarding both mode of testing (treadmill versus level ground), walking speed (self-selected versus imposed), calculation of energy cost, and preparation of the subjects.

Moreover, they often do not report true energy expenditure in caloric units or Joules, but rather oxygen expenditure (VO_2). Since substrate utilization (fatty acids versus carbohydrates) per liter oxygen results in different amounts of energy expenditure, this is an important distinction. For these reasons, new methodology has been proposed in recent literature to evaluate energy expenditure during gait. These changes include (1) use of energetic outcomes versus oxygen utilization and (2) net versus gross outcomes.

Reproducibility of energy expenditure during ambulation in children with SB should be considered carefully when using these measures in the evaluation of gait. High reliability of energy expenditure measurements makes these measurements appropriate to use as discriminative tools in children with SB, while agreement of only gross EC seems acceptable to use as an evaluative tool in children with SB. Overall, measures of reliability and agreement seem higher in young children than in adolescents. Further research is recommended to determine clinically relevant changes in energy expenditure in children with SB.

In earlier studies (Chapter 2 and 3), we had reported reduced VO_{2peak} values, using a treadmill exercise test in ambulatory children with SB. At the same time, low HR_{peak} and RER_{peak} in both our study and the literature raised questions regarding the true maximal character of VO_{2peak} values obtained from this mode of testing. In **Chapter 5,** a supra-maximal test was used to confirm that VO_{2peak}, measured during an adapted graded treadmill exercise test, reflects VO_{2max} in ambulatory children with SB.

In **Chapter 6,** the purpose reproducibility of both maximal and sub-maximal outcomes of exercise testing in ambulatory children with SB is assessed. Since research labs and clinical settings differ in both equipment and experience in exercise testing, both physiologic and performance parameters were analyzed in this study. While some less common measures, such as Oxygen Uptake Efficiency Slope (OUES) and Heart Rate Response (HRR) were subjects of study, we concluded that better known measures such as HR and VO_{2peak}, as well as performance outcomes (speed and 6MWD), can be used in the evaluation of exercise capacity at the maximal or submaximal level in ambulatory children with SB. Maximal measures are more reliable than those at the ventilatory threshold; and HR measures seem more reliable than oxygen measures, with functional outcomes – both treadmill speed and the 6MWD - being superior to all in detecting change.

Many ambulatory children with Spina Bifida (SB) experience functional decline in ambulation despite stable or even improving motor exams. Improving or maintaining low energy cost of locomotion during childhood and throughout the teenage years, could be an important goal for children with SB. In **Chapter 7,** the effects of a home-based treadmill training program on both ambulatory measures and aerobic fitness are evaluated. The training consisted of intervals of different speeds, increasing throughout the 12 week period based on fatigue and heart rate intensity during exercise. Results show the intervention to be effective for both short term and long term outcomes regarding ambulation, with moderate short term effects on aerobic fitness in ambulatory children with SB.

Finally, in **Chapter 8** the main results of the USAGE study are discussed and considered in the context of the study as a whole. While we did find large effect sizes for both over-ground ambulation during the six-minute walk test and treadmill walking, these changes could not be related to our initial hypothesis of “diminished physiologic reserve”. We did not find large changes in either VO_{2peak} or energy cost of locomotion. The functional changes cannot be explained by an increase of the

physiological reserve, but seem more in line with theories of skill acquisition and neural plasticity. This raises possibilities for future research to improve our understanding of the optimal intensity, frequency, repetition and timing of functional training in children with motor delay or reduced motor function. Despite some limitations regarding sample size and heterogeneity, this is the first randomized study to show it is possible to improve ambulation in children with SB. Next to the functional benefits in daily life, being able to walk is an important factor in maintaining an active lifestyle, crucial for optimizing health-related fitness, prevention of obesitas and other riskfactors for disease in children with SB.

Based on this study, the main recommendations are (1) to include lifestyle advice in early childhood in order to prevent a vicous cycle of inactivity and deconditioning later on, (2) to use the six-minute walk test and the USAGE treadmill protocol to measure (functional) endurance and ambulation. Based on these measures, the individual training parameters can be determined for each child; and (3) when aiming to improve ambulation in normal or community ambulatory children, treadmill training has been proven effective.

Samenvatting

In **Hoofdstuk 1** wordt de aanleiding en de relevantie van de *U*trecht *S*pina Bifida *A*nd *G*raded *E*xercise (*USAGE*) studie besproken. In eerste instantie wordt vanuit het model van Bouchard het belang van fysieke activiteit voor gezondheidsgerelateerde fitheid bij kinderen uitgelegd. Terwijl gezonde Nederlandse kinderen steeds minder actief en minder fit zijn, hebben kinderen met een aandoening of motorische beperking, zoals Spina Bifida (SB) een verhoogd risico op een inactieve leefstijl en de daaraan gerelateerde gezondheidsrisico's. Eerdere studies hebben inderdaad al aangetoond dat er verbanden zijn tussen inactiviteit en verminderde fitheid bij jongvolwassenen met SB. Het is natuurlijk de vraag of deze zaken niet al eerder spelen en in de kinderjaren beginnen.
Een tweede belangrijke factor die in dit hoofdstuk aan bod komt is het verhoogde energieverbruik bij kinderen met SB tijdens het lopen; met de kennis dat de tienerjaren vaak bepalend zijn of een persoon met SB blijft lopen, kan het verlagen van het energieverbruik tijdens het lopen een belangrijk doel zijn voor kinderen met SB. Ten slotte worden deze twee factoren, een verlaagde fitheid enerzijds en een verhoogd energieverbruik anderzijds gecombineerd in de hypothese van een "verlaagde fysiologische reserve", waardoor activiteiten te vermoeiend worden om te blijven doen; de USAGE studie bouwt verder op deze hypothese dat het verhogen van fitheid en/of het verlagen van de energiekosten tijdens het lopen, het lopen weer gemakkelijk wordt voor kinderen met SB.

Hoofdstuk 2 is een cross-sectionele studie, waarin beschreven wordt wat de beperkingen zijn wat betreft spierkracht, de 6 minuten wandeltest (6MWT), uithoudingsvermogen (VO_{2piek}) en fysieke activiteit. Daarnaast worden de relaties tussen deze factoren bij lopende kinderen met SB besproken. Resultaten laten zien dat deze kinderen significant lager scoren op deze uitkomstmaten in vergelijking met gezonde Nederlandse leeftijdsgenoten. VO_{2piek} en de 6MWT waren significant geassocieerd met spierkracht in vooral de heupabductoren en de kuitspieren.

In **hoofdstuk 3** worden de bevindingen van hoofdstuk 2 verder geanalyseerd en geïnterpreteerd. Wanneer de uitkomsten van de inspanningstesten (VO_{2piek}) verder geanalyseerd worden, dan lijkt het uithoudingsvermogen vooral gelimiteerd door

tekenen van een verlaagde conditie en mogelijk ook door ventilatoire factoren. Hierbij twee groepen kinderen met elkaar vergeleken, n.l. kinderen die geclassificeerd zijn als “buitenshuis ambulant” en kinderen die geclassificeerd zijn als “normaal ambulant ”. De eerste groep heeft een rolstoel voor het overbruggen van lange afstanden, de tweede groep niet. Tussen kinderen met SB die “buitenshuis ambulant” of “normaal ambulant ”zijn, zijn er significante verschillen wat betreft VO_{2piek} ,de 6 MWT en energiekosten tijdens het lopen, in het voordeel van de “normaal ambulante” kinderen. Tenslotte wijzen zowel hoge absolute als relatieve ($\%VO_{2piek}$ en $\%HR_{piek}$) energiekosten op een hoge intensiteit van het lopen bij vooral de “buitenshuis ambulante” kinderen, maar ook bij de “normaal ambulante” kinderen met SB. Een trainingsprogramma lijkt geïndiceerd voor lopende kinderen met SB, met als hoofddoelen het verhogen van het uithoudingvermogen en het verlagen van de energiekosten tijdens het lopen.

Hoofdstuk 4 beschrijft de reproduceerbaarheid van de maten voor energieverbruik tijdens het lopen bij kinderen met SB. Hoewel er veel studies zijn die laten zien dat het energieverbruik en de energiekosten sterk verhoogd zijn bij kinderen met SB in vergelijking met gezonde kinderen zonder een motorische beperking, zijn er geen eenduidige meetprotocollen of gegevens over reproduceerbaarheid. De protocollen verschillen op punten als lopen op de loopband versus lopen in de gang, opgelegde loopsnelheid versus zelfgekozen loopsnelheid, de analyse van de data en de voorbereiding van de proefpersonen. Daarnaast wordt vaak niet berekend naar energetische waarden (kcal of kJ), maar wordt enkel de zuurstofconsumptie (VO_2) berekend. Aangezien het uitmaakt of vetzuren versus koolhydraten worden verbrand per hoeveelheid zuurstof is dit verschil van belang. Vanwege deze redenen wordt in de recente literatuur aangeraden om (1) energetische uitkomstmaten te gebruiken i.p.v. zuurstofmaten en (2) netto en bruto waarden apart te vermelden. De reproduceerbaarheid van energetische waarden tijdens het lopen bij kinderen met SB is belangrijk wanneer deze maat wordt gebruikt om effecten van interventies (zoals training of orthoses) te evalueren. De resultaten van dit onderzoek lieten een hoge betrouwbaarheid (uitgedrukt als ICC) zien, wat goede maten zijn wanneer groepen worden gevolgd. Tegelijkertijd was de meetfout

van de meeste uitkomstmaten vrij groot, wat het een lastig bruikbaar instrument maakt om de individuele verschillen aan te tonen voor of na interventie. De bruto energiematen hebben een acceptabele meetfout en kunnen best gebruikt worden voor de individuele evaluatie van een interventie. In het algemeen leken zowel de betrouwbaarheid als de meetfout beter in jonge kinderen in vergelijking met de oudere kinderen, maar de groep is te klein om daar een harde uitspraak over te kunnen doen. Toekomstig onderzoek zou moeten kijken naar de klinisch relevante verandering van energetische maten tijdens het lopen bij kinderen met SB.

In hoofdstuk 2 en 3, hadden we lage VO_{2piek} waarden gevonden bij de lopende kinderen met SB. Tegelijkertijd vonden we ook een lage maximale hartslag (HR_{piek}) en een lage "respiratoire exchange ratio" (RER_{piek}) in overeenstemming met met bestaande literatuur. Dit deed vraagtekens rijzen bij het maximale karakter van de loopbandtest die gebruikt was voor de bepaling van VO_{2piek}. In **Hoofdstuk 5,** is een supra-maximaal protocol gebruikt met een kleine aanpassing van het loopbandprotocol om de VO_{2piek} te bevestingen. Er waren geen significante verschillen tussen de VO_{2piek} en de supra-maximale VO_{2piek}, daarbij werden nu wel hogere RER_{piek} en HR_{piek} en dus werd geconcludeerd dat het vernieuwde protocol een goede methode is om het uithoudingsvermogen bij lopende kinderen met SB te meten.

In **Hoofdstuk 6** is de reproduceerbaarheid van een aantal submaximale en maximale maten van inspanningstolerantie geanalyseerd bij lopende kinderen met SB. Aangezien onderzoekscentra en fysiotherapie praktijken verschillen in meetapparatuur en expertise, werd de reproduceerbaarheid van zowel fysiologische maten als functionele maten beschreven. Een aantal maten, zoals de Oxygen Uptake Efficiency Slope (OUES) en Heart Rate Response (HRR), dat onafhankelijk is van het maximale karakter van de inspanningstesten werd ook meegenomen in de analyse. Desondanks was de conclusie dat naast de functionele maten (maximale loopsnelheid en de afstand van de 6MWT), hartslag VO_{2piek} goede uitkomstmaten zijn om de inspanningstolerantie van lopende kinderen met SB te evalueren of te gebruiken om trainingsprogramma's op te

stellen. Maximale uitkomstmaen waren bovendien betrouwbaarder dan submaximale uitkomsten en hartslag maten waren stabieler dan zuurstof maten.

Veel lopende kinderen met SB ervaren een achteruitgang in de loopfunctie ondanks een stabiel laesie niveau. Het verbeteren van het lopen gedurende de kindertijd en adolescentie kan een belangrijk doel zijn voor interventie voor kinderen met SB. In **Hoofdstuk 7,** worden de effecten van een loopbandtraining beschreven op zowel het lopen als uithoudingsvermogen. Gedurende 12 weken werd twee keer per week thuis getraind onder supervisie. Op basis van hartslag en vermoeidheid werd de intensiteit van de training verhoogd. Na de interventie periode waren significante en grote positieve effecten te zien met betrekking tot de loopfunctie (zowel de gelopen afstand tijdens de 6MWT als de maximale snelheid op de loopband) en het uithoudingsvermogen (VO_{2piek}). Drie maanden na afloop van de training zijn de effecten op het lopen nog steeds zichtbaar, maar niet meer op het uihoudingsvermogen. De conclusie is dat de loopbandtraining op zowel korte als langere termijn een groot positief effect heeft op de loopfunctie bij lopende kinderen met SB te verbeteren. Daarnaast bemerken zowel kinderen als ouders een positief effect van de training op loopfunctie en uithoudingvermogen op participatie niveau in het dagelijks leven.

Tot slot worden in **Hoofdstuk 8** de belangrijkste resultaten van de USAGE studie besproken in de context van de hele studie. Hoewel we grote effecten vonden van training op het lopen, kunnen deze effecten niet worden verklaard door de initiële hypothese van de “verminderde fysiologische reserve”. Ondanks het verschil in uithoudingsvermogen, waren er geen grote veranderingen in VO_{2piek} en/of energiekosten tijdens het lopen. De functionele vooruitgang lijkt wel in overeenstemming met theorieën van motorisch leren en neurale plasticiteit. Dit levert een mooie basis voor toekomstig onderzoek om de optimale intensiteit, frequentie, tijd en periode te bepalen voor training van motorische vaardigheden bij kinderen met een motorisch achterstand of motorisch beperkingen. Dit is de eerste studie die laat zien dat de loopfunctie bij kinderen met SB door training verbeterd kan worden. Dit is niet alleen een functioneel voordeel, maar ook een positieve uitkomst in het kader van een actieve leefstijl bij kinderen met SB. Lopende

kinderen met SB zijn actiever dan niet lopende kinderen met SB, met mogelijk positieve gevolgen op fitheid, preventie van obesitas en andere gezondheidsrisicofactoren op lange termijn.

Dankwoord

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Curriculum Vitae and List of Publications

Curriculum Vitae

Janke de Groot was born on February 24, 1971 in Enschede, The Netherlands. A graduate of Stedelijk Gymnasium Haarlem (1989), she completed her MSc degree in Rehabilitation Sciences at the Katholieke Universiteit Leuven in Belgium in 1994. In that same year, she emigrated to the United States of America. There she lived and worked for seven years as a physical therapist in the beautiful Northwest, first at Oregon Health Sciences University Medical Center (Portland, OR) and then in the rehabilitation department of Swedish Medical Center, Seattle, WA (1996-2001). At Swedish M.C. she served as lead physical therapist and chaired the continuous-quality-improvement committee. During those same years, she also earned a certificate in Medical Management from the University of Washington Medical School and became an APTA-certified Clinical Instructor.

In 2001, she returned to the Netherlands, where she taught neuro-rehabiliation and physiology at Thim van der Laan school of physical therapy. Desiring to combine teaching with research, she began teaching in the newly-established MSc-degree program in Physiotherapy Sciences at Utrecht University and at the University of Applied Sciences in Utrecht. In 2005, she joined the research group “Lifestyle and Health”, beginning her PhD research the following year at Wilhelmina Children’s Hospital, University Medical Center, Utrecht in 2006. During her PhD years, she has continued to teach at the University of Applied Sciences in the departments of physical therapy and exercise therapy. Since 2009, she has chaired that school’s curriculum committee for the department of physical therapy (bachelor-degree). Janke currently lives in Utrecht with her husband, Tim Schilling, and their two children, Annegien (11) and Pieter (7).

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de Groot JF, Takken T, Schoenmakers MACG, Gooskens R, Van Brussel M, Versteeg C, Vanhees L Helders PJM. Randomized controlled study of home-based treadmill training for ambulatory children with Spina Bifida. Accepted for publication in Physical Therapy.

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Funding for USAGE study

Hogeschool Utrecht: PhD voucher for the period January 2007 - January 2011.

KNGF: Accelerometry study 2008.

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