

# Physical fitness, functional ability and quality of life in children with severe haemophilia: a pilot study

J. VAN DER NET,\* R. C. VOS,\* R. H. H. ENGELBERT,\* M. H. VAN DEN BERG,† P. J. M. HELDERS\* and T. TAKKEN\*

\*Department of Paediatric Physiotherapy and Paediatric Exercise Physiology, University Children's Hospital, UMC Utrecht; and †Van Crevelt Clinic, UMC Utrecht, the Netherlands

**Summary.** In the Netherlands comparable levels of sports-participation between persons with haemophilia and healthy controls have been reported. This raises the question if children with haemophilia under the currently available prophylaxis do reach comparable levels of physical fitness and health-related quality of life (HRQoL) as their healthy peers. The aim of this study was to investigate the level of physical fitness, functional ability and quality of life and to determine the feasibility to safely test the exercise capacity of boys with severe haemophilia A. Thirteen subjects participated in this study. Physical fitness was determined using the measurement of maximal oxygen uptake ( $VO_{2peak}$ ) attained during a graded maximal exercise test to volitional exhaustion. Joint health, physical activity levels and health-related quality of life (Haemo-QoL) were also measured. Mean  $VO_{2peak}$  was  $1.86 \pm 0.77$  L  $min^{-1}$  (Z-score:  $-0.39 \pm 1.61$ ) which was not significantly

different from reference values. Relative  $VO_{2peak}$  was  $47.42 \pm 8.29$  mL  $min^{-1}$   $kg^{-1}$  (Z-score:  $-0.52 \pm 1.43$ ), which did not differ significantly from reference values either. One boy suffered a joint bleeding one day after the test. Haemo-QoL scores in parents and children ranged from 3.2% to 36.7% (100% reflects poor outcome). Relationship between the child or parent reports of Haemo-QoL and both absolute and relative  $VO_{2peak}$  ranged from  $R = 0.00$  and  $R = 0.4$ . Exercise testing in children with severe haemophilia A was a safe procedure. Patients with severe haemophilia A with good joint health and no limitations of activities have comparable physical fitness and physical active lifestyle with healthy peers and good HRQoL.

**Keywords:** exercise, haemophilia, physical function, quality of life

## Introduction

Before the era of prophylaxis regimes, the life of a patient with haemophilia was to a great extent dependent on the severity of the disease and the frequency of bleeding episodes, often resulting into an inactive lifestyle [1,2]. The introduction of factor replacement, home treatment and prophylaxis regimes made it possible for persons with haemophilia to live a life in which participation in household, school or work; even sports and leisure

activities became feasible. A survey at the end of the millennium in the Netherlands showed that there is almost no difference in the level of sports-participation between persons with haemophilia and healthy controls [3]. Recently, it is widely recognized and abundantly propagated that physical activity is also beneficial for subjects with haemophilia [4,5]. This raises the question if children with haemophilia under the currently available prophylaxis do reach comparable levels of physical fitness as their healthy peers. More than two decades ago, Koch *et al.* reported a significantly reduced aerobic fitness in 11 boys in the age of 8.3–15.5 years with mild to severe haemophilia [6]. This finding was based on the maximal power output attained on a bicycle ergometer test to exhaustion. However, this test was performed without direct measurement of oxygen uptake, which is regarded as the golden standard in exercise testing according to the World Health

Correspondence: Dr J. van der Net, Department of Paediatric Physiotherapy and Paediatric Exercise Physiology, University Children's Hospital, UMC Utrecht, suite KB02.056.0, PO Box 85090, 3508 AB Utrecht, the Netherlands.  
Tel.: +31 30 250 4030; fax: +31 30 250 5333;  
e-mail: j.vandernet@umcutrecht.nl

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Organization [7]. Koch *et al.* hypothesized that although children with haemophilia were encouraged to be physically active at that time, most children do not exercise enough during daily physical activities, such as play and physical education, to reach an aerobic training level. Moreover, they expected that the intensity of exercise was too low as well, as only in competitive sports or sustained exercise children reach a physiological stimulus that produces training stimulus [6].

When children with haemophilia participate on the same level of physical activities as their healthy peers today, it is relevant to know if this coincides with a good level of health-related quality of life (HRQoL). Recently, von Mackensen *et al.* proposed a new disease-specific HRQoL questionnaire (Haemo-QoL) for children with haemophilia. Using this instrument one can get insight in the possible mechanisms that support the concepts of HRQoL [8]. In the context of the present study we were specifically interested in the possible relationship between the physical domains of HRQoL and physical fitness. In this study we therefore raise the following questions: (i) Is it feasible to safely test the exercise capacity of boys with severe haemophilia A, (ii) What is the level of physical fitness in these boys and (iii) What is the possible relationship between physical fitness, functional ability and HRQoL in this sample.

## Patients and methods

### Patients

Subjects were recruited from the 'Van Creveldklinik'. Boys with severe haemophilia A, who were born between 1990 and 1998, and visited the haemophilia outpatient clinic 'Van Creveldklinik' of the University Medical Centre Utrecht during the period of March till half of June 2005 were included in this study. All patients received primary prophylactic treatment, i.e. three times weekly 20–40 IU kg<sup>-1</sup>. The study was approved by the Institutional Medical Ethics Committee. Patients with an inhibitor were excluded.

### Anthropometry

Bodyweight and height were determined using an electronic scale and a wall assembled stadiometer. Body mass index (BMI) was calculated as weight/height<sup>2</sup>. Body composition was assessed using the sum of seven skinfolds ( $\sum$ 7-skinfolds) method according to Pollack *et al.* [9] using a Harpenden skinfold caliper. The measurements were taken, in

accordance with the American College of Sports Medicine guidelines, at the right side of the body at seven places: biceps, triceps, supra iliac, midabdominal, subscapular, medial thigh and calf.

### Haemophilia Joint Health Status

The joint health status of the subjects was assessed using the Haemophilia Joint Health Status (HJHS). This instrument has been recently developed by the Physiotherapy Expert Working Group of the International Prophylaxis Study Group on Haemophilia on behalf of the World Federation of Haemophilia and showed to be reliable [10]. The HJHS is especially designed to track an individual's joint health over time. It assesses the target joints (knee, elbow and ankle joints) in which a person can experience joint bleeding or arthropathy. The instrument allows assessment of an individual joint or several joints and provides a method for transferring raw data that has been collected during a thorough musculoskeletal evaluation based on consensus and normative values, into a compound score. The HJHS evaluates swelling, duration of swelling, muscular atrophy, axial alignment, crepitus on motion, range of motion (flexion loss and extension loss), instability, joint pain on overpressure, strength and gait.

### Maximal exercise test

After the HJHS was determined, subjects performed a maximal exercise test. The maximal oxygen uptake (VO<sub>2peak</sub>) attained during a graded maximal exercise to volitional exhaustion, is considered as the single best indicator of aerobic physical fitness by the World Health Organization [7]. Nine of the subjects performed a maximal exercise test using an electronically braked bicycle ergometer (Lode Examiner, Lode BV, Groningen, the Netherlands). The seat height of the bicycle ergometer was adjusted to the patient's leg length. After 1 min of unloaded cycling, workload was increased with a constant increment of 20 W every minute, until volitional exhaustion was reached, despite verbal encouragement of the test leader. Because of logistic reasons four patients performed a maximal exercise test on a motor-driven treadmill (Enmill, Enraf BV, Delft, the Netherlands) using the Bruce *et al.*'s protocol [11].

During the maximal exercise test, subjects breathed through a facemask (Hans Rudolph Inc., Kansas City, MO, USA) connected to a calibrated expired gas analysis system (Oxycon Pro, Viasys, Bilthoven, the Netherlands). Expired gas was passed through a flow meter, an oxygen analyzer and a

carbon dioxide analyzer. The flow meter and gas analysers were connected to a computer, which calculated breath-by-breath minute ventilation, oxygen uptake, carbon dioxide production and respiratory exchange ratio (RER) from conventional equations. Throughout the maximal exercise test, heart rate (HR) was monitored continuously by a three-lead electrocardiogram (Hewlett-Packard, Amstelveen, the Netherlands), and oxygen saturation (SaO<sub>2</sub>) was measured by pulse oximetry (Nellcor 200 E, Breda, the Netherlands).

Absolute peak oxygen uptake (VO<sub>2peak</sub>) was taken as the average value over the last 30 s during the maximal exercise test. Relative VO<sub>2peak</sub> (VO<sub>2peak</sub> kg<sup>-1</sup>) was calculated as absolute VO<sub>2peak</sub> divided by body mass. Predicted VO<sub>2peak</sub> values were obtained from established values from age- and sex-matched historical Dutch controls [12]. The children were asked to report 3 days after the test procedures whether or not they had experienced adverse effects.

### Questionnaires

The patients were asked to report the hours of physical activities at home, school, extra curricular sports and leisure time over a week period. The activity level of the children was furthermore assessed using the Dutch translation of the Activities Scale for Kids (ASK) [13]. The ASK is a generic instrument that measures physical activities in childhood musculoskeletal conditions. The questionnaire consists of two parts: the ASK capability (ASKc) and the ASK performance (ASKp), both were completed by the children. The ASKc assess *how well* a child performed an activity during the last week and the ASKp assess *how often* the child performed this activity during the last week. The Dutch version of the ASKc and ASKp consists of 43-items. This is 5-items more than the original 38-item version. The five extra items have been added to meet cross-cultural validation of the Dutch version and consist of items, such as bicycle riding. Both parts were scored on a 5-point scale (ASKc: 0 = I could not, 1 = with a big problem, 2 = with a moderate problem, 3 = with a little problem, 4 = with no problem; ASKp: 0 = none of the time, 1 = once in a while, 2 = sometimes, 3 = most of the time, 4 = all of the time).

Health-related quality of life was assessed with a Dutch translation of the Haemo-QoL (long version) [8]. The Haemo-QoL is a recently developed disease-specific HRQoL questionnaire for children with haemophilia. For the Haemo-QoL three different age group versions exist: I, 4–7 years; II, 8–12 years; III, 13–16 years. The Haemo-QoL consists of 21-

64- and 77-items, respectively, and is divided into eight (version I), nine (version II) and 10 (version III) subclasses [physical health, feeling, attitude, family, friends, other people, sport and school, coping (only versions II and III), treatment, future (only version III) and relationship (only version III)]. Parents filled out a similar questionnaire and were asked to judge their children's quality of life and also to give information about their own quality of life as well as their perception of haemophilia and its care. The parents and children scored each item on a 5-point scale according to how often they encountered problems during the last 4 weeks (1 = all the time, 2 = often, 3 = sometimes, 4 = seldom, 5 = never).

### Statistics

All data were entered and analysed in Statistical Package for the Social Sciences for Windows (version 12.0, SPSS Inc., Chicago, IL, USA).

Descriptive statistics [mean, range and standard deviation scores (sds)] have been used to present the anthropometric data. Independent sample *t*-tests were used to test differences between patients and reference values. The compound scores on Joint Health (HJHS), ASK scores, VO<sub>2peak</sub> outcome and domains of quality of life outcome have been calculated as percentages of maximum and are presented as median, interquartile range (IQR) and range. Anthropometric data and VO<sub>2peak</sub> outcomes have been transformed in sds (*Z*-scores) and are compared with a historic normative sample of the Dutch population [12,14]. Pearson's correlation coefficient was calculated to describe the relationship between the 'parent report' and the 'self report' for the Haemo-QoL scores and the relationship between VO<sub>2peak</sub> and both versions of the Haemo-QoL. In all tests an  $\alpha$ -level of <0.05 was considered as statistically significant.

### Results

The mean age of the boys at the time of the study was 6.6 years (range: 8.0–14.6). Anthropometric characteristics did not differ significantly from a normative sample of the Dutch population (Table 1). One boy was overweight (weight: >P97, BMI: 23.62 kg m<sup>-2</sup>,  $\sum$ 7-skinfolds: 218.53 mm, *Z*-score: +5.06).

The mean HJHS was 1.1% and ranged from 0% to 8.3% indicating very little joint impairment (Table 1). Eight of 13 children did not have any impairment, three boys had a joint health impairment of 1.4%, one 2.1% and one 8.3%.

The mean time for self-reported physical activities at school, extracurricular sports and leisure time

	N	Range	Minimum	Maximum	Mean	SD
Age (years)	13	6.63	8.00	14.63	11.04	2.45
Height (m)	13	0.55	1.22	1.78	1.49 <sup>ns</sup>	0.17
Weight (kg)	13	52.6	19.1	71.7	39.97 <sup>ns</sup>	15.65
Body mass index (kg m <sup>-2</sup> )	13	10.79	12.83	23.63	17.19 <sup>ns</sup>	3.33
∑7-Skinfolds (mm)	12	168.33	50.20	218.53	77.25 <sup>ns</sup>	47.97
HJHS impairment (%)	13	8.3	0	8.3	1.12	2.30
Physical activity (min)	13	450	90	540	245	133.2
					Median	IQR
ASKc (%)	13	21.1	77.9	100	100	4
ASKp (%)	13	10	90	100	100	4

HJHS, Haemophilia Joint Health Status; ASKc, Activity Scale for Kids/capability scale; ASKp, Activity Scale for Kids/performance scale; *ns*, not significant; IQR, interquartile range.

activities was 245 min week<sup>-1</sup> (SD: 133.2; range: 90–540). This is between ±60% and ±180% of the Dutch Norm for Physical Activity and Health [15]. For children under the age of 18 years this norm promotes moderate intensive physical activity for at least 420 min week<sup>-1</sup> (including twice a week vigorous sports activities [15]).

The median level of functional ability on both ASK scales was normal (100%) with an IQR of 4% (Table 1). In 61.5% of all patients full functional ability was scored on the ASKc and 53.9% of all patients scored full functional performance on the ASKp scale. There were three outliers (exceeding 1.5 times IQR), two suffered from a joint bleeding in the week before testing. These two had a mild-to-moderate loss on the ASKp (11–22.1%). One boy with an ASKc score 90.1% reported a poor Haemo-QoL score (36.7%).

Mean VO<sub>2peak</sub> was 1.86 ± 0.77 L min<sup>-1</sup> (Z-score: -0.39 ± 1.61) which was not different from reference values significantly. Relative VO<sub>2peak</sub> was 47.42 ± 8.29 mL min<sup>-1</sup> kg<sup>-1</sup> (Z-score: -0.52 ± 1.43), which did not differ significantly from reference values either (Table 2). The HR<sub>peak</sub> and the RER<sub>peak</sub> indicated that the children tested were able to perform at maximal or near-maximal level [HR<sub>peak</sub>: 190 ± 9 beats min<sup>-1</sup> (range: 171–206); RER<sub>peak</sub>: 1.22 ± 0.14 (range: 0.86–1.33); Table 2]. No complications were reported during exercise

testing. Eleven of the 13 boys scored for absolute VO<sub>2peak</sub> and relative VO<sub>2peak</sub> between -2 and +2 SD compared to Dutch reference values. One boy with a physical active lifestyle scored for absolute VO<sub>2peak</sub> above +2 SD compared with Dutch reference values (Z-score: +2.61) and one boy who was very sedentary scored an absolute VO<sub>2peak</sub> below -2 SD compared with Dutch reference values (Z-score: -4.28). The latter patient had a reduced relative VO<sub>2peak</sub> as well (Z-score: -2.89). The patient with overweight had also a reduced relative VO<sub>2peak</sub> (Z-score: -3.38). Peak workload (W<sub>peak</sub>) could only be measured in the nine children that performed a bicycle ergometer test. The average W<sub>peak</sub> was 139 ± 62.79 W (range: 87–292).

None of the participants reported adverse effects during or within a few hours after the test procedures. Only one boy reported a joint bleeding in his right ankle the day after the test procedures. The boy performed the exercise test on a bicycle ergometer. This boy did have a joint bleeding earlier that same week. It concerned a sedentary boy with reduced aerobic capacity.

In all cases parent reports and child reports on the Haemo-QoL were calculated. Scores presented as percentage from maximum, a score of 0% represent the highest HRQoL and a score of 100% the lowest HRQoL. The parents reported a Haemo-QoL score between 3.2% and 31.2% (mean score: 15.24; SD:

Table 1. Patient characteristics.

Table 2. Descriptive statistic for peak values of aerobic exercise test.

	N	Range	Minimum	Maximum	Mean	SD	Z-score	SD
Absolute VO <sub>2peak</sub> (L min <sup>-1</sup> )	13	2.62	1.13	3.75 <sup>ns</sup>	1.86	0.77	-0.39	1.61
Relative VO <sub>2peak</sub> (mL min <sup>-1</sup> kg <sup>-1</sup> )	13	31.05	27.88	58.93 <sup>ns</sup>	47.42	8.29	-0.52	1.43
HR <sub>peak</sub>	13	35	171	206	190	9.00		
RER	13	0.47	0.86	1.33	1.22	0.14		
W <sub>peak</sub> (W)	9	205	87	292	139	62.79	xx	xx

HR, heart rate; RER, respiratory exchange ratio; W, workload; NS, not significant.

8.41; range: 3.24–34.17). The HRQoL reported by the children ranged from 7.03% to 36.7% (mean: 15.90; SD: 10.16; range: 3.24–36.72).

A strong correlation was observed between the Haemo-QoL total score of the parent and child ( $R = 0.73$ ;  $P = 0.007$ ). A comparison between the results of age group II (8–12 years) and age group III (13–16 years) are illustrated in Fig. 1. The children in age group II scored highest on the subcategories 'Friends' and 'Perceived support'. The children in age group III scored not only high on these subcategories as well, but also reported high scores on 'Physical health', 'Dealing' and 'Treatment'.

There was no significant relationship between the child report of Haemo-QoL and both absolute ( $R = .24$ ) and relative  $VO_{2peak}$  ( $R = 0.14$ ) respectively. Neither did we find a significant relationship between the HRQoL as reported by the parents and the children's physical fitness as measured with absolute and relative  $VO_{2peak}$  ( $R = 0.00$  and  $R = 0.4$ ) respectively.

## Discussion

This study explores the feasibility of exercise testing in a convenience sample of 13 children with severe haemophilia A and describes the reported functional ability and HRQoL. The study revealed that exercise testing was feasible and that it was a safe procedure in the great majority of the children. All children were able to meet the criteria for maximal exercise performance [16], both exercise modes that were applied, i.e. bicycling and running seemed equally effective and no adverse effects occurred during or immediately following the test procedures. We found a normal physical fitness in the population tested.

One boy reported a joint bleeding one day post-testing. Remarkable enough this boy had cycled and not ran, which could be regarded as the mildest mode concerning joint (mis-)loading. His history of bleeding showed a joint bleed in the same ankle joint the week preceding the test, which might indicate a level of vulnerability in that target joint. From our data it is hard to tell whether our testing procedures are causally linked to this bleeding incident. However, to increase the safety of exercise testing, a bleed-free interval of at least a week could be considered. In contrast with Koch *et al.* [6] we found a normal physical fitness in children with haemophilia A. They showed in a group of 11 patients with haemophilia between the age of 8.3 and 15.5 years a 67% decrease in total work (49% less mean power, 30% less minutes of exercise and 8% lower maximal HR) compared with normal references [7]. Those differences in findings might be explained by the historic context. Koch *et al.* performed their study in the 1980s; at that time prophylaxis regimes were just recently implemented and joint impairment and physical restrictions were more commonly found. The children in that study were not suffering from acute bleeds or orthopaedic conditions; however, the lack of a clinical instrument to quantify joint impairment, limits further comparison with our study. The newly developed HJHS quantifies the level of joint impairment more accurately. In our study the participants suffered no significant joint impairment based on the HJHS outcome. Further clinical testing of the HJHS is needed to learn its value in a clinical setting and in clinical research. The level of activity limitation as measured with the ASK did not significantly differ from that of healthy peers. The time involved in moderate to vigorous physical activity was found not to differ from what is expected in healthy peers. This is in accordance with earlier observations of Heijnen *et al.* [3]. The observation that the time involved in physical activity ranges from as little as 60% to as much as 180% of the Dutch Norm for Physical Activity and Health for children under the age of 18 years underlines that some boys with haemophilia need the same encouragements to participate in physical activities as their healthy peers. However, for both the level of activity limitation (ASK) and the time involved in physical activities further studies are necessary as our patient group is not representative for the haemophilia population or the Dutch population in that age group. Analysis between both versions of the Haemo-QoL revealed no discordance between parents and children, making parents reliable proxy reporters. However, this is not in accordance with

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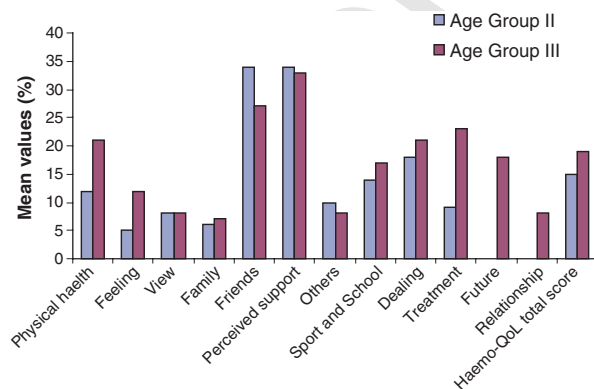


Fig. 1. Mean values in percentages of maximum of the Haemo-QoL dimensions in groups II (8–12 years,  $n = 10$ ) and III (13–16 years,  $n = 3$ ).

the earlier findings of Bullinger *et al.* who found that parents overestimated the problems in their children [17]. A likely explanation for this finding is that in this physically healthy patient group there are not many concerns to be raised and consequently not 'over'-reported. The QoL profile we found in our patient group; however, is comparable with an earlier report of Gringeri *et al.* [18]. In both of the Haemo-QoL age groups the domains 'Friends' and 'Perceived Support' showed the highest impact on HRQoL. Based on the answers it is not clear if the children fully appreciated the question or if they 'did not bother' to address/share problems (as there were so few problems) with their healthy peers. Further investigations should solve this particular question.

6 Relationships between physical fitness and HRQoL are weak and underscore the fact that patients with a good physical health not necessary report good HRQoL. A notion that needs to be further explored. Moreover, the marked ceiling effects in the scores and limited variance could also influence the results. This emphasizes the need of a greater cohort and more variability in the included population, e.g. physically active and inactive children with both moderate and mild haemophilia.

In conclusion, exercise testing in children with severe haemophilia A can safely be performed in those patients. Patients with severe haemophilia with good joint health and no limitations of activities, physical fitness and physical active lifestyle are comparable with healthy peers. However, HRQoL is slightly different between different age groups while impact on health perception becomes more prominent at older age. Future studies should incorporate a larger sample size and all subtypes of haemophilia.

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