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A Prospective Uncontrolled Intervention Study

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DOI
10.1109/TNSRE.2020.3018786

Publication date
2020

Document Version
Accepted author manuscript

Published in
IEEE Transactions on Neural Systems and Rehabilitation Engineering

Citation (APA)
Waterval, N. F. J., Brehm, M. A., Altmann, V. C., Koopman, F. S., Den Boer, J. J., Harlaar, J., & Nollet, F. (2020). Stiffness-Optimized Ankle-Foot Orthoses Improve Walking Energy Cost Compared to Conventional Orthoses in Neuromuscular Disorders: A Prospective Uncontrolled Intervention Study. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *28*(10), 2296-2304. https://doi.org/10.1109/TNSRE.2020.3018786

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Stiffness-optimized ankle-foot orthoses improve walking energy cost compared to conventional orthoses in neuromuscular disorders; a prospective uncontrolled intervention study

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Abstract In persons with calf muscle weakness, walking energy cost is commonly increased due to persistent knee flexion and a diminished push-off. Provided ankle-foot orthoses (AFOs) usually lower walking energy cost. To maximize the reduction in energy cost, AFO bending stiffness should be individually optimized, but this is not common practice. Therefore, we aimed to evaluate whether individually stiffness-optimized AFOs reduce walking energy cost compared to conventional AFOs in persons with non-spastic calf muscle weakness and, secondarily, whether stiffness-optimized AFOs improve walking speed and gait biomechanics. Thirty-seven persons with non-spastic calf muscle weakness using a conventional AFO were included. Participants were provided a new, individually stiffness-optimized AFO. Walking energy cost, speed and gait biomechanics were assessed, at delivery and 3-months follow-up. Stiffness-optimized AFOs reduced walking energy cost with 9.2% (-0.42J/kg/m, 95%CI: 0.26 to 0.57) compared to the conventional AFOs while walking speed increased with 5.2% (+0.05m/s, 95%CI: 0.03 to 0.08). In bilateral affected persons the effects were larger compared to unilateral affected persons (difference effect energy cost: 0.31J/kg/m, speed: +0.09m/s). Although individually gait biomechanics changed considerably, no significant group differences were found ($p>0.118$). We demonstrated that individually stiffness-optimized AFOs considerably and meaningfully reduced walking energy cost compared to conventional AFOs, which was accompanied by an increase in walking speed. Especially in bilateral affected persons large effects of stiffness-optimization were found. The individual differences in gait changes substantiate the recommendation that the AFO bending stiffness should be individually tuned to minimize walking energy cost.

***Index Terms*— Plantar flexor weakness, ankle foot orthosis, gait biomechanics, neuromuscular diseases**

I. Introduction

Increased walking energy cost [1, 2] and reduced walking speed [2, 3] are common walking problems in persons with neuromuscular disorders exhibiting calf muscle weakness. These problems are largely caused by deviations in the gait pattern like excessive ankle dorsiflexion in terminal stance, persistent knee flexion during stance and a diminished ankle push-off power [4-7]. These gait deviations, in combination with an increased walking energy cost, often lead to fatigue [8, 9] and, consequently, a reduction of daily activities [10, 11].

To improve walking ability, a diversity of ankle foot orthoses (AFOs) is applied [12, 13]. The mechanical properties of these AFOs as well as their effects on walking energy cost, speed and gait biomechanics vary largely [13-15]. Likely, the variation in properties is explained by the lack of AFO prescription guidelines as, consequently, these properties are based on the preferences of the physician [13]. This results in a mismatch between the AFO's mechanical properties, in particular ankle bending stiffness, and the severity of (calf) muscle weakness and other personal characteristics, causing the large variety in efficacy [15, 16].

For persons with non-spastic calf muscle weakness, support of the ankle power during push-off is warranted to reduce walking energy cost [17-19]. Spring-like AFOs have the advantage over other AFO designs that they can store energy in the stance phase and unleash this energy during push-off, thereby potentially enhancing the ankle power and reducing walking energy cost.

This work was supported by Prinses Beatrix Spierfonds under grant [W.OR 14-21]

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The effect of spring-like AFOs depends on its stiffness and the optimal AFO is a trade-off between sufficient AFO bending stiffness to normalize ankle and knee kinematics and AFO ankle flexibility to store and recoil energy during push-off [14, 20, 21]. As this trade-off largely depends on personal characteristics such as severity of (calf) muscle weakness, body weight and walking speed [16, 19], the optimal AFO bending stiffness varies between individuals [20-22].

We previously found that individually optimizing the AFO bending stiffness can reduce walking energy cost among persons with calf muscle weakness [20, 21], and is therefore recommended to maximize treatment outcome [20]. In usual orthotic care, AFOs are prescribed on a trial-and-error basis and optimization of AFO bending stiffness is not common practice. Consequently, conventional AFOs likely reduce walking energy cost to a lesser extent than stiffness-optimized AFOs, although to what extent and whether optimized AFOs also improve other outcome measures has not been previously assessed. Therefore, the aim of this study is to test to what extent individually stiffness-optimized AFOs reduce walking energy cost compared to conventional AFOs among persons with neuromuscular disorders demonstrating calf muscle weakness. Secondarily, we evaluate if stiffness-optimized AFOs improve walking speed, gait biomechanics, daily step activity and perceived fatigue.

Methods

Design

We conducted a prospective uncontrolled intervention study with measurements at baseline, directly post–provision of the stiffness-optimized AFO and at 3-months follow up. The study was performed at the department of Rehabilitation, Amsterdam UMC, location Academic Medical Center (AMC) in Amsterdam, The Netherlands.

Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the AMC Medical Ethics Committee. All participants provided written informed consent. The design of the study was published previously [23] and is registered as the PROOF-AFO trial in the Dutch Trial Register with number NTR5170.

Participants

We enrolled participants between July 2015 and July 2017 from 12 hospitals and rehabilitation centers in different regions throughout the Netherlands and through the Dutch patient organization of neuromuscular diseases. Inclusion criteria were: 1) diagnosed with a neuromuscular disease or nerve damage and presence of non-spastic calf muscle weakness (unilateral or bilateral), defined as a manual muscle strength score <5 on the Medical Research Council (MRC) scale or unable to perform three heel rises standing on a single leg; 2) using a conventional AFO/AFOs or high orthopedic shoes with shaft reinforcement for lower leg muscle weakness; 3) able to walk for at least 6 minutes, if necessary with an assistive device; 4) age between 18 and 80 years and 5) weight below 120 kg. Exclusion criteria were: indication for a knee-ankle-foot orthosis, not being able to reach >0 degrees of ankle dorsiflexion (pes equinus) during weight-bearing and severe ankle-foot deformities that could not be fitted with an AFO to assure a dorsal leaf AFO was an appropriate orthotic design for the included participants.

Intervention

<u>*Conventional AFO*</u>

The stiffness-optimized AFO was compared to an AFO as prescribed in usual orthotic care for lower leg muscle weakness (referred to as “conventional AFO”). As in usual care, the AFO characteristics are not always matched to the patients’ functional deficits [24], the conventional AFO could be any type of AFO or high shaft reinforced orthopedic shoe., Included participants used the following; 9 participants used ventral AFOs, 14 participants dorsal AFOs, 6 participants hinged AFOs and for 8 participants high orthopedic shoes with shaft reinforcement. The mechanical properties of the conventional AFOs have been described in detail previously [24].

<u>*Experimental AFO*</u>

A certified orthotist provided participants with the experimental spring-like dorsal AFO (made by OIM orthopedie, Noordwijkerhout, The Netherlands), which was worn in combination with the patients’ confection shoe if possible, or otherwise with newly provided custom-made shoes. The AFO consisted of a custom-made carbon calf casing and semi-stiff full-length footplate, and a replaceable carbon Ankle7 leaf®, which is clinically available in various stiffness levels (Otto Bock, Duderstadt, Germany). The carbon Ankle7 leaf® was attached to the calf casing and footplate with screws (for image see previous publication [23]) allowing the stiffness (K) setting to be varied within the same AFO. The AFO was aligned by the orthotist and if needed the alignment was adjusted using heel wedges.

For each participant, we evaluated the effects of five AFO stiffness settings (range: K1: 2.8 Nm/degree to K5: 6.6 Nm/degree, with approximately 1 Nm increments) in a random order on walking energy cost, speed and gait biomechanics. The optimal AFO bending stiffness was selected according to a predefined selection algorithm (Figure 1), which was primarily based on walking energy cost and secondarily on speed and a clinical appraisal of the gait biomechanics by three assessors. A detailed description of the optimization procedure has been published previously [23].

After optimization, participants were provided with the stiffness-optimized AFO and contacted after one week to check for adverse events (e.g. pressure sores) and AFO fitting. If no complaints were reported, a 3-month follow-up period started. The participants’ compliance with wearing the AFO was measured during the last week of follow-up using a temperature-based adherence monitor (@monitor, Department of Medical Technology and Innovation, Amsterdam UMC location AMC [25]), which was fitted inside the calf casing of stiffness-optimized AFO. Before optimization, we measured compliance with the conventional AFO for one week. Adverse events during follow-up were reported at the final measurement.

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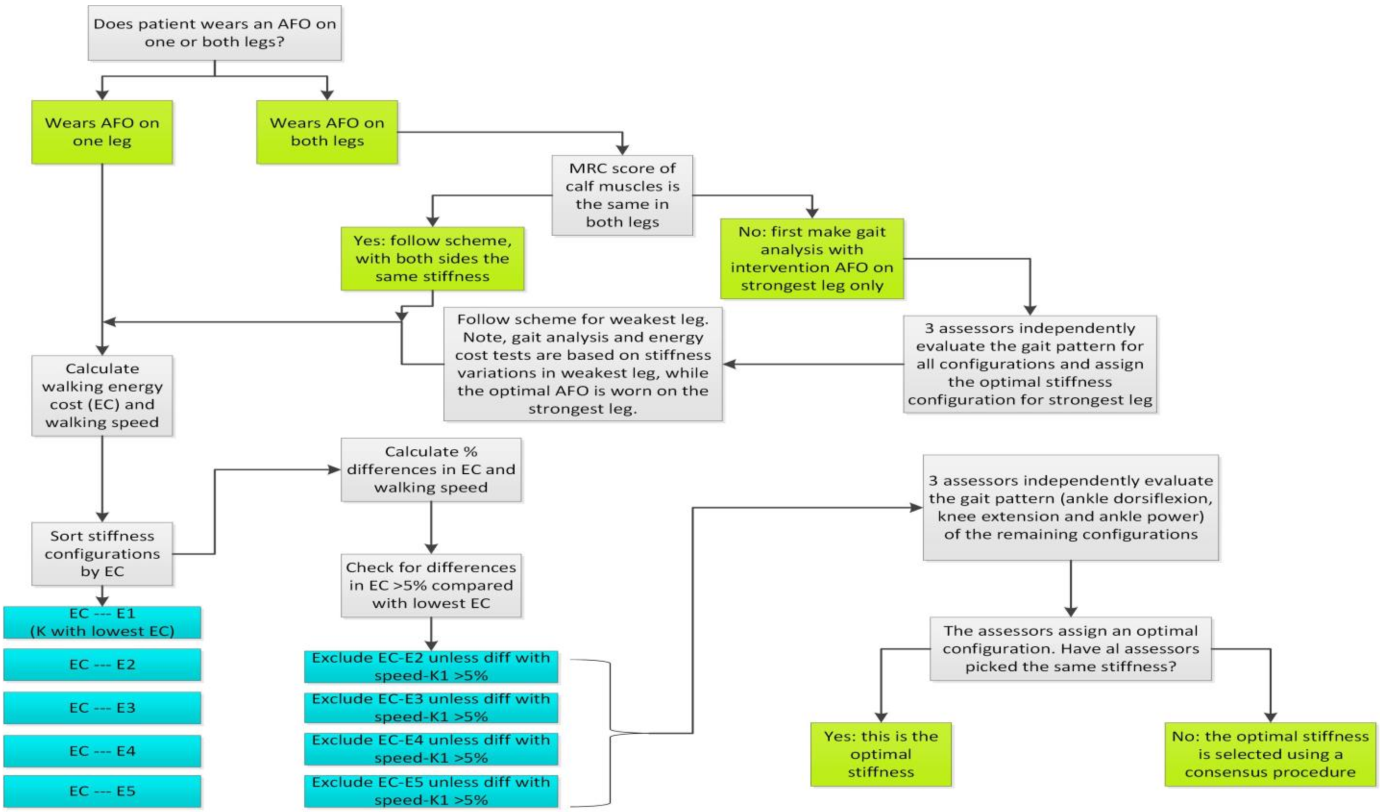

Figure 1. Selection algorithm used to determine the optimal AFO ankle stiffness.

Outcomes

All outcomes were collected, post-processed and entered into an OpenClinica database by one trained researcher (NW). The primary outcome, walking energy cost, and the main secondary outcome, walking speed, were assessed for walking without AFO and the conventional AFO at baseline (T1) and for the stiffness-optimized AFO directly post-provision (T2) and at 3 months follow up (T3). Secondary outcomes were assessed for the conventional AFO at baseline (T1) and for the stiffness-optimized AFO at 3-months follow-up (T3).

Primary outcome

Walking energy cost (J/kg/m) was assessed with a 6-minute walk test at self-selected, comfortable speed using breath-by-breath gas analysis on a 35-meter indoor oval track, which is a reliable method [2, 26]. Oxygen uptake (VO_2) and carbon dioxide production (VCO_2) were measured with a portable gas analyzer (Cosmed $K4B^2$, Rome, Italy). Participants were allowed to use their own assistive devices while walking, e.g. a stick, cane or walker, if necessary, and used the same device for the conventional and stiffness-optimized AFO condition. Before the test, participants rested for at least 10 minutes and were not allowed to consume food or sugar holding beverages in the 90 minutes before the measurement.

Using a custom-written Matlab script, the mean steady state VO_2 (ml/kg/min) and VCO_2 (ml/kg/min) were calculated for at least 60 seconds between the fourth and sixth minute during which walking speed (m/s) and VO_2 and VCO_2 were relatively constant (m/s). With these values, walking energy cost was calculated: $(((4.940 \times (VCO_2 / VO_2)+16.040) \times VO_2)/$ walking speed) [27].

Secondary outcomes

The main secondary outcome, walking speed, was measured during the steady-state period as described above.

Secondary outcomes included gait biomechanics at comfortable speed (assessed with 3D gait analysis using a 8-camera Vicon MX1.3 motion capture system (Vicon, Oxford,UK)), daily step activity (StepWatch3 Activity Monitor and activity diary), perceived fatigue (Fatigue Severity Scale (FSS)), perceived physical functioning (36-item Short-Form Health Survey physical functioning scale (SF36-PF)), walking satisfaction (7 self-selected questions rated on 11-point numeric rating scale, with 0= not satisfied and 10= totally satisfied), perceived improvement with the stiffness-optimized AFO (5-point Likert scale, with -2 = large decrement and +2 = large improvement) and AFO compliance. Descriptions and procedures of secondary outcomes have been described in detail in the protocol article, while details on the gait biomechanics are described in our article regarding AFO stiffness variation [20, 23]. Furthermore, perceived advantages and disadvantages of the optimized AFO were collected using open-end questions.

Clinical characteristics

Clinical characteristics such as unilateral or bilateral calf muscle weakness, self-reported maximal walking distance with the conventional AFO, and frequency of AFO use inside and outside the house were assessed at baseline with questionnaires. Manual muscle strength of the plantar flexors, measured

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according to the MRC scale [28], and maximal isometric strength of the plantar flexors, measured using a fixed dynamometer (System 3 PRO; BIODEX, Shirley, New York, USA), were also assessed.

Sample size

The sample size for this study was calculated based on the formula of Twisk for two repeated measures of the outcome ($N = ((Z_{\alpha}+ Z_{\beta})^2 \sigma^2 (r+1) (1+(T-1)\rho)) / (v^2 rT)))$ [29]. We anticipated a 0.52 J/kg/m difference (10%) in our primary outcome walking energy cost between the conventional AFO and the stiffness-optimized AFO. Based on an intention-to-treat analysis and with an assumed standard deviation of 0.70 J/kg/m, a correlation coefficient of the repeated measurements of 0.77, power of 90%, and alpha of 0.05, 34 patients were needed. Allowing for a 10% drop out, the sample size was set at 37 patients.

Statistics

Baseline demographic and clinical characteristics of participants were summarised with descriptive statistics. Differences in characteristics between patients who dropped-out and those who completed the study were tested with independent t-tests. We assessed the primary and main secondary outcome with linear mixed models, including the measurements at T1 (conventional AFO), T2 and T3 (both optimized AFO). The primary analysis was based on the intention to treat sample with multiple imputation to estimate missing values. Predictors used for imputation were; muscle strength, unilateral or bilateral muscle weakness, walking energy cost for the conventional AFO at T1 and for the stiffness-optimized AFO at T2 and walking speed at T1 and T2. In addition, secondary per protocol analyses with available data only were conducted. Furthermore, the difference in effect between uni- and bilateral affected patients was studied by adding this variable and the interaction with the intervention to the model. To test if the effect of the stiffness-optimized AFO changed over time (T2 versus T3) and if walking energy cost remained lower after wearing the stiffness-optimized AFO after 3 months, paired t-tests were used. Additionally, we tested the effect of stiffness-optimization on energy cost in the subgroup of participants who used a dorsal leaf AFO as a conventional AFO with a paired t-test. Lastly, to provide reference we tested the effect of the stiffness-optimized AFO versus walking without AFO.

For the 3D gait analysis outcomes, including maximal ankle dorsiflexion angle, maximal external dorsiflexion moment, peak ankle power, minimal knee angle and maximal external knee extension moment during stance, data at T1 were compared with data at T3 using multilevel linear mixed models to account for the dependence between legs in case patients were bilaterally affected. Data were clustered at three levels: patient (level 1), leg (level 2) and condition, standard or stiffness-optimized AFO (level 3). Only available data were used, and analyses were performed using MLwiN version 2.34 (Institute of Education, University of London, UK). In addition, individual effects on ankle angle, ankle power and knee moment were determined. Differences of 2 degrees in ankle angle, 0.2 W/kg in ankle power and 0.1 Nm/kg in knee moment were considered to express meaningful differences as these approximate the minimal detectable changes [30].

All other secondary outcomes were analysed with paired t-tests (T1 versus T3), except for AFO satisfaction, which was tested with a Wilcoxon signed rank test.

Statistical analyses were performed after the last follow-up visit in July 2018 with SPSS version 24.0 (IBM Corporation, Armonk, NY), unless otherwise stated. For all tests (2-sided), we used a p-value < 0.05 for significance.

Results

Participant flow

Baseline demographic and clinical characteristics of the 37 included participants are presented in Table 1. Thirty participants completed the 3-month follow up assessment. A flow diagram shows how participants progressed through the study, including reasons for dropping out and data lost (Figure 2). No significant differences with regard to age, weight or muscle strength between drop-outs and patients who completed the study were found. The mean time between enrolment and start of follow-up was 6.6±2.0 months. Mean follow-up time was 3.6±1.3 months as in 5 patients minor adjustments to the AFO, e.g. inlays, were made during the follow-up period.

Table 1. Baseline demographics and clinical characteristics of participants

	Participants with an optimized AFO (n=37)	Participants who completed study (n=30)	*P* value completed vs drop-out
Sociodemographic characteristics			
Age in years	56.9 ± 15.5	58.9 ± 13.2	0.073
Gender male/female	21/16	18/12	0.410
Height in cm	178 ± 10	178 ± 11	0.663
Weight in kg	85.6 ± 16.2	86.1 ± 14.7	0.467
Clinical characteristics			
Unilateral/bilateral affected	12/25	9/21	0.483
MRC[1] Legs with AFO / legs without AFO Plantar flexors Dorsiflexors Knee extensors	3 [2-4] / 5 [5] 2 [1-4] / 5 [5] 5 [5-5] / 5 [5]	3 [2-4] / 5 [5] 2 [1-4] / 5 [5] 5 [4.75-5] / 5 [5]	0.666 0.815 0.963
Isometric plantar flexor strength[1](Nm) Legs with AFO Legs without AFO	6 [0-18] 44 [35-54]	8 [0-18] 45 [38.5 – 58.5]	0.554 0.353
Self-reported walking distance Only in and around house Less than 1 kilometer More than 1 kilometer	3 (8%) 12 (32%) 22 (59%)	2 (7%) 10 (33%) 18 (60%)	0.797
Use of AFO inside/outside the house Always Mostly Rarely Never	11 (30%) / 28 (76%) 8 (22%) / 7 (19%) 14 (38%) / 2 (5%)	10 (33%) / 23 (77%) 6 (20%) / 5 (17%) 11 (37%) / 2 (7%)	0.792 / 0.634

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	4 (11%) / 0 (0%)	3 (10%) / 0 (0%)	
Assistive device None Cane 2 Canes Crutch Walker	 26 (70%) 3 (8%) 2 (5%) 3 (8%) 3 (8%)	 21 (70%) 2 (7%) 2 (7%) 3 (9%) 2 (7%)	
Diagnosis	Charcot-Marie-Tooth (n=16) Poliomyelitis (n=8) Radiculopathy (n=2) Spinal disc herniation (n=2) Spinal stenosis (n=2) Myotonic dystrophy (n=2) Myoshi distal myopathy (n=1) CIDP (n=1) * Peroneal nerve damage # (n=1) Partial cauda syndrome (n=1) Incomplete spinal cord injury (n=1)	Charcot-Marie-Tooth (n=14) Poliomyelitis (n=7) Radiculopathy (n=2) Spinal disc herniation (n=2) Spinal stenosis (n=1) Myotonic dystrophy (n=1) Myoshi distal myopathy(n=1) CIDP (n=1) * Incomplete spinal cord injury (n=1)	

Optimal AFO selection

In four participants, only one stiffness remained in the selection algorithm after ranking primarily for walking energy cost and speed. In the other 33 participants, gait biomechanics were secondarily judged, whereby 13 times an additional consensus meeting was needed to select the optimal AFO. Consensus was reached that the lowest AFO bending stiffness, which visually best normalized the peak ankle angle and knee extension angle and moment in terminal stance would be selected, as this stiffness was expected to restrain daily activities the least. The selected optimal AFOs were; K1 for 8 participants, K2 for 12 participants, K3 for 9 participants, K4 for 2 participants and K5 for 3 participants. In only 3 bilateral affected participants muscle weakness was asymmetric and stiffness was optimized for both legs separately. The optimized combinations consisted of K1/K3 (2 patients) and K2/K3.

The stiffness-optimized AFO had on average a stiffness of 3.6±0.8 Nm/degree, which was significantly higher compared to conventional AFOs (1.1±0.9 Nm/degree, $p<0.001$). Weight of the stiffness-optimized AFO (0.3 kg) was lower compared to the conventional AFOs (0.6±0.4 kg). When comparing only to conventional dorsal leaf AFOs, optimized AFOs had a higher stiffness (3.5±0.7 versus 1.1±0.8, $p<0.001$), but no differences in AFO weight were found.

AFO compliance

There was no difference in AFO compliance between the stiffness-optimized AFO (wearing time: 462±261 min/day) and the conventional AFO (wearing time: 482±295 min/day, $p=0.551$).

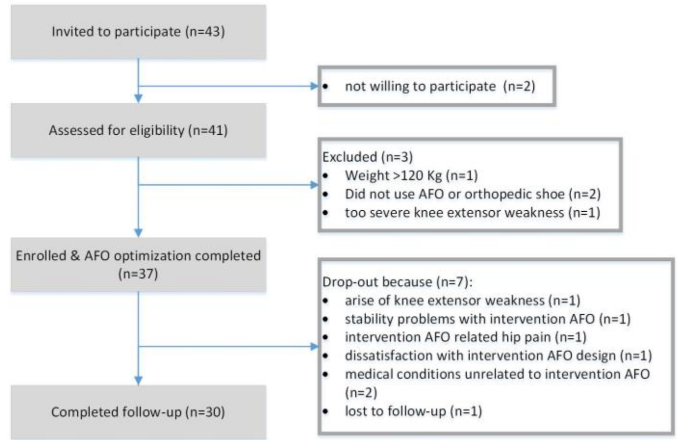

Figure 2. Study flowchart

Outcomes

Intention-to-treat analyses showed a reduction in walking energy cost of 9.2% or 0.42 J/kg/m ($p<0.001$, 95%CI: 0.26 to 0.57) with the stiffness-optimized AFO compared to the conventional AFO (4.17±0.14 vs 4.58±0.14). Walking speed increased with 5.2% or 0.05 m/s ($p<0.001$, 95%CI: 0.03 to 0.08) with the stiffness-optimized AFO compared to the conventional AFO (1.09±0.03 vs 1.03±0.03). Per protocol analysis showed similar results, walking energy cost reduced with 0.44 J/kg/m ($p<0.001$, 95%CI: 0.28 to 0.59) and walking speed increased with 0.06 m/s ($p<0.001$, 95%CI: 0.03 to 0.08).

Secondary analysis revealed the following. Walking energy cost at T2 was significantly lower compared to T3 (-0.17 J/kg/m, $p=0.029$, 95%CI: -0.32 to -0.02) (Figure 3), while walking speed at T2 did not differ from T3 (-0.02 m/s, $p=0.089$, 95%CI -0.05 to +0.00). At T3 after the follow-up period, walking energy cost was 6.7% lower compared to the conventional AFO (-0.31 J/kg/m, $p=0.007$, 95%CI -0.53 to -0.09), and 19% lower compared to walking without AFO (-0.99 J/kg/m, $p<0.001$, 95%CI -1.35 to -0.67). Additionally, walking speed was 4.3% higher compared to the conventional AFO (+0.04 m/s, $p=0.006$, 95%CI 0.01 to 0.07), and 22% higher compared to no AFO (+0.20 m/s, $p<0.001$, 95%CI +0.14 to +0.27).

In the subgroup of participants using a dorsal leaf AFO at baseline, walking energy cost with the stiffness-optimized AFO was 0.47 J/kg/m (-10.2%) lower at T3 compared to the conventional AFO (n=11, 4.58 ±0.85 versus 4.11±0.66, $p=0.035$). No significant effect on walking speed was found (1.09±0.16 versus 1.12±0.13, $p=0.137$).

In bilateral affected participants walking energy cost reduced with 0.31 J/kg/m more compared to unilateral affected participants ($p=0.051$, 95%CI: 0.00 to 0.65 J/kg/m). In bilateral

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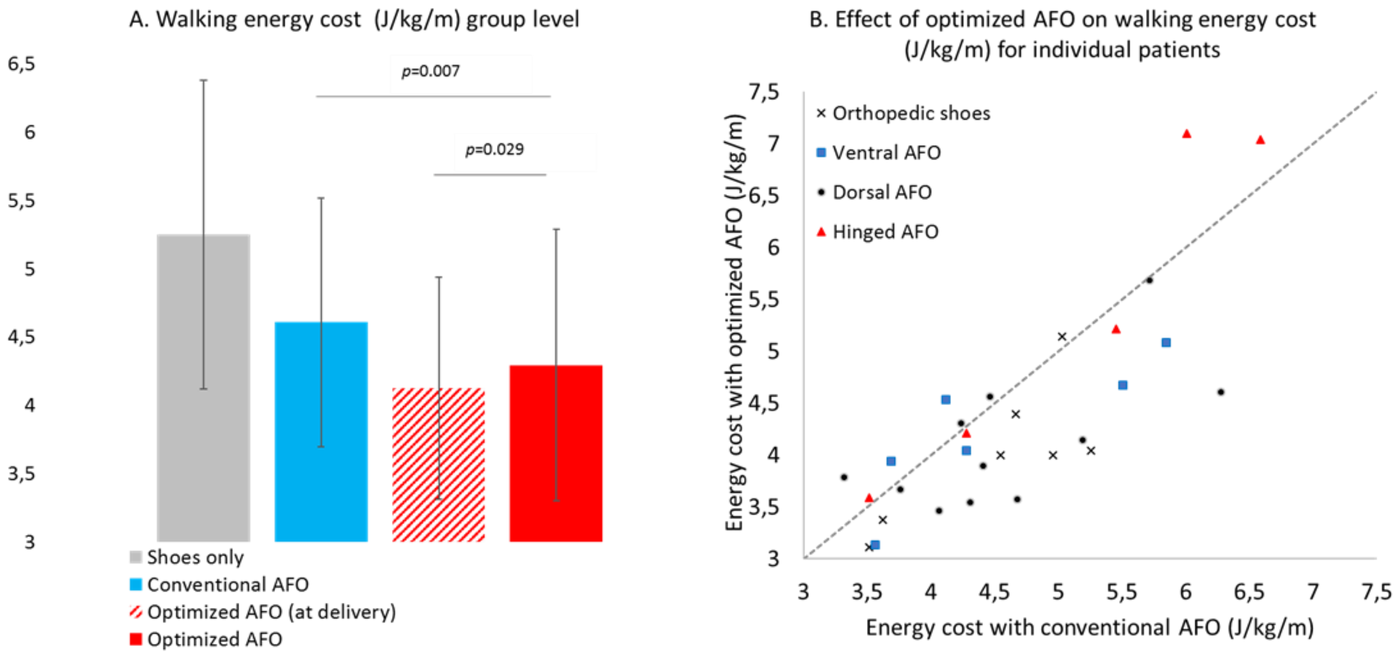

Figure 3. Effect of the stiffness-optimized AFO on walking energy cost. In Figure A the mean walking energy cost is shown. Figure B shows the comparison between the energy cost while walking with the stiffness-optimized AFO at T3 and the conventional AFO for individual subjects. A point below the dashed line means that the energy cost is lower with the stiffness-optimized AFO. AFO = ankle foot orthosis

affected participants walking energy cost reduced by 0.54 J/kg/m (from 4.58 to 4.04, p<0.001, 95%CI: -0.35 to -0.72 J/kg/m), while in unilateral affected participants walking energy cost reduced non-significantly with 0.21 J/kg/m (from 4.60 to 4.39, p=0.159, 95%CI: +0.09 to -0.52 J/kg/m).

With regards to walking speed, no effect of the stiffness-optimized AFO was found in unilateral affected participants (0.00 m/s, 1.09 vs 1.10 m/s, p=0.637, 95%CI: -0.02 to +0.04 m/s), while speed increased significantly with 0.09 m/s for bilateral affected participants (1.00 vs 1.09 m/s, p<0.001, 95%CI: +0.06 to +0.11 m/s). This was a significant larger effect (difference: 0.09 m/s, p<0.001, 95%CI: 0.04 to 0.14).

The results of the secondary outcomes are presented in Table 2. Stiffness-optimized AFOs did not significantly affect gait biomechanics on group level. On the individual level, ankle dorsiflexion angle in terminal stance decreased by at least 2 degrees in 15 (50%) participants (from 20.3±4.3 to 13.3±4.0 degrees), consisting of 7 dorsal AFO users, 6 ventral AFO users, 1 DF-stop AFO user and 1 OS user. Ankle angle increased by at least 2 degrees in 7 (23%) participants (from 7.7±5.0 to 14.9±4.5 degrees), of which 4 used a DF-stop AFO, 2 an OS and 1 a ventral AFO. Ankle power increased by 0.2 W/kg in 12 (40%) participants (from 0.8±0.5 to 1.4±0.6 W/kg), of which 4 used a dorsal AFO, 3 a DF-stop AFO, 3 a ventral AFO users and 2 an OS. Ankle power decreased by at least 0.2 W/kg in 9 (30%) participants (from 1.9±0.8 to 1.3±0.6 W/kg), of which 4 used a ventral AFO, 3 a dorsal AFO and 2 an OS. When walking with the conventional AFO, 10 (33%) participants walked with a persistent external knee flexion moment, of which 5 used a dorsal AFO, 2 an OS, 1 a ventral AFO and 1 an DF-stop AFO. In these participants, the stiffness-optimized AFO reduced the external knee moment towards an extension moment (from 0.12±0.12 to -0.01±0.13 Nm/kg), while little effect on the external knee moment in the other 20 participants was seen (from -0.24±0.18 to -0.21±0.20 Nm/kg).

Daily step activity was not affected by the stiffness-optimized AFO (Table 2). Perceived fatigue (-0.47 FSS points, 95%CI: -0.23 to -0.70) and physical functioning (+8.9 points, 95%CI: 2.6 to 15.3) had significantly improved at 3-months follow-up with the stiffness-optimized AFO compared to the conventional AFO. Regarding AFO satisfaction, a significant improvement in perceived walking intensity was found between the stiffness-optimized AFO and conventional AFO (Z= 2.26, p=0.025), while no improvements were found on the other aspects of satisfaction.

When walking with the stiffness-optimized AFO, 9 participants perceived large improvements (+2), 9 participants slight improvement (+1), 8 participants no improvement (0), 1 participants slight decrement (-1) and 3 participants large decrement (-2) in walking ability when compared to the conventional AFO.

Perceived advantages

Reported advantages of the stiffness-optimized AFO were; increased stability during walking/standing (n=14), "it walks more easily" (n=12) and lower weight of the optimized AFO (n=6). Reported disadvantages were; difficulties walking stairs (n=9), not able to drive a car (n=3), difficulty finding fitting shoes (n=5) and reduced stability (n=5).

Adverse events

Adverse events related with the stiffness-optimized AFO were pressure sores at the backside of the heel (in 13 of 37 participants) or underneath the foot (n=5), due to a difference in design between the baseline and optimized AFO. The sores could be resolved by placing soft material on the dorsal leaf or shoe inlay. Other reported adverse events were knee and/or hip

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pain (n=6), discomfort due to pressure on the tibia (n=2), oedema in the lower legs (n=2) and pain at the level of the Achilles-tendon (n=1). One participant stopped using the experimental AFO due to hip pain after 2 weeks of use.

Table 2. Effect of stiffness-optimized AFOs compared with conventional AFOs for secondary outcomes

	Conventional AFO T1	Optimized AFO T2	Optimized AFO T3	Effect size (95% CI)	*P* value
Gait biomechanics					
Max ankle dorsiflexion angle in degrees	16.1 ± 6.8	14.5 ± 4.2	14.3 ± 3.5	-1.8 (-4.0 to 0.5)	0.118
Max external ankle moment in Nm/kg	0.94 ± 0.37	1.04 ± 0.24	0.99 ± 0.25	0.06 (-0.03 to 0.15)	0.222
Peak ankle power in W/kg	1.35 ± 0.82	1.47 ± 0.54	1.33 ± 0.53	0.02 (-0.19 to 0.23)	0.840
Min knee angle in degrees	-1.0 ± 6.9	-2.1 ± 6.1	-1.6 ± 6.5	-0.5 (-2.0 to 1.0)	0.522
Max external knee moment in Nm/kg	-0.12 ± 0.26	-0.19 ± 0.21	-0.14 ± 0.21	-0.02 (-0.09 to 0.04)	0.536
Daily activity					
Wearing time AFO minutes	482±295	X	462±261	- 20 (-87 to + 47)	0.551
Daily total steps	8078 ± 2941	X	8222 ± 4364	+144 (-1056 to +1344)	0.805
Daily active minutes	288 ± 68	X	278 ± 97	-10 (-43 to +22)	0.523
Daily steps with AFO	5392 ± 2793	X	5565 ± 4210	+172 (-1059 to +1404)	0.773
Perceived fatigue (range 1-7)	4.84 ± 1.56	X	4.37 ± 1.57	-0.47 (-0.23 to -0.70)	<0.001
Physical functioning (range 0-100)	46.25 ± 16.0	X	55.18 ± 20.4	+8.9 (2.6 to 15.3)	0.008
AFO satisfaction (range 1-10) Z statistic					
Perceived walking safety	7.1 ± 1.8	X	7.4 ± 1.4	0.725	0.468
Perceived safety on uneven ground	5.1 ± 2.2	X	5.1 ± 2.1	0.260	0.795
Perceived walking stability	6.1 ± 2.2	X	6.8 ± 1.8	1.130	0.258
Perceived walking satisfaction	5.8 ± 2.0	X	6.4 ± 2.2	1.870	0.061
Perceived walking intensity	5.3 ± 1.9	X	6.4 ± 1.9	2.261	0.024
Perceive quality of stair climbing	5.6 ± 2.4	X	5.4 ± 2.6	0.277	0.782
Fear of falling	7.1 ± 2.4	X	7.3 ± 2.0	0.610	0.542

Abbreviations: AFO = ankle foot orthosis; Max = maximal; Min = minimal
Results are based on n=37 for T1 and T2, and on n=30 for T3 unless otherwise stated. For daily activity (n=22), physical functioning (n=28), perceived fatigue (n=30) and AFO satisfaction (n=30), only participants without missing values at T1 or T3 are presented.

Discussion

In line with our hypothesis, in persons with calf muscle weakness due to neuromuscular disorders, individually optimizing the AFO bending stiffness improved walking ability, by reducing its energy cost with 9% and increasing speed with 5% in addition to the effect of AFOs provided in usual orthotic care. This was accompanied by a reduction in perceived fatigue and improved perceived physical functioning and walking intensity. No effects of the stiffness-optimized AFO on gait biomechanics or daily step activity were found.

The 9.2% reduction in energy cost we found is similar to the reduction reported in the study of Kerkum et al. on individually optimizing AFO stiffness in children with cerebral palsy [31]. However, in the Kerkum study no statistical significance was reached due to a lack of power and also stiffness optimized AFOs were compared with shoes only. As such, the effect in our study can be considered much larger as we found a 9.2% reduction compared to conventional AFOs and a 20% reduction when compared to shoes only. The 9.2% reduction of stiffness-optimized AFOs compared to conventional AFOs can be considered highly relevant, as it almost doubles the beneficial energetic effect of AFO provision (Figure 3) [14, 32]. Additional, walking speed increased with 5% while walking with the stiffness-optimized AFO, which is of the same order as the maximal improvement in walking speed achieved when systematically varying AFO bending stiffness [33].

When evaluating the effect of stiffness-optimized AFOs for unilateral and bilateral affected persons separately, we found much larger effects in bilateral affected persons. That the differences between the subgroups did not reach significance, probably is caused by a lack of power. A larger effect in bilateral affected persons on walking energy cost may can be explained by the fact that in unilateral affected persons the gait pattern remained asymmetric despite the AFO assistance. As gait symmetry has been shown important for gait efficiency, this might explain the modest effect of AFO stiffness optimization on walking energy cost in unilateral affected persons [34].

The effect of stiffness-optimized AFOs on walking energy cost and walking speed slightly declined between the post-provision and 3 months follow-up measurement (Figure 3), which was also found in a previous publication in children with cerebral palsy using a spring-hinged AFO [31]. The decline in effect in our study may be caused by changes in (calf) muscle weakness or changes in gait biomechanics, but this is unlikely as most participants have relative stable diseases [35, 36] and gait biomechanics did not change after

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acclimatization [37] (see Table 2). Therefore, we hypothesize that wear of the dorsal leaf may have reduced the AFO bending stiffness and thereby its effect, suggesting that monitoring of the AFO bending stiffness over time is warranted. Nevertheless, after 3-months of use, the stiffness-optimized AFO still significantly lowered the walking energy cost by 7% compared to conventional AFOs, which is comparable with the effect of taking off a 4 kilogram backpack [18].

We hypothesized that the energy storing and releasing effect of the optimized AFO would increase ankle power. However, in contrast no effect on ankle power or other biomechanical gait parameters were found. The absence of these effects may be caused by the heterogeneity of the patient population, such as additional dorsiflexion weakness, which causes inter-individual gait differences. In addition there was heterogeneity in conventional AFO properties and their effect on the gait pattern. Both factors are likely to result in inter-individual differences in effect of the stiffness-optimized AFO on the gait pattern.

Therefore, we argue that the reduction in walking energy cost is explained by three mechanisms, or a combination of these three, found in our participants. First, in 40% of our participants and most notably in the DF-stop users, ankle push-off power increased by at least 0.2 W/kg. Such an increment is substantial enough to decrease walking energy cost [38] as it reduces inefficient hip compensations [6, 39, 3, 40]. Second, as stiffness-optimized AFOs have a higher stiffness compared to conventional AFOs, they provide a larger portion of the internal plantarflexion moment, which reduces the energy cost of the calf muscles especially in the patients who had some remaining force [18, 41]. Third, in persons walking with a persistent external knee flexion moment, the stiffness-optimized AFO reduced the peak external knee flexion moment during mid- and terminal stance which reduces the necessary quadriceps activation and hence walking energy cost [7]. However, to which extent these factors played a role in the reduced walking energy cost found in our study is unknown as the relation between pathological gait and walking energy cost is poorly understood [3, 42].

The importance of AFO stiffness-optimization for daily life is indicated by the reduction in perceived fatigue and improvement in physical functioning. However, caution is warranted as these improvements might be biased as participants invested a lot of time and expected that the stiffness-optimized AFO would improve their walking ability. Despite the noticeable effort-related improvements, participants did not increase AFO compliance or daily activities. Participants took on average 8000 steps at baseline, which is comparable with a healthy population and limits room for improvement [43]. However, post-hoc analysis revealed a small increase in step length during the gait analysis (+0.03 m, 0.61±0.11 vs 0.64±0.10, p=0.001) which suggest that with the stiffness-optimized AFO a larger distance was covered, although it cannot be concluded that this increase in step length translates to daily life activities.

An important strength of our study is that we are the first to compare individually stiffness-optimized AFOs with conventional AFOs provided in usual orthotic care. Furthermore, we included a heterogeneous group of persons with neuromuscular diseases, which indicates that our findings may apply to a large number of patients with varying disorders. As we found clinically relevant beneficial effects of the AFO stiffness-optimization, application in usual orthotic care seems warranted, although the highly labor intensive stiffness-optimization procedure may hamper implementation. Especially in bilateral patients with strength differences between legs, the optimization procedure was complex. We only needed it for 3 patients and consequently cannot draw conclusions about whether this extensive procedure is required. To make the stiffness-optimization less laborious and feasible for usual orthotic care, prediction of the optimal AFO stiffness on patient characteristics is needed and requires further research.

A limitation of our study is the drop-out rate of 19% overall and of 8% due to AFO-related problems, which should be taken into consideration when interpreting our results. However, we are confident that this did not bias our results as indicated by the similar effects of the analysis with and without imputation. Furthermore, the dorsal leaf AFO used in our study has some disadvantages. First, the angle of the dorsal leaf is fixed, which makes it harder to personalize the fitting of the AFO. Secondly, due to the higher stiffness compared to conventional AFOs, the stiffness-optimized AFO may hinder more in daily activities such as stair walking, which can be partially resolved by physiotherapy and instructions, specifically directed toward these activities. Thirdly, our modular AFO system allowed for the stiffness-optimization, but consequently is more susceptible to wearing at the attachment to the foot plate and calf casing.

In conclusion, we showed that in persons with neuromuscular disorders demonstrating calf muscle weakness individually optimizing the AFO bending stiffness doubles the effect on walking energy cost, increases walking speed and improves fatigue and walking satisfaction compared to conventional AFOs. Bilateral affected patients benefit the most, especially with regard to walking speed. The improvements are the result of changes in ankle and knee biomechanics, which differ between individuals. We therefore recommend that in orthotic care, the AFO bending stiffness should be individually optimized in order to improve orthotic care.

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