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Interacting effects of AFO stiffness, neutral angle and footplate stiffness on gait in case of plantarflexor weakness: A predictive simulation study

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A R T I C L E I N F O

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A B S T R A C T

To maximize effects of dorsal leaf ankle foot orthoses (AFOs) on gait in people with bilateral plantarflexor weakness, the AFO properties should be matched to the individual. However, how AFO properties interact regarding their effect on gait function is unknown. We studied the interaction of AFO bending stiffness with neutral angle and footplate stiffness on the effect of bending stiffness on walking energy cost, gait kinematics and kinetics in people with plantarflexor weakness by employing predictive simulations.

Our simulation framework consisted of a planar 11 degrees of freedom model, containing 11 muscles activated by a reflex-based neuromuscular controller. The controller was optimized by a comprehensive cost function, predominantly minimizing walking energy cost. The AFO bending and footplate stiffness were modelled as torsional springs around the ankle and metatarsal joint. The neutral angle of the AFO was defined as the angle in the sagittal plane at which the moment of the ankle torsional spring was zero. Simulations without AFO and with AFO for 9 bending stiffnesses (0–14 Nm/degree), 3 neutral angles (0–3-6 degrees dorsiflexion) and 3 footplate stiffnesses (0–0.5–2.0 Nm/degree) were performed.

When changing neutral angle towards dorsiflexion, a higher AFO bending stiffness minimized energy cost of walking and normalized joint kinematics and kinetics. Footplate stiffness mainly affected MTP joint kinematics and kinetics, while no systematic and only marginal effects on energy cost were found.

In conclusion, the interaction of the AFO bending stiffness and neutral angle in bilateral plantarflexor weakness, suggests that these should both be considered together when matching AFO properties to the individual patient.

1. Introduction

Bilateral weakness of the plantarflexors is a common symptom in neuromuscular diseases like Charcot-Marie-Tooth disease (Vinci & Perelli, 2002). In case of bilateral plantarflexor weakness, the forward rotation of the tibia increases when the center-of-pressure (CoP) moves anterior of the ankle joint during gait. Consequently, when the CoP progresses forward during the stance phase of gait, the ankle moves into excessive ankle dorsiflexion, which forces the knee into flexion (Ploeger et al., 2017; Winter, 1983). The increased knee flexion during stance, together with a diminished ankle push-off power and consequent compensations in the hip and trunk lead to a lower walking speed and substantially higher energy cost of walking (Ploeger et al., 2014; Waterval et al., 2018). This, in turn, negatively impacts daily walking activity (Anens et al., 2015; McCrory et al., 1998).

A common treatment for people with plantarflexor weakness, is the provision of a dorsal leaf ankle foot orthosis (AFO) (Waterval et al., 2020a, Waterval et al., 2019). The effectivity of a dorsal leaf AFO on

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reducing ankle dorsiflexion and knee flexion and, hence reduction of compensations and energy cost of walking, depends on its mechanical properties such as AFO bending stiffness, neutral angle and footplate stiffness (Daryabor et al., 2022; Ploeger et al., 2019; Waterval et al., 2019). For example, the reduction of the maximal ankle dorsiflexion angle and knee flexion increases with a higher AFO bending stiffness, though at the cost of a reduced ankle power (Koller et al., 2021; Ploeger et al., 2019; Waterval et al., 2019). Additionally, an optimal bending stiffness for minimization of walking energy cost exists as has been demonstrated in adults with neuromuscular disorders and children with cerebral palsy (Harper et al., 2014; Kerkum et al., 2015; Waterval et al., 2021a; Waterval et al., 2019). Regarding the neutral angle, already a 3-degree change in neutral angle has been shown to affect the ankle and knee joint kinematics during stance in people with limb salvage, with a more dorsiflexed neutral angle shifting the ankle and knee towards more flexion (Brown et al., 2017). Furthermore, in people with nerve injuries such a change in neutral angle led to a delayed progression of the CoP along the foot, resulting in a smaller external knee extension moment and higher activation of the quadriceps musculature during stance, which potentially increases walking energy cost (Brown et al., 2017). Finally, footplate stiffness also affects CoP progression and ankle moment, with a higher stiffness leading to more forward displacement of the CoP and a higher maximal ankle moment, as shown in healthy subjects wearing an AFO (Kerkum et al., 2021). A more forward progression of the CoP may reduce energy cost, although this has only been shown in healthy individuals (Ray & Takahashi, 2020).

Although the separate effects of AFO properties, and most extensively bending stiffness, on gait function and energy cost have been demonstrated in various populations with walking difficulties, it remains unclear how alterations in neutral angle and footplate stiffness influence the AFO stiffness that minimizes the energy cost of walking. Establishing these interactive effects is needed to gain insights into potential effects and benefits of AFO property tuning in combination, which provides clinician's guidance into determining required properties or protocols to select these properties to maximize treatment outcomes. However, determining this experimentally requires testing a large number of combinations of bending stiffness, neutral angle and footplate stiffness, which is unfeasible for people with walking difficulties. Predictive simulations are an alternative, as they allow to systematically alter the different AFO properties without patient burden. We previously demonstrated that such simulations are valid for predicting the effects of bilateral plantarflexion weakness (Waterval et al., 2021b) and of AFO bending stiffness on gait (Kiss et al., 2022). Here, we extend the previously developed model by also incorporating variations in neutral angle and footplate stiffness. By employing predictive simulations with a model with bilateral plantarflexor weakness, we aimed to:

1) Validate the implementation of varying neutral angle and footplate stiffness in the neuro-musculoskeletal model against experimental data;

2) Determine how neutral angle and footplate stiffness interact with the effect of AFO bending stiffness on energy cost of walking;

3) Determine how neutral angle and footplate stiffness interact with the effect of AFO bending stiffness on lower limb joint kinematics and kinetics;

2. Methods

2.1. Simulation framework

We extended the planar model used in previous research (Veerkamp et al., 2021; Waterval et al., 2021b) with a metatarsal (MTP) joint and two toe muscles (the Flexor Hallucis Longus and Extensor Hallucis Longus), to create a model with nine segments, eleven degrees of freedom and eleven muscles per leg. Muscles were modelled using the Millard-Equilibrium muscle model (Millard et al., 2013), while muscle parameters were set according to the OpenSim Gait2392 model (Delp et al., 2007), except for the muscle path of the Flexor Hallucis Longus. This path was adjusted at the MTP joint to match the moment arm with previous studies (Aper et al., 1996; Tanaka et al., 2008). The MTP joint was set at a neutral angle of 5 degrees of dorsiflexion, with a passive stiffness of 0.8 Nm/degree in both directions, which matches the joint characteristics during walking (Mager et al., 2018). To model ground contact, we used three viscoelastic Hunt-Crossley contact spheres on each foot (Hunt & Crossley, 1975). The sphere settings on the heel and at the MTP joint were set according to (Veerkamp et al., 2021), while we added a third sphere 2.7 cm in front of the MTP joint to model toe contact. The model was created as a Hyfydy musculoskeletal model (Geijtenbeek, 2021), which is specifically designed to perform forward dynamic simulations in SCONE, an open-source optimization toolbox (Geijtenbeek, 2019).

To generate walking bouts of 10 s, the muscles were excited by a previously developed gait state-dependent reflex-based controller (Waterval et al., 2021b) that was adapted from (Geyer & Herr, 2010). Optimization of controller and initial pose was performed in SCONE by minimizing a cost function using the Covariance Matrix Adaptation Evolution Strategy (CMA-ES). The optimization stopped when over the last 500 simulation generations, the improvement in cost function outcome was smaller than 0.001% (Hansen et al., 2003). The cost function was adapted from previous research (Veerkamp et al., 2021; Waterval et al., 2021b) and consisted of minimizing energy cost (JCost) (Uchida et al., 2016) and head accelerations (JHeadAcc), besides avoiding falling down (JFall) and avoiding extreme joint angles (JAng). Compared to (Veerkamp et al., 2021; Waterval et al., 2021b), we incorporated a maximum activation of 50% of the Soleus and Gastrocnemius (JMuscleAct), instead of including muscle activation squared in the cost function. We made this change to avoid the negative effects of minimizing muscle activation squared on walking speed (Veerkamp et al., 2021) and to avoid compensations by extremely high muscle activations in case of plantarflexor weakness (Waterval et al., 2021b), which would cause rapid muscle fatigue (Bigland-Ritchie et al., 1986; Potvin & Fuglevand, 2017). Other muscles did not show the tendency to be maximally activated. The weightings of the different optimization criteria were: $0.15{*}JCost + 0.1JHeadAcc + 1E8{*}JFall + 0.1{*}JAng + 1E4{*}JMuscleAct$. An overview of our simulation framework and AFO is presented in Fig. 1.

2.2. Plantar flexor weakness and AFO model

To impose bilateral plantarflexor weakness, we reduced the isometric force of the Soleus, Gastrocnemius and Flexor Hallucis Longus of both legs by 80% and adapted the passive fibre and tendon force–length curves to maintain the same passive force by a given ankle angle as in the healthy model (Waterval et al., 2021b). The force reduction of 80% was based on experimental data against which this model was validated in previous studies (Waterval et al., 2022; Waterval et al., 2021b). AFOs were modelled as torsional springs around both ankles, for which the bending stiffness and neutral angle could be changed, while AFO footplate stiffness was modelled by increasing the passive stiffness around the MTP joint. We varied the bending stiffness levels between 0.9 Nm/degree and 14.0 Nm/degree in steps of 1.7 Nm/degree, to cover the range applied in clinical practice (Fatone et al., 2022; Shuman & Russell Esposito, 2021; Waterval et al., 2020b). Furthermore, we modeled three neutral angles (0, 3, and 6 degrees of ankle dorsiflexion) based on our clinical experience, and three footplate stiffness levels covering the range used in clinical practice (0, 0.5 and 2 Nm/degree) (Waterval et al., 2020b).

We generated walking simulations for all combinations of AFO bending stiffness levels (9 conditions), neutral angles (3) and foot plate stiffness levels (3), as well as without AFO (i.e., bending stiffness of 0 Nm/degree and MTP joint stiffness of 0.8 Nm/degree). Additionally, a healthy walking simulation was generated with a model with the same height (1.80 m) and weight (75.1 kg), but without weakness and without

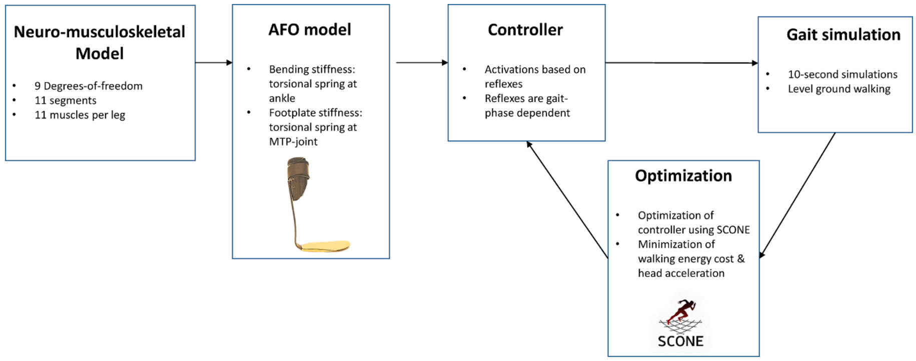

Fig. 1. An overview of the simulation framework. AFO = Ankle foot orthosis.

AFO for comparison, making a total of 83 simulated conditions. Each condition was simulated three times with different random initial guesses, and the simulation with the lowest cost function score was regarded the outcome for that particular condition.

2.3. Validation

Our framework has been previously validated and used to predict the effects of changes in AFO bending stiffness on gait function (Kiss et al., 2022; Waterval et al., 2022). To ensure that the added components in the model reflecting neutral angle and footplate stiffness indeed predict the effects of these AFO properties, we first replicated experimental studies systematically changing these components. This is a necessary step to establish the validity of our model components. To validate for neutral angle changes, we compared the effects of changing the neutral angle by 6 degrees to experimental data of (Brown et al. 2017), specifically looking at the maximal ankle angle in stance, and the knee angle and moment in terminal stance. These three outcome parameters were chosen as they are meaningful in the evaluation of AFOs in case of plantarflexor weakness and are sensitive to change in neutral angle (Brown et al., 2017). As Brown et al. did not report the AFO properties, we chose to use a bending stiffness of 5.2 Nm/degree based on the model's weight (Waterval et al., 2021b) and no footplate stiffness.

For validation of the effect of footplate stiffness, we mimicked the study of Kerkum et al., who evaluated the effect of footplate stiffness in healthy subjects walking with an AFO (Kerkum et al., 2021). To match the experimental data, additional simulations of a healthy model walking at 1.2 m/s without footplate stiffness, and a footplate stiffness of 1 Nm/degree were generated. As in the experiment, the neutral angle was set at zero. The stiffness of the AFO was set at 5.2 Nm/degree based on the subject's weight, similar to how the stiffness was individualized in the experiments. We compared the simulated effects of footplate stiffness variation with experimental results on CoP progression and maximal ankle moment.

2.4. Interaction between AFO properties

For each condition, energy cost of walking and specific gait outcomes important for assessing the effects of AFOs in plantarflexor weakness were calculated. The selected gait outcomes were the minimal knee angle and maximal external knee extension moment, maximal ankle and MTP joint angle and moment, ankle moment during midstance and CoP progression during stance, defined as the difference between CoP at heel strike and maximal CoP during single stance.

The optimal stiffness for energy cost minimization was defined as the stiffness associated with the minimum of a third order polynomial fit between AFO bending stiffness and energy cost, which was calculated for the nine combinations of neutral angle and footplate stiffness. To analyze whether interactive effects of neutral angle and footplate stiffness exist, we qualitatively analyzed the differences in optimal stiffness value, the energy cost associated with this optimal stiffness and differences in the polynomial fits, among the nine combinations of different neutral angles and footplate stiffness levels. As each condition has only 1 simulation, no statistical analyzes was used to determine interactive effects.

Additionally for each combination of neutral angle and footplate stiffness (9 combinations), the effect of bending stiffness on gait outcomes was determined using a second order polynomial fit, as a parabolic relation was expected. The interactive effects of neutral angle and footplate stiffness were analyzed by qualitatively describing the changes in the parabolic fits between AFO stiffness and gait parameters.

3. Results

3.1. Validation

The effects of adjusting the neutral angle and footplate stiffness on gait with an AFO of 5.2 Nm/degree can be seen in Fig. 2. In the simulation, the maximal ankle angle reduced by 4.6 degrees, while experimentally this was 4.5 degrees. Regarding the minimal knee angle, the more dorsiflexed neutral angle reduced knee extension by 3.4 degrees, which was 3.2 degrees experimentally. For the knee moment in terminal stance, the simulated effect of a more dorsiflexed neutral angle (-0.22 Nm/kg) was in the same direction but twice as large as found experimentally (-0.10 Nm/kg) (Fig. 3).

The simulated effect of 1 Nm/degree additional footplate stiffness on maximal ankle moment was in the same direction but smaller compared to experimental data (0.06 versus 0.25 Nm/kg increment), while the simulated effect on CoP (+1.3 cm) was close to experimental results (+1.0 cm) (Fig. 3).

3.2. Interactive effects of neutral angle and footplate stiffness on the effect of AFO bending stiffness on gait

Regarding energy cost of walking, all combinations of neutral angle and footplate stiffness had a R^2 larger than 0.78 and demonstrated a convex relationship between bending stiffness and walking energy cost. At bending stiffness levels up to 4 Nm/degree, no substantial differences in energy cost between the models differing in neutral angle and footplate stiffness were found. For stiffness levels above 4 Nm/degree, higher reductions up to 0.5 J/kg/m in energy cost were found for AFOs with a more dorsiflexed neutral angle (Fig. 4). The effect of footplate stiffness level on the stiffness maximally reducing energy cost depended on the neutral angle. With a neutral angle of 0 degrees, a higher footplate stiffness resulted in a higher AFO bending stiffness for maximally reducing energy cost (from 4.2 to 5.3 Nm/degree), while with a neutral angle of 6 degrees dorsiflexion, the bending stiffness maximally reducing energy cost was lower with increasing footplate stiffness (from 9.4 to 7.7 Nm/degree) (Fig. 4). From all combinations, the lowest energy cost was found for an AFO with a stiffness of 9.4 Nm/degree, neutral

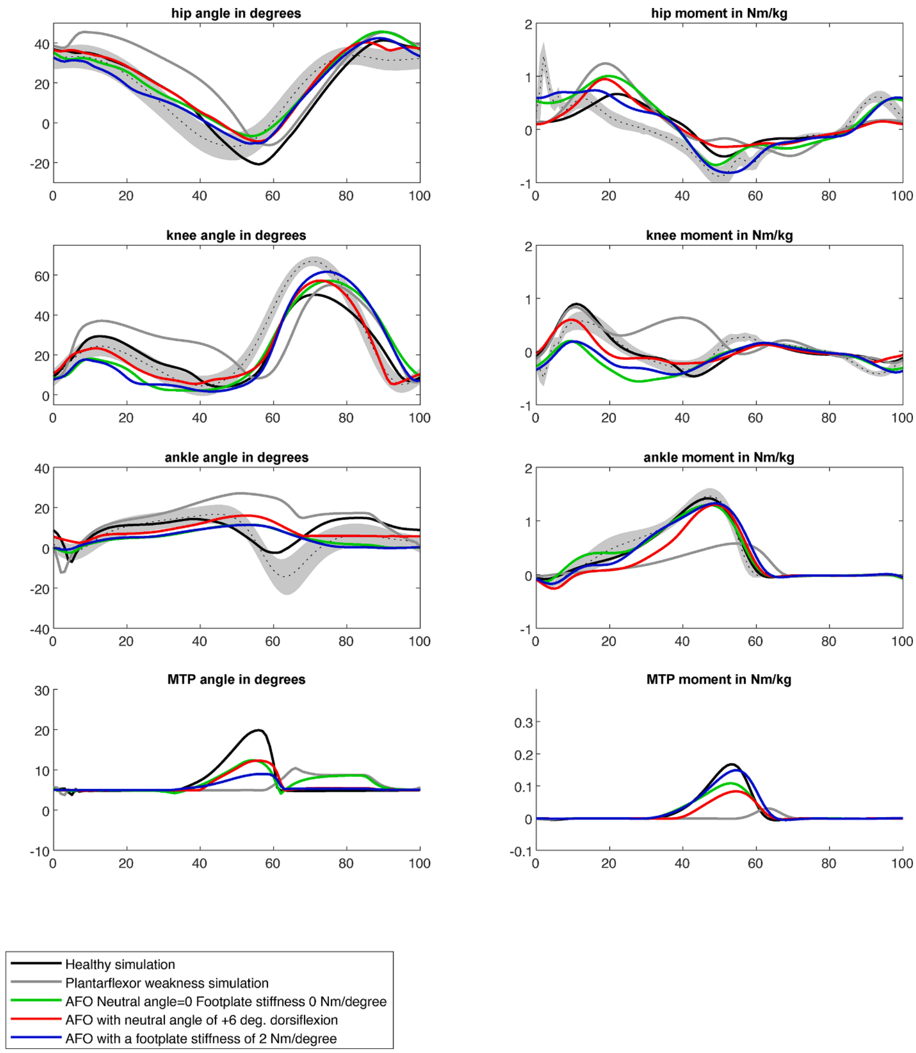

Fig. 2. Simulated joint kinetics and kinematics. In black is the healthy simulation. In grey the simulation with 80% plantarflexor weakness with an AFO with a bending stiffness of 5.2 Nm/degree, neutral angle of 0 and footplate stiffness of 0 Nm/degree. In red is the simulation in which the neutral angle was changed to 6 degrees dorsiflexion. In blue the simulation where the footplate stiffness was changed to 2 Nm/degree. NA = neutral angle, Fp = footplate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

angle of 6 degrees dorsiflexion and no footplate stiffness.

Regarding gait kinematics and kinetics, changing the neutral angle from 0 to 6 degrees dorsiflexion increased the AFO bending stiffness at which the minimal knee moment, maximal external knee extension moment and ankle angle reached the values of the healthy simulation. Regarding the maximal ankle moment, a slightly lower maximum was reached with a more dorsiflexed neutral angle (Fig. 5). Changing the footplate stiffness only affected maximal ankle moment. At bending stiffness levels above 4 Nm/degree, a higher footplate stiffness resulted in a slightly higher ankle moment and in more forward progression of the CoP during stance (Fig. 5).

Regarding the MTP kinematics and kinetics, with increasing AFO bending stiffness both the maximal MTP angle and moment increased (Fig. 5, bottom row). A more dorsiflexed neutral angle decreased the effect of bending stiffness on MTP angle and moment, resulting in both a lower MTP angle and lower MTP moment at a given stiffness. A higher footplate stiffness reduced the maximal MTP angle, but increased the MTP moment.

4. Discussion

Simulations with the extension of an MTP joint, predicted ankle and knee joint changes due to varying AFO neutral angle and footplate stiffness with reasonably small differences with experimental data. Furthermore, the simulations indicated that in people with bilateral plantarflexor weakness, AFO bending stiffness, neutral angle and footplate stiffness interact regarding the reduction of walking energy cost and normalization of gait. Higher reductions up to 0.5 J/kg/m or an approximate 33% higher effect in walking energy cost were achieved with AFOs with a dorsiflexed neutral angle in combination with relatively higher AFO bending stiffness (greater than 4 Nm/degree) compared to AFOs with a neutral angle of 0 degrees. Regarding gait, AFO bending stiffness and neutral angle affected knee, ankle and MTP kinetics and kinematics, while footplate stiffness mainly affected MTP kinetics and kinematics.

Our simulations can predict the separate effects of varying neutral angle and, to some extent, footplate stiffness, as they are in in line with previous experimental results (Brown et al., 2017; Kerkum et al., 2021), and AFO bending stiffness as previously demonstrated (Kiss et al., 2022). With a neutral angle of zero, the knee and ankle kinematics and kinetics were normalized when applying bending stiffness levels between 4 and 5 Nm/degree, which is in the range of bending stiffness levels found to normalize gait and maximally reduce energy cost in individuals with plantarflexor weakness (Waterval et al., 2020b). The effects of changing the neutral angle in steps of three degrees towards dorsiflexion in combination with bending stiffness levels within the range of 2 and 8 Nm/degree are in the same order of magnitude as found by Brown et al. (2017) in trauma patients using a relatively stiff AFO. At low bending stiffness levels, changing the neutral angle had small effects in our simulations, probably because at low stiffness levels the AFO does not meaningfully affect gait. Simulating the effects of a stiff footplate increased the CoP progression in the same order of magnitude as found

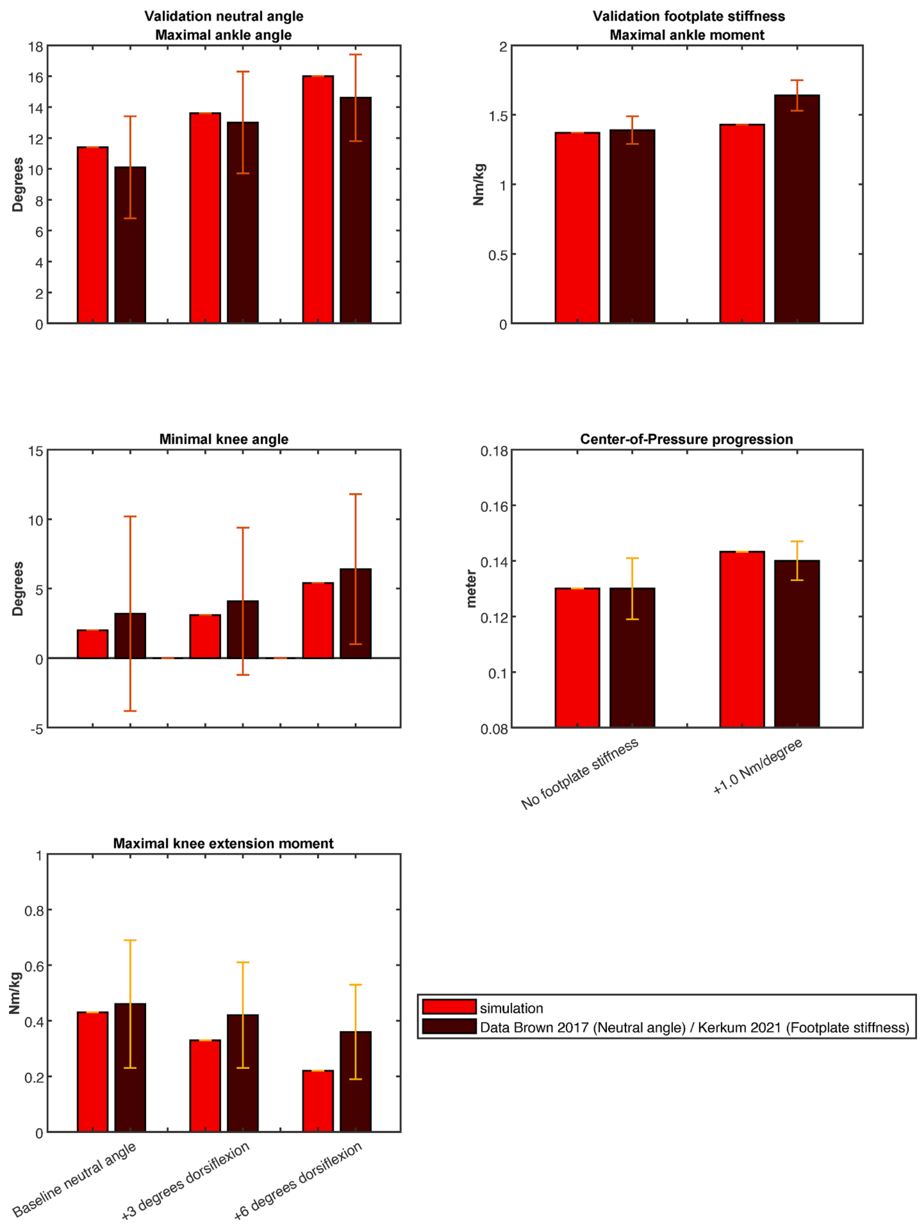

Fig. 3. Validation of the simulations; comparison with experimental results.

in healthy subjects walking with an AFO with relatively high bending stiffness (Kerkum et al., 2021). Additionally, increasing footplate stiffness reduced the MTP joint angle, as also reported in healthy individuals (Zullo et al., 2021). However, the increase in ankle moment with stiff footplates was much lower than experimentally found, which might be explained by our simplified foot model, which assumes the foot is rigid except by the MTP-joint, thereby neglecting the movements in the midfoot.

Where AFO bending stiffness and neutral angle demonstrated large effects on the ankle and knee joints angles and moments as well as on energy cost, changes in footplate stiffness only marginally affected gait and energy cost. As expected, and comparable with studies in healthy individuals, a higher footplate stiffness reduced MTP range of motion and increased MTP and ankle moments by increasing the lever arm of the CoP (Ray & Takahashi, 2020; Zullo et al., 2021). However, we only showed this effect to some extent at relatively high AFO bending stiffness levels. Besides our model limitations, this may be explained by two factors; first, at low AFO bending stiffness levels, the CoP will not move anterior of the MTP joint as the AFO does not provide enough support moment to restrain the forward rotation of the tibia in case of plantarflexor weakness (Ploeger et al., 2019; Waterval et al., 2019). Secondly, slower walking reduces the forward progression of the CoP, and hence MTP joint moments (Dubbeldam et al., 2011; Eerdekens et al., 2019; Lelas et al., 2003). Therefore, in people with plantarflexor weakness, increasing footplate stiffness only seems relevant if the patient walks relatively fast and the AFO has an appropriate combination of bending stiffness and neutral angle. In such combinations the footplate also has a marginal effect on energy cost, although much smaller compared to bending stiffness or neutral angle and possibly not meaningful for the patient.

The lowest energy cost of walking was achieved by an AFO with a neutral angle of 6 degrees dorsiflexion, although at the expense of a high bending stiffness, which may hinder people in daily life activities. By changing the neutral angle towards dorsiflexion, a higher bending stiffness was necessary to achieve knee extension and an external knee extension moment during terminal stance, which contributes to reducing energy cost in people with plantarflexor weakness (Ploeger et al., 2014; Winter, 1983). Our simulations show that ankle moment at

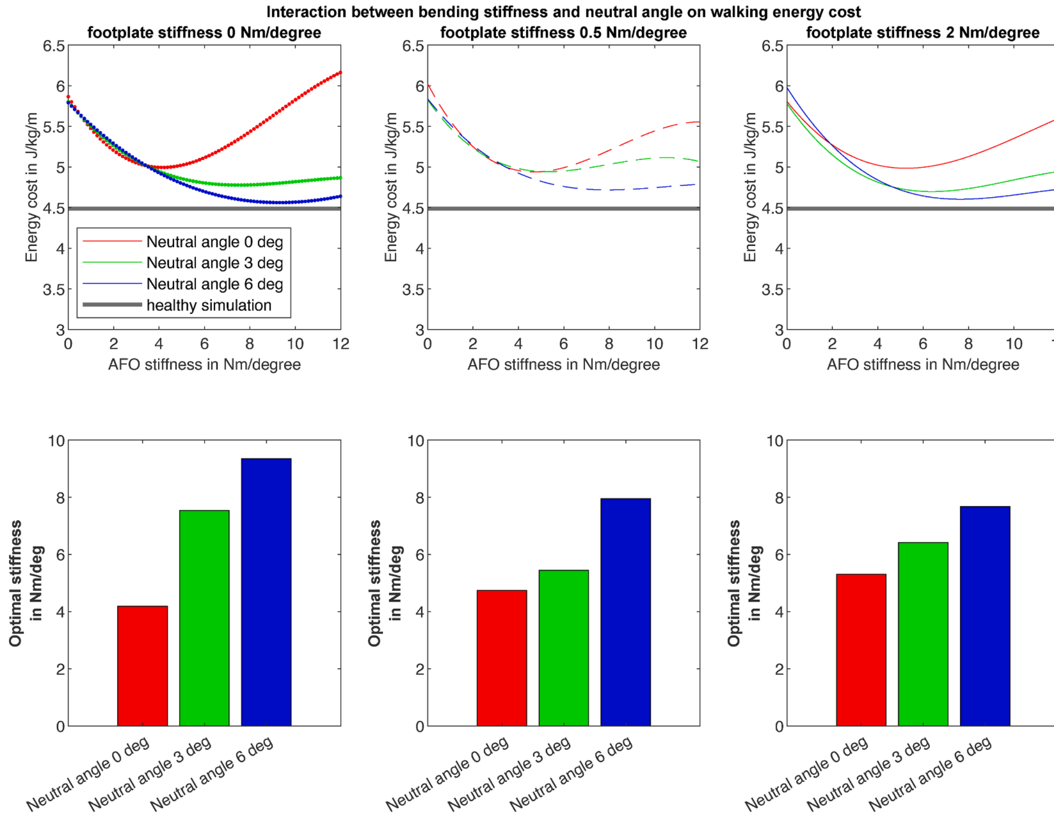

Fig. 4. The interactive effect of AFO bending stiffness, neutral angle and footplate stiffness on energy cost. NA = neutral angle, Fp = footplate.

optimum stiffness is higher with a more dorsiflexed neutral angle. With a more neutral alignment, such ankle moments can be achieved by further increasing bending stiffness, but at the cost of knee hyper-extension and larger knee moments. However, whether AFOs with a dorsiflexed neutral angle and high stiffness are most beneficial in daily life is questionable. The high stiffness restricts ankle movements, which is experienced as a disadvantage during activities of daily living (Ploeger et al., 2020; Van Der Wilk et al., 2018; Waterval et al., 2020b; Waterval et al., 2019; Zuccarino et al., 2021). Thus, despite the potential additional reductions in energy cost, applying AFOs with a high stiffness and dorsiflexed neutral angle might not improve treatment outcomes.

Although we demonstrated that our simulations can predict most effects of relevant AFO properties, our framework contains various assumptions. First, we only tested our interactions using a planar model with severe weakness, which neglects possible interactions between AFO properties and medial–lateral balance (Meyns et al., 2020) or subject characteristics (Waterval et al. 2022). Secondly, we used a simplified rigid foot model, containing of three contact spheres at a fixed position. Such model neglects movements within the foot and assumes the CoP is at the same location (at the toe-contact sphere) during toe-off for each footplate stiffness, which is not the case in experimental data (Ray & Takahashi, 2020). Improvements in our foot model may therefore be needed to improve the validity of our outcomes regarding footplate stiffness. Thirdly, we only used a model with 80% plantarflexor weakness limiting the generalizability of the results. Possibly, in people with less severe weakness and more forward progression of the center-of-pressure, footplate stiffness has a more substantial effect. Future research should therefore analyze the interaction between optimal properties and model characteristics, although this requires substantial computational time.

Despite these shortcomings, our work provides valuable insights into how changes in neutral angle and footplate stiffness affect the optimal AFO stiffness for energy cost minimization that would not be possible to gain from experiments. Based on our results, in clinical practice all properties should be tuned together as our simulations showed that changing the neutral angle by 3 degrees and/or footplate stiffness by 0.5 Nm/degree alters the optimal stiffness for energy cost minimization by more than 1 Nm/degree. Such a change is substantial, as experimentally such a difference in stiffness increased energy cost by 6% compared to the optimal stiffness (Waterval et al., 2021b). Additionally, our simulations indicate that in case of severe plantarflexor weakness (80% weakness), a stiffness of a least 4 Nm/degree should be provided. This is a higher stiffness compared to currently provided in usual care (Waterval et al., 2020b) or what is available off-the-shelf (Shuman & Russell Esposito, 2021), indicating the necessity to fabricate custom-made AFOs of a higher stiffness in this population. Our results further stress the importance of testing and tuning AFOs in shoes that are used in daily life, as different shoes will affect the neutral angle of the AFO, thereby substantially changing the effect of the AFO. To enable easy personalization of AFO properties within the clinic, future research should focus on creating realistic subject-specific simulations that can predict optimal settings of the individual user. Another research direction is the development of AFO devices in which the properties can be altered instantaneously in order to optimize them using human-in-the-loop optimization (Zhang et al., 2017).

In conclusion, our simulations indicate that in people with bilateral plantar flexor weakness, AFO bending stiffness and neutral angle substantially interact regarding their effect on energy cost of walking. This suggests that these properties should be tuned together to achieve maximal treatment outcomes. Regarding footplate stiffness, our simplified foot model seems to indicate only marginal affects on gait and energy cost. Future research should aim to develop methodologies to enable clinical provision of AFOs with optimized AFO settings.

Ethics approval and consent to participate

All participants provided written informed consent before inclusion. The study protocol of the PROOF-AFO trial was approved by the medical

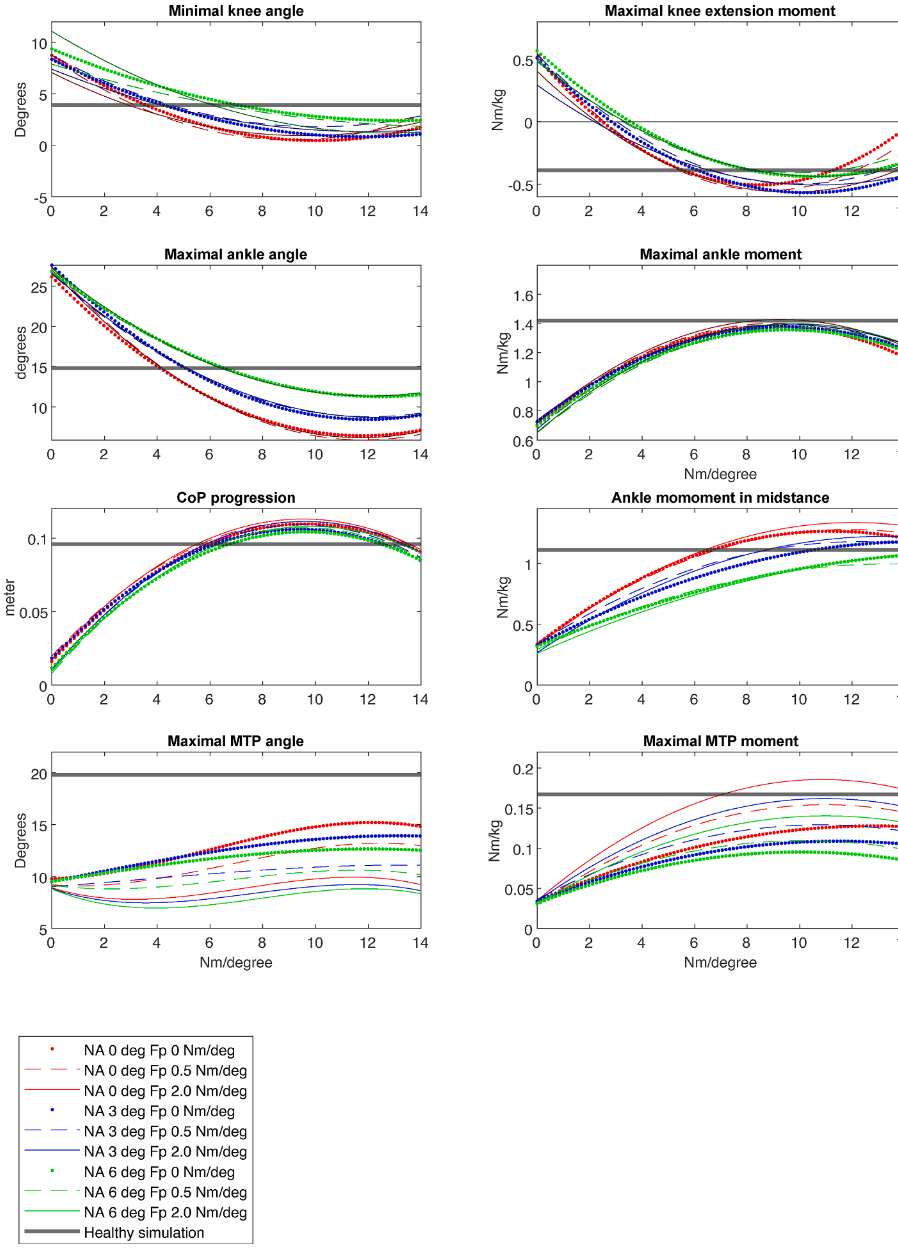

Fig. 5. Relationship between AFO stiffness and gait parameters for different neutral angles and footplate stiffness'. NA = neutral angle, Fp = footplate.

ethics committee of the Academic Medical Center (AMC) in Amsterdam, The Netherlands (register: METC_2014_397).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

N.F.J. Waterval: . **M.A. Brehm:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **K. Veerkamp:** Writing – review & editing, Software, Validation, Methodology. **T. Geijtenbeek:** Writing – review & editing, Visualization, Software, Validation, Methodology, Funding acquisition. **J. Harlaar:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **F. Nollet:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **M.M. van der Krogt:** Writing – review & editing, Validation, Visualization, Resources, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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