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Impaired gait function in adults with cerebral palsy is associated with reduced rapid force generation and increased passive stiffness

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HIGHLIGHTS

- Impaired toe lift during gait was most strongly correlated with increased passive ankle muscle stiffness and reduced rate of force development in ankle dorsiflexors in adults with CP.
- Reduced push-off velocity during gait was most strongly correlated with reduced rate of force development in ankle plantarflexors.
- Spasticity (evaluated clinically or biomechanically) was found not to be a disadvantage for gait.

ABSTRACT

Objective: It is still not clarified whether spasticity contributes to impairments of gait function. Here we compared biomechanical measures of muscle weakness and stiffness of ankle muscles to impairments of gait function in adults with cerebral palsy (CP).
Methods: Twenty-four adults with CP (mean age 34.3, range 18–57 years) and fifteen healthy age-matched controls were biomechanically measured for passive and reflex-mediated stiffness of the ankle plantarflexors at rest, maximal voluntary plantarflexion and dorsiflexion effort ($MVC_{pf,df}$) and rate of force development ($RFD_{pf,df}$). Kinematic analysis of the ankle joint during treadmill walking was obtained by 3-D motion analysis.
Results: Passive stiffness was significantly increased in adults with CP compared to controls. Passive stiffness and RFD_{df} were correlated to reduced toe lift. RFD_{pf} provided the best correlation to push-off velocity, range of movement in the ankle joint and gait speed. Reflex-mediated stiffness was not correlated to any parameters of impaired gait.
Conclusions: Impaired gait function in adults with CP is associated with reduced RFD and increased passive stiffness of ankle muscles.
Significance: These findings suggest that reduced rapid force generation and increased passive stiffness of ankle muscles rather than increased reflex-mediated stiffness (spasticity) likely contributes to impaired gait function in adults with CP.

1. Introduction

Spasticity is usually defined as a velocity-dependent increase in muscle tone related to exaggeration of the stretch reflex circuitry (Lance, 1980), although recent studies have pointed out that this definition may be too narrow to capture the full clinical picture of spasticity (Malhotra et al., 2009). Despite several decades of ever more advanced electrophysiological, biomechanical and clinical studies there is also still no clear consensus regarding the functional

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significance of spasticity defined in this way (Dietz and Sinkjaer, 2007, 2012; Malhotra et al., 2009). This is a concern for antispastic treatment, which is directed at diminishing muscle tone caused by hyperactive reflex activity (Dietz and Sinkjaer, 2007, 2012).

Several studies have documented that reflex modulation is abnormal during gait in spastic subjects with multiple sclerosis (Sinkjaer et al., 1996), stroke (Mazzaro et al., 2007), spinal cord injury (Faist et al., 1999) and cerebral palsy (CP) (Hodapp et al., 2007; Willerslev-Olsen et al., 2014), but it is unclear to what extent this contributes to the impairment of gait observed in these subjects. Although hyperactive reflexes may be elicited by external perturbations in specific phases of the gait cycle, sensory feedback mechanisms seem if anything to contribute less to the muscle activity recorded during gait in spastic subjects with stroke or CP (Mazzaro et al., 2007; Willerslev-Olsen et al., 2014). Other studies on subjects with hereditary spastic paraparesis have also failed to find any correlation between measures of exaggerated reflex activity and impairments of gait (Marsden et al., 2012).

Part of this controversy may be explained by difficulties in distinguishing reflex-mediated stiffness from other causes of pathologically increased muscle stiffness. As pointed out in several recent studies, increased passive stiffness of the muscles, connective tissue, tendons and joints is difficult to distinguish clinically from spasticity and requires a combination of biomechanical and electrophysiological techniques in order to be correctly evaluated (Mirbagheri et al., 2004, 2005; Lorentzen et al., 2010; Willerslev-Olsen et al., 2013). It was suggested already by Volker Dietz and his co-workers more than 30 years ago that such changes in passive muscle stiffness may be the dominant cause of gait impairment in spastic subjects (Dietz et al., 1981; Berger et al., 1982; Dietz and Berger, 1983). Several recent studies have now confirmed Dietz and co-workers original findings of the importance of increased passive muscle stiffness for the gait impairment in subjects with stroke (Lamontagne et al., 2000; Roy et al., 2013) and hereditary spastic paraparesis (Marsden et al., 2012). Impaired gait in adults with cerebral palsy (CP) is usually claimed to be associated to spasticity, but there is little available evidence to support this.

Muscle weakness is another factor that is often discussed in relation to gait function in CP (Dallmeijer et al., 2011; Eek et al., 2011; Thompson et al., 2011). Many everyday activities allow a limited time to develop muscle force (up to 200 ms) whereas the time required to develop maximal force takes considerably longer (Aagaard et al., 2002). Interestingly, the rate at which force or torque is produced, known as the rate of force development (RFD), have been shown to be a good predictor of functional performance in elderly (Bassey et al., 1992; Skelton et al., 1994) and recently also in children with CP (Downing et al., 2009; Moreau et al., 2011). Nevertheless, the importance of RFD for gait function has been largely overlooked in adults with CP.

It was therefore the purpose of the present study to investigate the relationship between muscle weakness (MVC and RFD), passive and reflex-mediated muscle stiffness to impairments of gait function in adults with CP.

2. Methods

2.1. Participants

Twenty-four adults diagnosed with CP (age 34.3, range 18–57 years; 15 men, 9 women) were recruited through the Danish Cerebral Palsy organization. Fifteen subjects were diplegic, eight hemiplegic and one quadriplegic and their Gross Motor Function Classification System (GMFCS) scores ranged from I-III (I: $n = 9$, II: $n = 8$, III: $n = 7$; Table 1). All subjects were described as spastic and most of the subjects had previously received anti-spastic medication for shorter or longer periods. Two subjects received anti-spastic medication (Chlorzoxazone) at the time of the study. Many subjects had a history of multiple surgeries (Table 1). They were all community ambulators except for two subjects, who both required personal assistance.

As a control group, 15 age-matched (age 32.9 years, range 23–47; 9 men, 6 women) neurologically healthy adults were recruited.

The study was approved by the local ethics committee (H-4-2012-107) and all procedures were conducted within the standards of the Helsinki declaration. Prior to the experiments all the participants received written and verbal information, and signed consent-form for participation was obtained.

2.2. Neurological examination

The neurological examinations were performed bilaterally for both knee- and ankle joints by trained clinicians (two of the authors: JL, HK). The clinical tests were performed at the ankle- and knee joint with the subject at rest lying comfortably on an examination-bed. The tests were performed in the following order: Passive range of motion (ROM) was measured with a handheld plastic goniometer by moving the foot slowly from a neutral position (90° position in relation to the tibia) and as far as possible in both plantar- and dorsiflexion direction. The largest excursion was measured and noted in both directions. Modified Ashworth Scale (MAS) (Bohannon and Smith, 1987; Bakheit et al., 2003) and Modified Tardieu Scale (Gracies et al., 2000) was evaluated by moving the joint passively from a neutral position. The investigated joint was first moved 2–3 times as slow as possible to evaluate the stiffness/resistance without the presence of stretch reflexes. Afterwards, the investigated joint was moved with a speed compared to the speed of gravity and finally it was moved as fast as possible to evaluate the reflex contribution to the stiffness/resistance of the joint.

2.3. Experimental set up

2.3.1. Measurement of passive and reflex-mediated stiffness

In order to objectively assess the passive and reflex-mediated stiffness components of the ankle plantarflexors, biomechanical and electrophysiological evaluations were performed on the leg that the subject reported to be the most affected (Lorentzen et al., 2010; Willerslev-Olsen et al., 2013). The subject was at rest throughout all measurements. Subjects were seated in a reclining armchair with the examined foot attached to a foot plate, which could be rotated by a motor (CEM model 26) causing a stretch of the plantarflexors. The motor was driven by a DC power amplifier (Brüel & Kjaer; model 2708) and could deliver maintained torques up to 80 Nm and peak torques up to 120 Nm. An electro-goniometer, connected to the foot plate, measured the angle of the ankle joint and a torque meter measured the torque exerted on the foot plate prior to and during the stretch perturbations. The subject was positioned with the hip joint in 80° flexion, the knee in 55° flexion and the ankle joint in 20° plantarflexion. Five subjects, in whom their passive, ankle ROM (Table 1) did not allow this ankle position, were instead positioned in 10° (subject 7, 15, 18 and 24) or 0° (subject 8) plantarflexion. The perturbations consisted of ramp and hold dorsiflexion with an amplitude of 6° at 17 different velocities between 5 and 220°/s and with a hold time of 460 ms. Perturbations were delivered in a software generated, pseudo-random order until 10 trials per velocity were collected. The interval between perturbations was 1 s. This short interval was chosen based on the observation by Grey et al. (2008) that the largest difference in reflex excitability between a group of subjects with

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Table 1
Overview of the CP subjects, including their: Sex, Age, Diagnosis, GMFCS, MAS, Tardieu, P-ROM, Surgical History, Walking-aid, Wheelchair.

Subject	Sex	Age	Diagnosis/most affected side	GMFCS	MAS (0–4)[a]		Tardieu Scale[b]		P-ROM PF		P-ROM DF		Surgical history	Walking-aid/ Wheelchair
					Right	Left	Right	Left	Right	Left	Right	left		
1	M	23	D/L	I	1+	1+	2	2	50	50	10	10	GS	
2	M	32	H/R	I	1+	1+	2	2	50	50	10	12	GS, THR	
3	M	43	H/R	I	0	0	0	0	50	50	25	25		
4	M	26	D/L	II	0	0	0	0	50	50	0	−10	GS, Hamstrings	
5	F	31	D/L	II	0	0	0	0	50	50	10	10	GS, ST, IL Hamstrings, Adductors	
6	M	23	H/L	II	1+	1+	3	3	50	50	15	5	GS	
7	M	38	D/L	II	0	0	0	0	20	20	10	10	GS, IL, Rectus, Hamstrings	Crutches
8	F	39	D/L	III	0	0	0	0	10	10	0	0	GS, ST	Crutches, Manual Wheelchair
9	F	18	H/L	I	0	3	0	2	50	50	20	5	GS	
10	M	44	D/L	II	0	1+	0	2	50	50	10	5	GS, IL, Adductors, Hamstrings	
11	F	47	Q/R	III	0	0	0	0	50	50	0	5	GS, Adductors, Hamstrings	Rollator outside, Electric wheelchair
12	M	28	D/R	III	0	0	0	0	50	50	0	0	ST, Hamstrings	Crutches
13	M	18	H/L	I	0	1+	0	3	50	50	25	10		
14	F	26	D/L	I	1	1+	1	2	50	50	10	12		
15	F	43	D/L	III	0	0	0	0	20	20	12	12	GS, Hamstrings, Adductors, Rectus	Crutches
16	M	23	D/L	I	1+	1+	2	3	50	50	10	10	GS, Hamstrings	
17	M	38	D/L	III	0	0	0	0	50	50	15	20	GS, ST, Hamstrings, Adductors	Crutches, Electric wheelchair
18	F	55	D/L	III	0	0	0	0	25	20	0	0	Hamstring, Adductors	Crutches
19	M	38	H/R	II	0	0	0	0	50	50	12	15	GS, Hamstrings, Adductors	
20	M	48	D/L	II	0	0	0	0	50	50	0	5	GS, Hamstrings, Adductors	
21	F	41	D/L	II	0	0	0	0	50	50	10	10		Crutches
22	M	23	H/R	I	0	0	0	0	50	50	8	22	GS, ST	
23	M	18	H/R	I	1+	1+	3	2	50	50	22	18		
24	F	57	D/R	III	0	0	0	0	20	20	5	10	GS, Hamstrings, Adductors	Rollator
SUM/ AVG	15 M 9F	34.3	8 H, 15 D, 1 Q	1.9										

Abbreviations: M, Male; F, Female; H, Hemiplegia; D, Diplegia; Q, Quadriplegia; L, Left; R, Right; GMFCS, Gross Motor Function Classification System; GS, Gastrocnemius-Soleus Recession; ST, Subtalar; IL, Iliopsoas; THR, Total Hip Replacement.

[a] Spasticity in plantarflexors according to the modified Ashworth Scale (Bohannon and Smith, 1987).

[b] Spasticity in plantarflexors according to the Tardieu Scale. P-ROM, passive range of motion; PF, plantarflexion; DF, dorsiflexion.

spasticity and a group of control subjects is observed at this interval.

2.3.2. Electromyographic (EMG) recordings

EMG activity was recorded using bipolar electrodes (Ambu Blue sensor N-10-A/25, Ambu A/S Ballerup. Recording area 0.5 cm^2 inter-electrode distance, 2 cm) placed over the soleus muscle. The skin was brushed softly with sandpaper (3 M red dot; 3 M, Glostrup, Denmark). A ground electrode was placed on the distal part of tibia. EMG signals were filtered (band-pass, 5 Hz–1 kHz), amplified (2000×), sampled at 2 kHz, and stored on a PC for off-line analysis.

2.3.3. Maximal torque response

The maximal torque response (T_{max}) was recorded and calculated as the peak-to-peak amplitude evoked by supramaximal stimulation of the tibial nerve in the popliteal fossa. Stimulation was increased until the M-wave did not increase more. The T_{max} was used to normalize the passive and reflex-mediated stiffness (see later). One subject (No. 16; Table 1) found the T_{max} recording uncomfortable and refused to participate in that recording. Data from this subject was therefore not included in the analysis of normalized passive and reflex-mediated stiffness.

2.3.4. Offline analysis of passive and reflex-mediated stiffness

Signal processing and analysis was carried out off line. The EMG records were rectified and low-pass filtered at 40-Hz (first order Butterworth). All trials were manually tested for compliance with the instruction to relax. The EMG baseline was calculated as a mean value in a 100 ms window preceding the perturbation. Any trials exceeding a 3 times baseline level due to voluntary or involuntary neural activation of the muscle in the mentioned 100 ms window was excluded from further analysis. The remaining trials, never less than 5 per velocity, were then ensemble-averaged to produce a single record for each velocity. Subsequently, the latency of the EMG responses to stretch of the soleus muscle was determined.

To be qualified as a stretch reflex, EMG activity in a window 30–100 ms after onset of perturbation had to be more than 50 μV above the baseline EMG. The window 30–100 ms was chosen since the onset latency of the short-latency reflex is around 40 ms in adults and the voluntary reaction time is around 100 ms. The onset-time was noted and peak-to-peak amplitude of the reflex was then calculated.

To calculate the passive and reflex-mediated stiffness (Nm/deg), the torque responses to the 6-degree perturbations were divided by 6 degrees. The torque response was defined as the difference between the baseline torque (measured as the mean torque in a

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100 ms window before perturbation) and the max torque (the peak torque in a 360 ms window starting 100 ms after the end of the incline ramp phase of the perturbation). Previous studies have demonstrated that the reflex responses to stretch of the ankle plantarflexors are manifested in the torque within this window (Toft et al., 1991). Passive stiffness was calculated as a mean of 4 ensemble-averaged trials of slow velocities (15°, 20°, 25°, 30°/s) that did not elicit stretch responses in any subjects. The 4 ensemble-averaged torque responses varied 1–2% from the mean. This minimal variation is also an indirect indication that the subjects were able to relax. Reflex-mediated stiffness was calculated as the average torque response to the fastest (220°/s) perturbations deducted by the passive stiffness (see Willerslev-Olsen et al. (2013)). This has previously been shown to give a valid estimate of reflex torque (Toft et al., 1991).

2.3.5. Measurement of MVC and RFD

The maximal voluntary isometric contraction strength (MVC) and rate of force development (RFD) of the dorsiflexors and plantarflexors were also measured in the stationary dynamometer. Subjects were carefully instructed to contract "as fast and forcefully as possible" and to hold the contraction for about 3 s. During each trial, the subject was verbally encouraged by the experimenter to produce maximal torque. Each subject first performed 3 dorsiflexions and then 3 plantarflexions with maximal effort. If an initial countermovement (identified by a visible drop in the torque trace) was observed, a new trial was performed. Data was recorded and stored on a personal computer (CED 1401+ with Spike 2.611 software; Cambridge Electronics Design, Cambridge, UK). Offline, all data was exported to Microsoft Excel and a torque plot was created for each trial in each subject. Each torque plot was visually inspected for possible spikes and the trial that produced the highest dorsiflexion (MVC_{df}) and plantarflexion MVC (MVC_{pf}) peak torque was determined. These trials were then used to calculate the RFD_{df} and RFD_{pf}, respectively, at different time points (30, 50, 100 and 200 ms; Fig. 1A) following the onset of contraction (0 ms, defined as the baseline torque in the 500 ms preceding the contraction plus 2 SDs).

2.3.6. 3-D gait analysis

Subjects were required to walk on a treadmill without incline. The subjects were asked to hold on to the bar if they used other walking aids in their daily life or if they felt insecure (18 of the adults with CP chose to do so). They walked in their own sports shoes without shoe inserts or braces. Following 3 min of familiarization, the subjects selected their own comfortable walking speed. Passive reflexive markers (size 12 mm) were then placed bilaterally at (1) Processus Spinosus L5 – Vertebra, (2) Spina Iliaca Anterior Superior – Coxae, (3) Trochanter Major – femur, (4) Epicondylus Lateralis – femur, (5) Tuberositas Tibia, (6) Malleolus Lateralis – Tibia, (7) Tuber Calcanei – Calcaneus, (8) Tuberositas Ossis Metatarsi Quinti. After marker placement, the subjects walked at the chosen speed for three minutes. After two minutes, a 60 s recording was obtained while the subjects kept their walking speed steady. Three-dimensional kinematic data was obtained by a Qualisys motion capture system (Qualisys, Gothenburg, Sweden) with six, synchronous Oqus 1 cameras operating at a sampling frequency of 200 Hz. Data was processed using Qualisys Track Manager and exported into MATLAB (The MathWorks Inc., Natick, MA) for further analysis.

Two measures of foot drop were obtained from the 3-D motion analysis (Fig. 1B): (1) The amplitude of the 2nd toe lift late in the swing phase just prior to ground contact and (2) the position of the ankle joint at ground contact. The amplitude of the 2nd toe lift has been shown to provide a functionally important measure of foot drop in patients with spinal cord injury (Barthelemy et al., 2010). This measure was obtained through detection of a peak in the *Z*-axis position of the toe marker of greater than 4 mm within 200 ms prior to ground contact. Selected peak displacements were subsequently verified visually. The position of the ankle joint at initial ground contact was determined and compared to the position when the foot was flat on the ground i.e. in early stance within a 150 ms window post ground contact. The difference between the angle at initial contact and the angle in early stance phase with foot flat was taken as an indication of the range of active dorsiflexion.

Finally, the push-off velocity was calculated by differentiating the movement of the ankle joint in the second part of the stance-phase and identifying the peak of the derivative. All measures were averaged over all steps within the 60 s recording period.

2.3.7. Statistics

Sigma Plot statistical software version 12.5 was used for all statistical analysis. Pearson correlation was used for all correlations, whereas Student's *t*-test was applied for all comparisons between subjects with CP and control subjects. Best subset and multiple linear regression analysis were used to evaluate the best relation between muscle stiffness and function (MVC and RFD) and the various gait parameters (lift of toes, angle of ankle joint at ground contact, range of movement and push-off velocity). The best model was selected based on the highest adjusted r^2 value. Statistical significance was given for *p*-values smaller than 0.05. Data are presented as means ± standard error unless reported otherwise.

3. Results

3.1. Passive and reflex-mediated stiffness

There was a significantly larger passive stiffness in adults with CP compared to controls regardless whether the stiffness was normalized to T_{max} (73 ± 13% vs. 22 ± 2%; $p = 0.003$) or not ($p = 0.020$). Fig. 2A shows the normalized passive stiffness in order to compare directly to the reflex-mediated stiffness in Fig. 2B. The reflex-mediated stiffness was very similar in the two populations and showed no statistically significant difference ($p = 0.969$; Fig. 2B). In 16 of the adults with CP a larger passive stiffness than the range of passive stiffness in healthy controls (9.9–38.5% of T_{max}) was observed. In only two of the adults with CP were a larger reflex-mediated stiffness than the range in controls (1.9–55.6% of T_{max}) observed. These two subjects (subject 15 and 23; Table 1) scored 0 and 1+ on the MAS and 0 and 3 on the Tardieu scale, respectively. The EMG response to stretch consisted of a single short-latency response in all control and CP subjects. It was not possible to make a reliable discrimination of different reflex peaks (i.e. M1, M2 and M3 as shown previously during contraction; Toft et al., 1991) within this response.

3.2. MVC and RFD

Fig. 3A shows the RFD_{df} and MVC_{df} for the CP-group and the healthy controls. For all RFD intervals, the average muscle strength of the CP-group was much lower than the controls. For the 0–200 ms time-interval ($RFD200_{df}$), which is often regarded as the maximum time available for many everyday movements to occur (Suetta et al., 2004; Moreau et al., 2011), the adults with CP produced only 21% of the torque produced by the controls (28.3 ± 6.6 Nm/s vs. 137.5 ± 11.2 Nm/s; $p < 0.001$). For the MVC_{df}, the adults with CP produced 42% of the torque produced by the controls (15.8 ± 3.8 Nm vs. 37.7 ± 2.4 Nm; $p < 0.001$).

The difference in RFD and MVC between adults with CP and controls was even more marked for plantarflexion (Fig. 3B). For

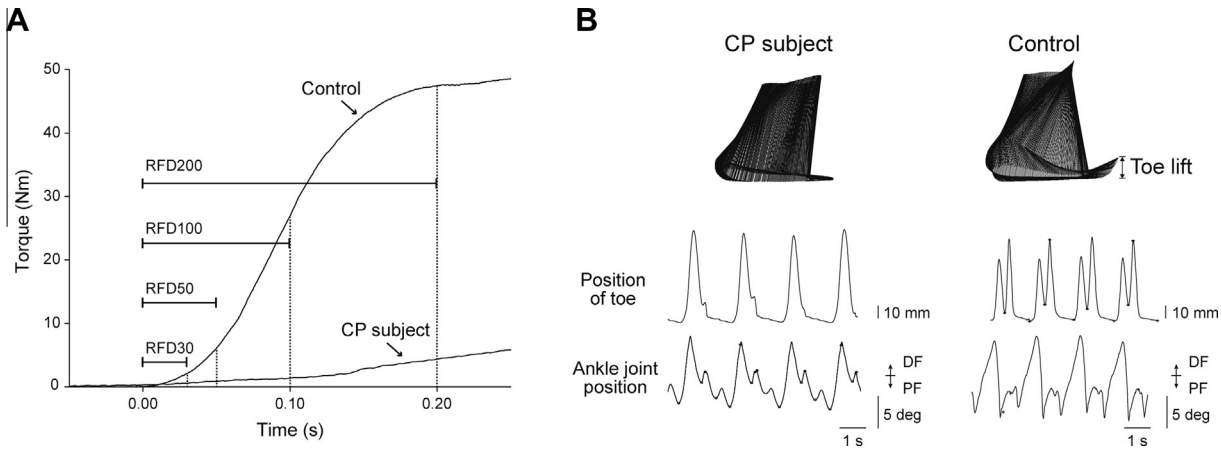

Fig. 1. Overview of the measurements of RFD (A) and gait kinematics (B). (A) Example of torque traces used to calculate plantarflexion RFD from an adult with CP and a control subject. RFD was calculated as the peak torque in the first 30 (1st dotted line), 50 (2nd dotted line), 100 ms (3rd dotted line) and 200 ms (4th dotted line) following onset of contraction (time 0 ms). (B) Example of the 3-D kinematic analysis of an adult with CP (left) and a control subject (right). On top is a kinematic stick illustration showing the excursion of the ankle joint. Notice the difference in toe lift. The middle graphs show the vertical position of the toe in the two subjects. Notice the lack of a 2nd toe lift (normally occurring just prior to ground contact) in the adult with CP. The bottom graph shows the ankle joint position during 4 gait cycles. DF = dorsiflexion. PF = plantarflexion.

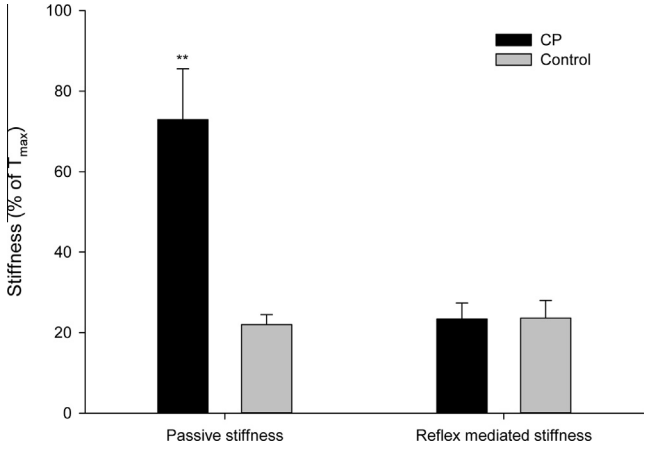

Fig. 2. Average passive stiffness and reflex-mediated stiffness of the ankle plantarflexors measured as the resistance of the ankle joint to a 6 degree slow (passive) or fast (reflex-mediated) stretch of the plantarflexors in adults with CP (black columns) and controls (grey columns) normalized to T_{max}. The reflex-mediated stiffness is calculated as the amplitude of the torque response to the fastest perturbation subtracted by the passive stiffness. ** = Significantly larger passive stiffness in adults with CP compared to controls ($p = 0.003$). Error bars represent standard error of the mean.

$RFD200_{pf}$ and MVC_{pf}, the adults with CP produced 19% (33.3 ± 9.2 Nm/s vs. 174.4 ± 22.6 Nm/s; $p < 0.001$) and 32% of the torque produced by controls (23.0 ± 5.6 Nm vs. 71.0 ± 10.2 Nm; $p < 0.001$; Fig. 3B), respectively.

3.3. Gait kinematics

The adults with CP chose a slower walking speed (2.6 ± 1.1 km/h (mean ± SD), range 0.4–4.8 km/h) than the healthy controls (mean 4.2 ± 0.3 km/h, range 3.3–4.6 km/h) during the gait kinematic measurements.

The adults with CP had a smaller amplitude of the lift of the toes prior to ground contact during the swing phase compared to the controls ($p < 0.001$; Fig. 4A). In line with this, they also made contact with the ground at a more plantarflexed angle than the controls ($p < 0.05$; Fig. 4B) and the difference in angle between the ground and the foot was therefore significantly smaller in the CP population. The maximal range of movement in the ankle joint during the individual gait cycles was also significantly smaller in the adults with CP as compared to the controls ($p < 0.01$; Fig. 4C). Finally, the adults with CP had significantly fewer number of toe lifts just prior to ground contact as compared to the controls ($p < 0.001$; Fig. 4D).

3.4. Correlations

Table 2 summarizes Pearson correlation coefficient values for the relation between the different measures of ankle muscle and joint function and the measures of gait kinematics. Significant relations ($p < 0.05$) are shown in bold. The relations with the highest correlation coefficient are shown in Fig. 5. Passive stiffness provided the best correlation with the amplitude of the toe lift (Fig. 5A), $RFD200_{df}$ with the range of movement of the ankle joint during gait (Fig. 5B), and $RFD200_{pf}$ with the angle of the ankle joint at ground contact with respect to the floor (Fig. 5C), the push-off velocity (Fig. 5D), and the gait speed (Fig. 5E).

Note that reflex-mediated stiffness showed a positive correlation with the amplitude of toe lift ($r = 0.45$; $p < 0.01$). Patients with large reflex-stiffness in ankle plantarflexors were in other words more able to lift the toes in late swing than subjects with low reflex stiffness. Also, MAS and Tardieu were correlated with higher gait velocity. The patients who were found to be the most spastic clinically were in other words able to walk the fastest.

The clinical measures of spasticity, MAS and Tardieu, showed no relation to either the passive or the reflex-mediated stiffness. Passive stiffness was negatively correlated to the passive ROM in the ankle joint ($r = 0.46$; $p < 0.01$), so that subjects with low stiffness had high mobility. Passive ROM was positively correlated to the MAS and Tardieu scales ($r = 0.50$ and $r = 0.49$; $p < 0.01$, respectively), so that subjects with the highest score on the scales had the highest mobility.

Passive and reflex-mediated stiffness were not correlated to each other or to RFD200 or MVC for either plantarflexion or dorsiflexion.

Subsequent multiple linear regression indicated that passive stiffness and $RFD200_{df}$ both contributed significantly to the variation in toe lifts (adjusted $r^2 = 0.51$; $F = 11.46$; $p < 0.001$; residual error: 232), whereas $RFD200_{df}$ (adj. $r^2 = 0.46$; $F = 15.98$; $p < 0.001$; residual error: 35.92) and $RFD200_{pf}$ (adj. $r^2 = 0.26$; $F = 6.9$;

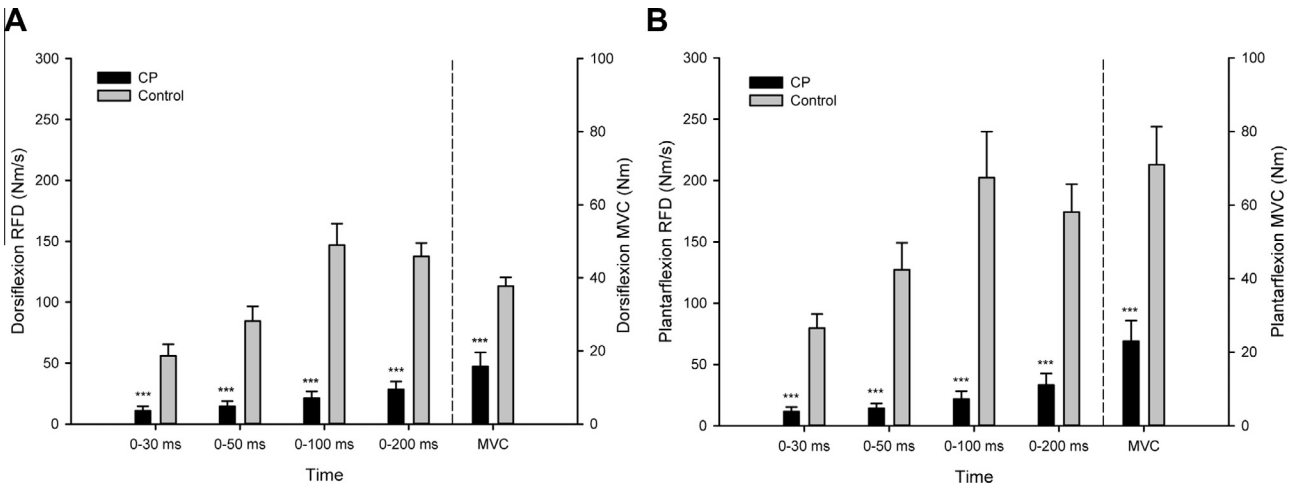

Fig. 3. Average dorsiflexion (A) and plantarflexion (B) RFD and MVC in adults with CP (black columns) and controls (grey columns). Note that the *y*-axis on the left (RFD; Nm/s) refers to the bars to the left of the dashed line, while the *y*-axis on the right (MVC; Nm) refers to the bars to the right. *** = Significant difference between the two groups ($p < 0.001$) at this time-interval. Error bars represent standard error of the mean.

$p < 0.001$; residual error: 0.117) were found to be the only significant predictors of the movement range in the ankle joint during gait and the push-off velocity, respectively. Gait velocity was found to be significantly predicted by $RFD200_{pf}$ and $RFD200_{df}$ (adjusted $r^2 = 0.34$; $F = 8.7$; $p < 0.01$; residual error: 0.107). No other combinations were found to be significant in multiple linear regression analysis.

4. Discussion

The main findings are that passive stiffness of plantarflexors was significantly increased and RFD of plantar- and dorsiflexors significantly decreased in adults with CP compared to control subjects, and that these parameters correlated with measures of gait function. This suggests that reduced RFD and increased passive stiffness might contribute to impaired gait function in adults with CP. Reflex-mediated stiffness at rest, however, was not increased in adults with CP compared to controls and did not correlate with gait function.

Spasticity has been assumed for a long time to be the main functional problem in adults with CP, but recent studies in other patient populations have raised concerns about the definition, the evaluation and the functional significance of spasticity (Mirbagheri et al., 2004; Wood et al., 2005; Dietz and Sinkjaer, 2007, 2012; Malhotra et al., 2009; Lorentzen et al., 2010; Willerslev-Olsen et al., 2013). These concerns also challenge previous assumptions regarding the significance of spasticity in the population of people with CP (Willerslev-Olsen et al., 2014). The fundamental problem that these new studies have identified is that muscle resistance caused by pathological changes in passive muscle properties is extremely difficult to distinguish from the muscle resistance caused by hyperactive stretch reflexes, especially since these often co-exist to some extent in many of the patients (Mirbagheri et al., 2004; Lorentzen et al., 2010; Willerslev-Olsen et al., 2013). It also causes confusion that spasticity is sometimes used as a designation for both of these contributions to muscle resistance, although they are caused by fundamentally different pathological mechanisms and require very different treatment (Wood et al., 2005; Dietz and Sinkjaer, 2007, 2012). Without proper distinction of spasticity and altered passive muscle properties it is difficult to evaluate to what extent spasticity poses a functional problem for the patients. The value of studies on the functional significance of spasticity in which this distinction has not been made is therefore unclear. This is especially the case of studies in which 'spasticity' has been determined by clinical evaluation and scored by either the Ashworth or Tardieu scales (Sehgal and McGuire, 1998; Biering-Sorensen et al., 2006; Haugh et al., 2006; Mutlu et al., 2008; Alhusaini et al., 2010; Fleuren et al., 2010; Ansari et al., 2013). As shown by several recent studies, the clinical determination of spasticity often cannot be verified when the patient is subsequently tested by objective biomechanical and electrophysiological techniques (Lorentzen et al., 2010; Willerslev-Olsen et al., 2013). There are probably also other neural mechanisms, unrelated to stretch reflex hyperexcitability, which contribute to the clinical observation of 'spasticity' such as spastic dystonia (Gracies, 2005). It should be noted that we had no way of evaluating the contribution of this component to the functional gait impairment in the present study.

The findings in the present study confirm that the distinction between passive and reflex-mediated contributions to muscle stiffness is also difficult, if not impossible, to make in adults with CP without the aid of electrophysiological and biomechanical measures. Although all patients had been diagnosed as spastic prior to inclusion in the study, seven of the patients who were found spastic clinically showed no sign of hyperexcitable stretch reflex activity on subsequent electrophysiological and biomechanical evaluation. The two patients who showed the largest reflex excitability scored 0 and 1+ on the MAS and 0 and 3 on the Tardieu scale, respectively. It was therefore not surprising that neither of the two scales showed any correlation with reflex-mediated stiffness at rest in this patient population. This is somewhat in contrast to a recent study that reported a significantly larger reflex-mediated stiffness in 23 adolescents (range 12–19 years) with CP compared to an age-matched, healthy control group (de Gooijer-van de Groep et al., 2013). However, in that study a stretch of 30° lasting 250 ms was used. This provides ample time for other reactions to the stretch than the spinal stretch reflex circuitry to contribute to the measured torque. We avoided this by measuring the evoked torque immediately after a short stretch while still allowing sufficient time for the mechanical effect of the spinal stretch reflex to manifest itself.

Two different factors may explain the relatively low reflex excitability in the adults with CP: One is that reflexes generally show a decline with age (Kido et al., 2004) and any hyperreflexia in childhood may therefore have vanished in this group of adults

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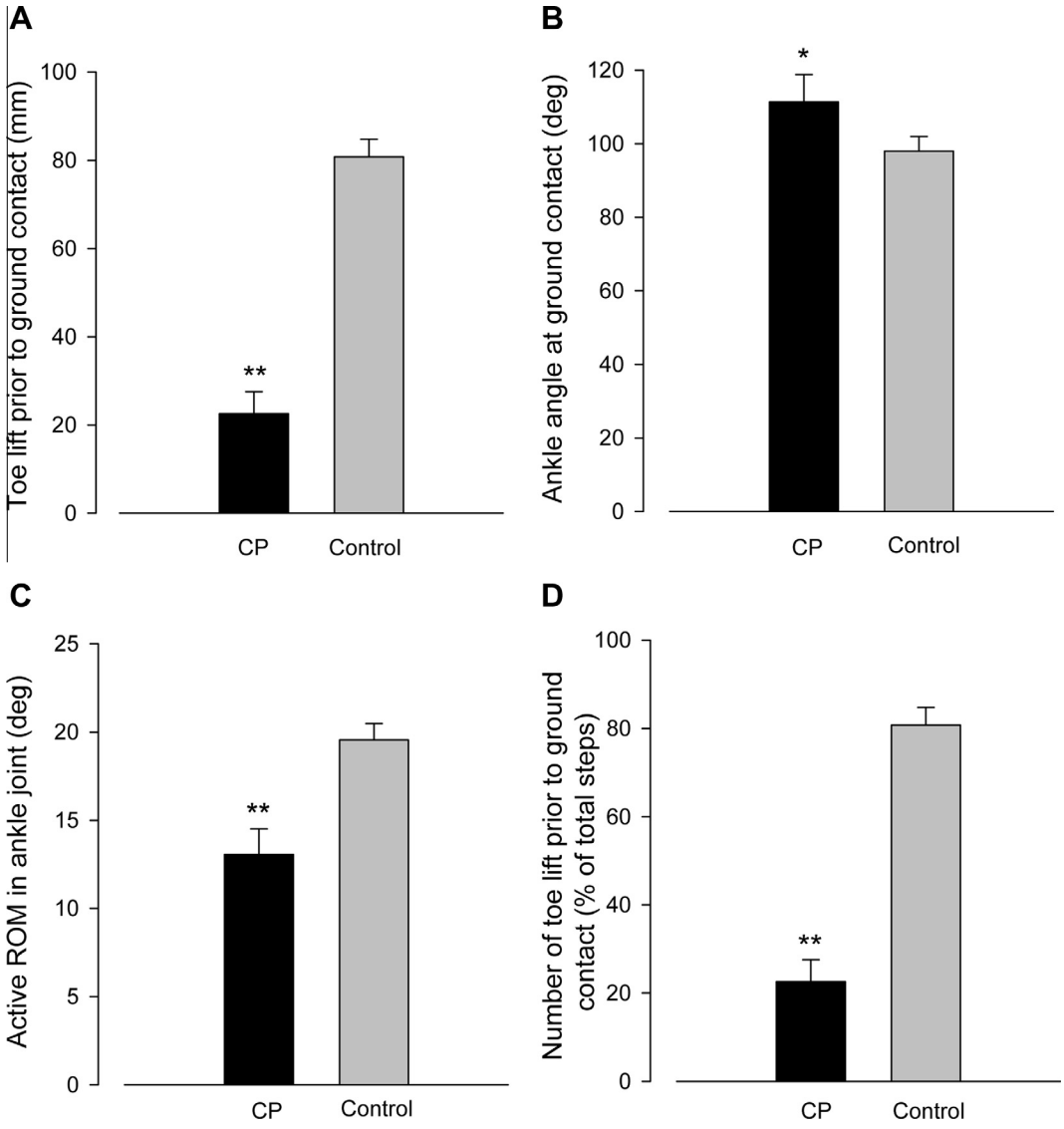

Fig. 4. Gait kinematics in adults with CP (black columns) and controls (grey columns). (A) Peak amplitude of the toe lift just prior to ground contact (in millimeters). (B) Angle of the ankle joint at ground contact (in degrees) with respect to the floor. (C) Active range of motion of the ankle joint (in degrees) during gait. (D) Number of toe lifts just prior to ground contact in percent of the total number of steps. $*$ and $**$ = Significant difference between the two groups ($p < 0.05$ and $p < 0.01$, respectively). Error bars represent standard error of the mean.

with CP. Neuroplastic adaptations may contribute to this (Wolpaw and Tennissen, 2001). Secondly, the pronounced passive stiffness and contractures may have prevented efficient stretch of muscle spindles and thereby obscured the clinical manifestation of hyperreflexia. It should also be pointed out that the short stretch we used may have prevented us from determining a contribution from stretch reflex activity that might have been elicited with a longer stretch resembling the clinical evaluation to a larger extent. Indeed, this could potentially explain why we, in contrast to other studies in which longer stretches were used (de Gooijer-van de Groep et al., 2013), did not observe reflex hyperexcitability in this patient group.

We found no correlation between reflex-mediated stiffness at rest and any of the measures of functional capacity in the patients, including MVC, RFD and the various kinematic measures of gait ability. This suggests that reflex-mediated stiffness at rest plays no or only a very small role for the functional ability of these patients at least based on the measures that we have included here. This is consistent with other studies, which have failed to find any relation between the extent of spasticity measured biomechanically and the functional ability of patients with spasticity (Sinkjaer and Magnussen, 1994; Marsden et al., 2012; Willerslev-Olsen et al., 2014). The finding underscores that spasticity is not the cause of functional impediments by necessity, but may in some cases help to ensure sufficient muscle activity for the patients to maintain upright posture and walk (Dietz, 2003). This is not surprising in view of the central integration of voluntary motor commands and sensory feedback mechanisms at all levels of the nervous system, which has been documented in human electrophysiological experiments during the past 20 years (Nielsen and Sinkjaer, 2002a,b; Pierrot-Deseilligny and Burke, 2012; Nielsen, 2004).

We measured passive muscle stiffness from the resistance to a 6° muscle stretch at a velocity below the threshold for eliciting stretch reflex activity. Previous studies have demonstrated that this measure is independent of the velocity of the stretch (as long as it is below stretch reflex threshold) and provides a measure of passive stiffness that is also representative for longer stretches

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within the range of movement of the joint (Lorentzen et al., 2010; Willerslev-Olsen et al., 2013). For this population of adults with CP, we found the majority (16 out of 23) to have increased passive muscle stiffness as compared to an age-matched population of healthy controls, whereas only 2 adults with CP showed larger reflex-mediated stiffness at rest. This is similar to what has been reported for adults with stroke, spinal cord injured and multiple sclerosis and in children with CP (Mirbagheri et al., 2004; Lorentzen et al., 2010; Willerslev-Olsen et al., 2013). This was independent of whether the stiffness was normalized or not to the maximal muscle torque (T_{max}) in order to take differences in muscle mass into account.

For correlations to the functional ability of the patients, we decided to use only non-normalized measures, since T_{max} is influenced by the ability of the muscle to form active cross-bridges and the normalized measures of passive stiffness would therefore be biased towards the functional capacity of the muscle.

Non-normalized increased passive muscle resistance was related to the range of movement in the ankle joint and in particular to the lift of the toes just prior to heel contact towards the end of the swing phase. It makes sense that rigid plantarflexor muscles would limit the ability of the patients to move the ankle in the opposite direction – and this probably also relates to the development of contractures and severely limited dorsiflexion ability in several of the patients. Marsden et al. (2012) reported increased passive muscle stiffness in the ankle plantarflexors in their patients with spastic hereditary paraparesis, but they did not report any functional limitations in this relation. However, increased passive stiffness in knee extensors was shown to severely limit gait ability (Marsden et al., 2012).

We chose to focus on ankle joint function in this study, but it is likely that weakness in knee and hip muscles would also influence some of the gait parameters measured here, such as gait speed and push-off velocity. We used two different measures that relate to muscle weakness in the subjects. MVC is a measure of the maximal strength that the subjects may generate when given ample time, whereas RFD is a measure of the ability of the subjects to generate force as quickly as possible within the early part of a muscle contraction (Aagaard et al., 2002; Moreau et al., 2011; Suetta et al., 2004). RFD of either dorsiflexors or plantarflexors correlated better

Table 2
Overview of Pearson product correlation values for the relations between the different measures of ankle muscle and joint function and the measures of gait kinematics. Significant ($p < 0.05$) correlations are indicated in bold.

	Toe lift	Angle heel to floor	Active ROM	Push-off velocity	Gait velocity
Passive stiffness	**−0.48**	−0.18	−0.15	−0.14	−0.11
Reflex-mediated stiffness	**0.45**	0.24	0.39	0.07	0.07
MVC_{df}	**0.40**	0.26	**0.49**	0.13	**0.44**
MVC_{pf}	0.14	0.32	**0.42**	0.32	0.36
$RFD200_{df}$	**0.36**	0.17	**0.57**	0.23	**0.45**
$RFD200_{pf}$	0.11	**0.42**	**0.53**	**0.55**	**0.48**
Passive ROM	0.05	0.33	0.16	0.16	0.26
MAS	−0.18	**0.44**	0.31	0.15	**0.55**
Tardieu	−0.10	0.40	0.30	0.16	**0.46**

Abbreviations: MVC = maximal voluntary isometric contraction strength; df, dorsiflexion; pf, plantarflexion; RFD200, rate of force development measured as the peak torque in the first 200 ms after the onset of contraction; Passive ROM, passive range of motion; MAS, Modified Ashworth Scale; Toe lift, Amplitude of toe lift just prior to ground contact; Angle heel to floor, difference between the ankle joint angle at initial ground contact and the angle in early stance with the foot flat on the ground; Active ROM = range of motion of the ankle joint during gait.

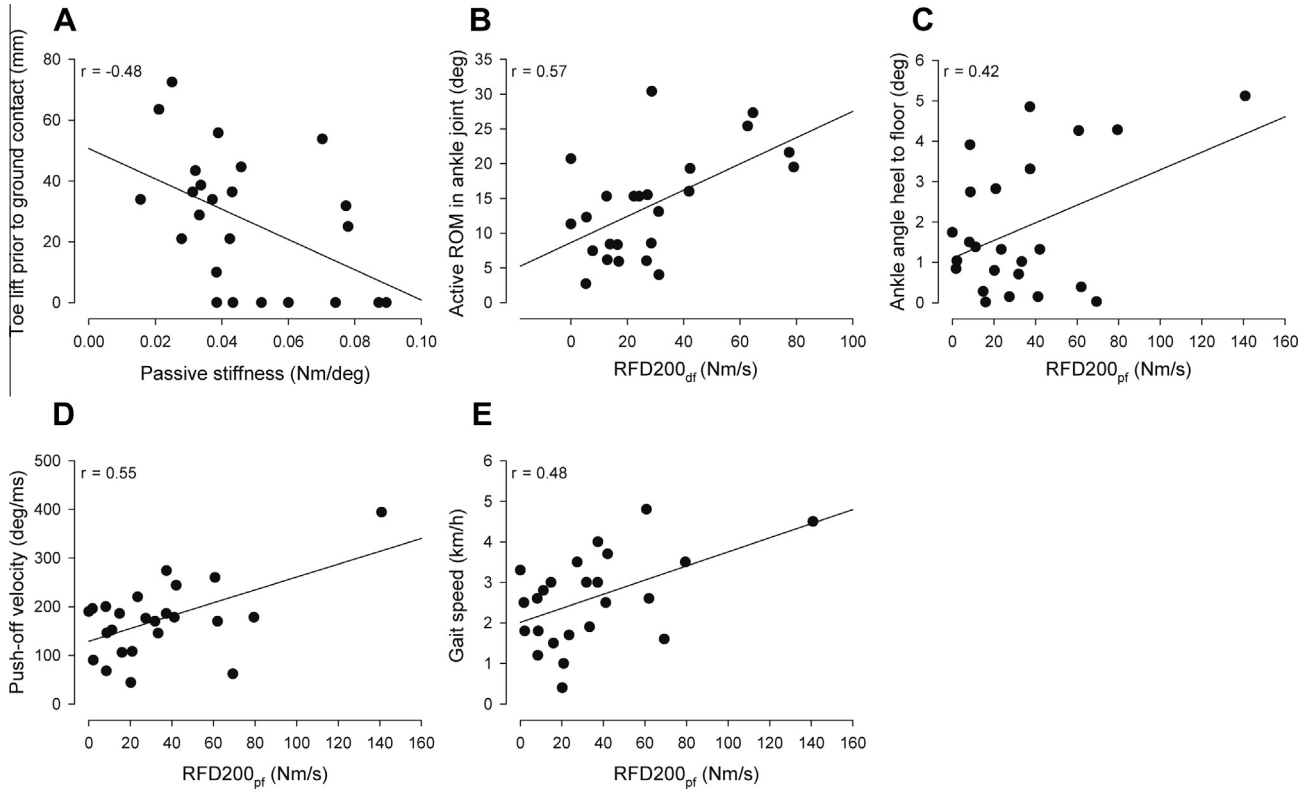

Fig. 5. Correlation between gait kinematics and muscle stiffness and rate of force development (RFD) in adults with CP. (A) Correlation between passive stiffness and peak amplitude of toe lift just prior to ground contact. (B) Correlation between $RFD200_{df}$ and active range of motion of the ankle joint during gait, respectively. (C–E) Correlation between $RFD200_{pf}$ and the difference between the ankle joint angle at initial ground contact and the angle in early stance with the foot flat on the floor (C), push-off velocity (D) and gait speed (E), respectively.

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than MVC for all kinematic measures of gait function. This may not be surprising considering the motor skill challenges of gait. For example, lifting the toes towards the end of the swing phase must be carefully timed to avoid tripping over obstacles and safely place the heel on the ground, so it makes sense that RFD_{df} correlated with the amplitude of the second toe lift. The push-off requires that the plantarflexors are activated strongly within a short time period to push the body forward and produce the propulsion, which is ultimately the basis of the gait speed. It is therefore not surprising that RFD_{pf} correlated best with these gait parameters. Overall, RFD is determined to a large extent by the neural drive to the muscle and may be seen as the most important factor for the ability to perform optimized and movement-economic motor skills.

4.1. Possible limitations

In this study, we measured the passive and reflex-mediated stiffness at rest in a seated position with the ankle in 20 degrees plantarflexion. It has previously been shown in healthy subjects and hemiplegic stroke patients that passive stiffness of the ankle plantarflexors is position dependent and increases with increasing dorsiflexion position (Mirbagheri et al., 2000, 2008). Although we observed a large, significant difference in passive stiffness between adults with CP and control subjects in the investigated position, it is possible that we would have observed even larger passive stiffness responses if we would have measured in a more dorsiflexed ankle position. However, we did observe a positive correlation between passive stiffness and toe lift indicating that the stiffness measures might have a functional implication for dorsiflexion ability during gait. Another possible limitation is that the amplitude of the perturbations used in this study was only 6 degrees and therefore only covered a small part of the range of motion of the ankle joint. As already mentioned, it is a possibility that a longer stretch would evoke reflex excitability that more closely resembles the clinical evaluation of spasticity. Furthermore, the clinical measures of spasticity, MAS and Tardieu, were positively correlated with measures of gait function, suggesting that spasticity, if anything, was of functional benefit for the subjects.

4.2. Clinical implications

The observed finding that passive stiffness of plantarflexors was significantly increased, whereas there was no difference in reflex-mediated stiffness, in adults with CP compared to control subjects, raises several questions about the appropriate therapy to improve the gait ability in this patient group. The fact that increased passive stiffness and reduced rate of force development are associated with impaired gait function suggests that interventions should more optimally be aimed at reducing passive muscle stiffness and improve rapid force generation.

5. Conclusion

We have shown in this study that gait kinematics in adults with CP are associated with altered passive ankle muscle properties and impaired neural drive to the muscles. Reflex-mediated muscle stiffness measured at rest, however, did not correlate with any gait parameters measured in this study.

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