Passive mechanical properties of gastrocnemius in people with multiple sclerosis

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ABSTRACT

Background: There is evidence to suggest that contractile properties of muscles in people with multiple sclerosis change as a consequence of demyelination in central nervous system. However, passive properties of muscles in people with multiple sclerosis have not been previously investigated. The purpose of this study was to characterise passive mechanical properties of gastrocnemius in people with multiple sclerosis and to compare these properties with those of gastrocnemius in neurologically normal people.

Methods: Ten people with multiple sclerosis having signs and symptoms of weakness in the legs (Disease step 1–3) and 10 age- and sex-matched healthy people participated in the study. Ultrasound images of muscle fascicles of medial gastrocnemius as well as passive ankle torque and ankle angle data were obtained simultaneously as the ankle was rotated through its full range with the knee in a range of positions. Analysis of ultrasound images and passive ankle torque–angle relations allowed us to derive the slack lengths and maximal strains of the whole muscle–tendon units, muscle fascicles and tendons. Paired-samples t-tests were used to compare these variables in the two groups.

Result: There was no difference between subjects with multiple sclerosis and healthy controls in the mean slack lengths and mean maximal strains of the whole muscle–tendon units or of their fascicles or tendons.

Interpretations: These data suggest that typically, in people with multiple sclerosis who have impaired lower limbs but are still ambulatory, the passive mechanical properties of the gastrocnemius muscles are normal.

1. Introduction

There is evidence that the muscles of people with multiple sclerosis undergo changes due to both a central impairment (de Haan et al., 2000; Rice et al., 1992) and chronically reduced physical activity (Kent-Braun et al., 1997; Ng and Kent-Braun, 1997). A few studies have reported changes in the contractile properties of muscles in people with multiple sclerosis, such as atrophied muscle fibers, reduced enzyme activities or a shift in fiber composition (Garner and Widrick, 2003; Kent-Braun et al., 1997). Clinical observations suggest that, in the later stages of the condition, changes to the passive properties of muscles (contracture) may be a major cause of disability.

Spasticity, a velocity-dependent increase in tonic stretch reflexes in response to a passive stretch, is evident in ~80% people with multiple sclerosis (Rizzo et al., 2004). It was reported that spastic muscles in people with multiple sclerosis have increased non-reflex stiffness and that reflex-mediated stiffness during a sustained voluntary contraction does not differ from that in healthy people (Sinkjaer et al., 1996; 1993). However, these studies (Sinkjaer et al., 1996; 1993) did not directly investigate changes to the passive properties of muscles because the measures of stiffness were obtained from electrically stimulated muscles – the muscles were not relaxed. Moreover, the authors examined stiffness at the ankle joint. Ankle stiffness is likely to be due partly to the stiffness of muscles but also to other structures that cross the joint such as ligaments.

Passive properties of muscle, which can be expressed by length–tension relations, have not been measured in people with multiple sclerosis. We hypothesised that passive mechanical properties of muscles affected by multiple sclerosis would be different from the properties of normal muscles.

Ultrasoundography has been used extensively by many groups in the past decade to study the lengths of muscle fascicles and tendons in both normal subjects (e.g. Kubo et al., 2000; Muraoka et al., 2005; Narici et al., 1996) and in patients with neurological impairment (e.g. Li et al., 2007; Shortland et al., 2001). But unless ultrasonographic measures of lengths are combined with a measure of muscle tension they are difficult to interpret. When comparing muscle passive properties between neurologically abnormal and normal groups, the measured lengths of whole muscle–tendon units or fascicles or tendons need to be compared at the same tensions.

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We recently reported a reliable method to measure length–ten-
tion properties of human relaxed gastrocnemius muscle in vivo
(Hoang et al., 2005). By combining this method with ultrasound
imaging to measure muscle fascicle lengths we were able to iden-
tify slack lengths of the relaxed muscle–tendon unit of gastroce-
mius, the muscle fascicles and the tendon, as well as to calculate
the strain of these components when the muscle was passively
stretched through its physiological length in vivo (Hoang et al.,
2007). The aim of this study was to apply the new method in com-
bination with ultrasound imaging to characterise the passive prop-
e rties of gastrocnemius muscles of patients with multiple sclerosis
and to compare those properties with the properties of neurologi-
cally normal gastrocnemius. Specifically, the measurements of
interest were the slack lengths and maximum passive strains of
the whole muscle–tendon unit, muscle fascicles and tendon of gas-
trocnemius. The term slack length as used here signifies the great-
est length at which there was no measurable tension. Unless
otherwise stated, the term gastrocnemius is used to describe both
medial and lateral parts, which are considered as a functional unit
although there are some anatomical differences between the two
components (Huijing, 1985). We used the term tendon to mean
both intramuscular tendon (aponeuroses) and extramuscular ten-
don (free tendon).

2. Methods

2.1. Subjects

Ten people diagnosed with multiple sclerosis (6 women, 4 men,
49 ± 7 years) participated in the study. Subjects were included if
they had signs and symptoms of multiple sclerosis in one or both
lower limbs, and were at Disease Steps 1–3, i.e. they have only mild
symptoms in walking gait or need to use a cane or other form of
unilateral support for greater distances but can walk at least 25
feet without it (for further details see Hohol et al., 1995; 1999).
Spasticity of the affected leg from each subject with multiple scle-
rosis was tested manually using the Ashworth scale. This is a scale,
ranged between 0 and 4, often used clinically to describe increases
in muscle tone and resistance to passive movement stretching of
spastic muscles (for detailed description see Ashworth, 1964). Sub-
jects were excluded if they had multiple sclerosis-related condi-
tions or other medical conditions that prevented them from
maintaining the prone position for an hour or the kneeling position
for 15 min. Subjects with multiple sclerosis were compared to age-
and sex-matched healthy subjects. While we tried to match the leg
lengths, defined as the distance between the middle of lateral epi-
condyle of the femur and the middle of lateral malleolus, between
multiple sclerosis and control subjects it was not possible to find
optimal images of the muscle fascicles and the intramuscular
tendons (superficial and deep) of medial gastrocnemius could be
visualised. Measurements of muscle fascicles were made over the
mid belly of the muscle as the fascicle length changes at this site
provides a good approximation to the average fascicle length
changes across the length of the muscle (Lichtwark et al., 2007).
Once the images were considered optimal, the transducer was
manually stabilized while the ankle was rotated. Markers around
the transducer were marked on the skin to ensure that when the
knee angle was changed the same part of the muscle was scanned
and orientation of the ultrasound head with respect to the muscle
fascicles was the same. The markers also helped to detect if there
was any significant relative skin movement under the transducer
during ankle rotation. The images were displayed in real time
and digitally sampled and recorded at 25 frames per second.

Surface electromyography was used to monitor muscle relaxa-
tion during ankle movement. Bipolar surface electrodes (Ag–AgCl,
10 mm diameter) were placed over the muscle bellies of lateral gas-
trocnemius, soleus and tibialis anterior with an inter-electrode
distance of 3 cm. The signals were amplified (>1000), bandpass fil-
tered (100–1000 Hz, Grass, IP 511, West Warwick, USA) and sam-
pled at 2000 Hz.

2.3. Measurement

For patients with multiple sclerosis, measures were taken from
the most affected leg. Measurements were taken from the same leg
of matched controls. Passive ankle torque–angle relations were
measured at eight knee angles (0°, 10°, 20°, 50°, 60°, 70°, 90° and
100° in random order; 0° represents full knee extension). The sub-
ject’s foot was firmly strapped to a footplate so that the lateral mala-
leolus was aligned with the centre of the potentiometer. The
footplate was manually rotated from planar flexion to dorsiflexion
and back at ~0.05 Hz (average angular speed of 6°/s). Our previous
experiments on neurologically healthy subjects showed this speed
was too slow to elicit involuntary muscle activity (Hoang et al.,
2005; 2007). However, in subjects with multiple sclerosis, espe-
cially those with signs of spasticity, a slightly slower speed (~0.03–0.04 Hz) was sometimes applied to avoid involuntary mus-
cle activity. Subjects were asked to relax the leg as the ankle was
moved, but occasionally small bursts of EMG were evident. When
that occurred the data were omitted from subsequent analysis.

To minimize the effects due to the viscosity and thixotropy of
muscle, the ankle was rotated for 5 full cycles before data were re-
corded (Morse et al., 2008). Passive ankle torque, ankle angle, knee
angle, and ultrasound images of muscle fascicles of medial gastroce-
nemius were then recorded for three cycles of dorsiflexion–plantar-
flexion. This procedure was repeated at each knee angle.
Table 1
Anthropometric data of subjects with multiple sclerosis and healthy matched-control subjects.

<table>
<thead>
<tr>
<th>Subjects with MS</th>
<th>Age</th>
<th>Sex</th>
<th>Weight (Kg)</th>
<th>Leg length ($l_s$) (cm)</th>
<th>Reference length ($l_{ref}$) (cm)</th>
<th>Foot length ($l_f$) (cm)</th>
<th>6-min walk test (m)</th>
<th>Ankle range of movement ($^\circ$)</th>
<th>Affected leg</th>
<th>Disease steps&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Years since diagnosis</th>
<th>Spasticity level&lt;sup&gt;c&lt;/sup&gt;</th>
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<table>
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<th>Reference length ($l_{ref}$) (cm)</th>
<th>Foot length ($l_f$) (cm)</th>
<th>6-min walk test (m)</th>
<th>Ankle range of movement ($^\circ$)</th>
<th>Tested leg</th>
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</table>

$l_s$: leg length, defined as the distance between the middle of lateral epicondyle of the femur and the middle of lateral malleolus; $l_{ref}$: reference length of gastrocnemius, defined as the distance between the middle of the lateral epicondyle and the tip of the lateral malleolus; $l_f$: foot length, defined as the distance between the middle of the lateral malleolus and the tip of the second metatarsal.

<sup>a</sup> Indicates significant difference between MS subjects and Control subjects ($P < 0.05$).

<sup>b</sup> Disease Steps classification (Hohol et al, 1995; 1999).

<sup>c</sup> Spasticity level was tested using the Ashworth Scale (Ashworth, 1964).
2.4. Data analysis

The data analysis involves two steps: the first step was to derive passive length–tension relations of the whole muscle–tendon unit of gastrocnemius and the second step was to calculate slack lengths and changes in lengths of muscle fascicles and tendons. These two steps have been described in details elsewhere (Hoang et al., 2005; 2007). Key features of the analytical approach are repeated here.

2.4.1. Step 1: passive length–tension relation of the whole muscle–tendon unit

The passive properties of gastrocnemius (expressed as passive length–tension relations) and slack length of the whole muscle–tendon unit were derived from the measured passive ankle torques at different knee angles. This was based on the assumptions that the passive torque measured at the ankle depends on torques due to (i) single-joint structures such as single-joint muscles and ligaments that cross the plantar and dorsal aspects of the ankle joint but not the knee joint, and (ii) the two-joint muscle, gastrocnemius, which crosses the plantar aspect of the ankle and the dorsal aspect of the knee. Consequently, the key proposition is that differences in passive ankle torques measured at different knee angles are due to changes in the length of gastrocnemius. The contribution to the passive ankle torque from other two-joint structures such as the plantaris muscle, nerves and blood vessels was assumed to be negligible (for details see Hoang et al., 2005; 2007). Under this assumption, the total passive torque measured at the ankle is modeled as:

\[
\tau_{\text{ankle}}(\theta_a, \theta_k) = a_p e^{k_p (\theta_a - \theta_P)} - a_p \quad \theta_a > \theta_P
\]

\[
+ a_d e^{k_d (\theta_a - \theta_D)} - a_d \quad \theta_a < \theta_D
\]

\[
+ m_g (a_g e^{k_g (l_c - l_g)} - a_g) \quad l_b > l_c
\]

where \(\tau_{\text{ankle}}(\theta_a, \theta_k)\) is the passive torque at the ankle which is a function of both ankle and knee joint angles; \(a_p e^{k_p (\theta_a - \theta_P)} - a_p\) is the torque due to single-joint structures on the plantar aspect of the ankle; \(a_d e^{k_d (\theta_a - \theta_D)} - a_d\) is the torque due to single-joint structures on the dorsal aspect of the ankle and \(m_g (a_g e^{k_g (l_c - l_g)} - a_g)\) is torque due to the gastrocnemius, \(\theta_a\) and \(\theta_k\) are ankle angle and knee angle respectively, \(a_p, k_p, a_d, k_d, a_g, k_g\) are parameters that determine the stiffness of structures that cross the plantar and dorsal aspects of the ankle joint but not the knee joint, and \(l_b\) and \(l_c\) are ankle angles at which ankle plantar flexors and dorsiflexors are slack respectively. \(m_g\) is the moment arm of the gastrocnemius at the ankle. \(l_b\) is the length of the gastrocnemius muscle–tendon unit and \(l_c\) is the slack length of the gastrocnemius muscle–tendon unit. The parameters in equation (1) were estimated from the passive length–tension relations of the gastrocnemius and the slack lengths and changes in lengths of muscle fascicles and tendons.
lengths at the three knee angles (20°, 60° and 90°) were then synchronized with the values for ankle angle so that the relations between changes in the length of muscle fascicles and the whole muscle–tendon unit at each knee angle could be derived. We modeled these relations as a third order polynomial:

\[ l_f = l_k + \left( b \left( l_k - l_c \right) + c \left( l_k - l_c \right)^2 + d \left( l_k - l_c \right)^3 \right) \]

where \( l_f \) is the length of the muscle fascicle, \( l_k \) is the slack length of the muscle fascicle, \( l_g \) is the length of gastrocnemius and \( l_c \) is the slack length of the gastrocnemius muscle–tendon unit estimated from equation (1). This equation was used to calculate fascicle slack length. The form of this equation means that \( l_f = l_k \) when \( l_k = l_c \). It also means that if the slack length of the muscle–tendon unit \( (l_c) \) is shorter than the shortest length of the muscle obtained in vivo \( (i.e. l_k \text{ never equals to } l_c) \) the equation (3) cannot be used to calculate \( l_f \). The parameters in equation (3), \( l_k, b, c \) and \( d \) were estimated using the quasi-Newton algorithm.

As described above, the analysis of Eq. (1) and equation (3) provided estimates of slack lengths of the whole muscle–tendon unit \( (l_c) \) and of muscle fascicles \( (l_k) \). The slack length of the tendon \( (l_t) \) was calculated by subtracting \( l_k \cos(\alpha_k) \) (the projection of fascicle slack length onto the deep aponeurosis) from \( l_k \), where \( \alpha_k \) is fascicle pennation at slack length. The maximal tendon length was calculated by subtracting the projection of the maximal length of muscle fascicles onto deep aponeurosis \( (l_T \max \cos(\alpha_{max})) \), where the \( \max \) subscript indicates the longest in vivo length) from the maximal muscle–tendon length. The contribution of tendon lengthening to the maximal change in muscle–tendon length above slack length was calculated by dividing the maximal change in tendon length by the maximal change in muscle–tendon length. Maximal strains of the muscle–tendon unit, muscle fascicles and tendon were calculated using the slack length and maximal changes in lengths of these components.

As each multiple sclerosis subject was matched with a control subject of the same sex with a similar age and leg length (see Table 1), paired t-tests were used to compare the variables of interest in the multiple sclerosis and control group. The variables of interest were the slack lengths and strain of the whole muscle–tendon unit, the muscle fascicles and the tendon as well as the areas under passive length–tension curves of gastrocnemius across physiological length in vivo. Results were considered to be statistically significant if \( P < 0.05 \). Data are presented as means (SD).

3. Results

Passive mechanical properties of gastrocnemius from 10 adults with multiple sclerosis were compared with 10 age and sex

![Fig. 2. A frame of video file of medial gastrocnemius from a subject with multiple sclerosis. Three sets of three points were used to define the best fitting lines of superficial aponeurosis, deep aponeurosis and fascicle. The points were calibrated on X and Y coordinates. During ankle rotation changes in positions of the points (X and Y values) of the points were tracked with digitising software (and checked manually frame to frame). The length of fascicle (l) is defined as the distance between the intersections of the three lines (white filled circles). The pennation angle of the fascicles (a) is the acute angle between the fascicle line and the deep aponeurosis line. The longitudinal displacement of the fascicle (d) is used to calculate the length of the tendon (length of the muscle–tendon unit – d).](image-url)
matched control subjects. Characteristics of the subjects with multiple sclerosis and the control subjects are given in Table 1. They were well matched for age. There were differences in weight in some pairs of subjects but the overall mean weights were well matched.

There were signs of spasticity in half the multiple sclerosis subjects (Table 1). The mean range of ankle movement (Table 1) and maximal change in the length of the whole muscle–tendon unit in both groups were similar (Table 2). This indicates that there was no clinical evidence of contractures in subjects with multiple sclerosis.

The mean distance covered by multiple sclerosis subjects in the 6-min walk test was 274 (56) m, significantly lower than that covered by healthy controls, which was 314 (68) m ($P < 0.01$).

From the ultrasound images of the muscle fascicles we derived the relations between changes in the length of the whole muscle–tendon unit and the fascicles as well as the pennation angles between the fascicles and the deep aponeurosis when the muscle was stretched from a short length to its longest physiological length in vivo. Fig. 3 shows a typical example of these relations in one subject with multiple sclerosis (note that in this Figure, the pennation angle seemed to start changing slightly prior to the change in the length of muscle fascicles, it was not a systematic observation). The relations between changes in the length of the whole muscle–tendon unit and the fascicles at the three different knee angles $20^\circ$, $60^\circ$ and $90^\circ$ were similar and were observed consistently in both groups of subjects. This indicates that the contribution of the fascicles to the total change in the length of the whole muscle–tendon unit is not affected by the length of gastrocnemius. The relations between muscle fascicle and muscle–tendon unit lengths allowed estimation of the slack length of muscle fascicles and the slack length of the tendon. Once these values had been determined, strain in the muscle fascicle and the tendon was derived.

We could only estimate slack lengths of the muscle fascicles in 7 pairs of subjects because the slack lengths of gastrocnemius muscle–tendon unit in 2 subjects with multiple sclerosis and in 1 pair of multiple sclerosis and control subjects were shorter than the minimum length of muscle–tendon unit that we were able to attain in vivo. In these cases, we could not use equation (3) to derive the slack length of the muscle fascicles. A summary of the results of the seven pairs of subjects with multiple sclerosis and matched control subjects is given in Table 2. The mean slack lengths and strain of the whole muscle–tendon unit of gastrocnemius as well as its components, the muscle fascicles and the tendon were very similar in subjects with multiple sclerosis and healthy controls ($P > 0.05$ for all variables). This indicates the effect of multiple sclerosis on most parameters was close to zero, suggesting that MS had little effect on the parameters. However unsurprisingly, given the small number of data pairs, the confidence intervals for most parameters were wide. This means we cannot rule out clinically important effects of multiple sclerosis on most parameters. The exception is with the slack length of the muscle fascicles, which shortened by less than 5 mm.

Fig. 4 shows passive length–tension curves of gastrocnemius from 3 pairs of subjects with multiple sclerosis and their matched controls (only 3 pairs are shown for clarity). The curves of each pair have a similar shape but were not identical. This reflects differences in the slack length and the maximal changes in length of the muscle–tendon units among subjects as a result of differences in the leg lengths. To compare the passive length–tension relation between pairs of subjects, the areas under the curves were used. The mean area under the curves for multiple sclerosis subjects was $2.6 (0.5)$ N m and for the controls $3.0 (0.6)$ N m (Table 2). These values are not significantly different ($P = 0.08$).

4. Discussion

Ultrasound imaging has been used previously to investigate the passive properties of gastrocnemius muscle in healthy adults (De Monte et al., 2006; Herbert et al., 2002; Kubo et al., 2000; Muraoka et al., 2005; Narici et al., 1996) and the architecture of gastrocnemius from children with spastic diplegia (e.g. Shortland et al., 2001). In this study we used a novel approach that combined ultrasound imaging with a new method to measure passive length–tension relations of the gastrocnemius muscle–tendon unit in vivo (Hoang et al., 2005). The approach was used to measurement passive length–tension properties of muscle–tendon units, muscle fascicles and tendons in people with multiple sclerosis.
Contrary to our initial hypothesis the present findings suggest that the compliance of relaxed gastrocnemius muscle–tendon units, muscle fascicles and tendons, was not altered in multiple sclerosis subjects who are still ambulating and do not have clinical signs of contracture. The multiple sclerosis subjects had a similar maximal physiological length of gastrocnemius and ankle range of movement (Table 2) to the control subjects. The similarity of passive mechanical properties of gastrocnemius in both groups was reflected by the passive length–tension curves of the whole muscle–tendon unit, the areas under the curves and the strain of the whole muscle–tendon units, muscle fascicles and tendons. However, due to the small sample size of the study (7 pairs of subjects) the statistic power was low. Consequently, this study may have missed some important clinical effects of multiple sclerosis on most parameters of interest in this study except for muscle fascicle slack length, which shortened by less than 5 mm in people with multiple sclerosis.

From current evidence, it seems that stiffness of a relaxed muscle when stretched beyond its rest length is determined by at least two intramuscular structures: weakly bound cross-bridges and titin. Weakly bound cross-bridges account for passive mechanical properties of resting muscles at short lengths and titin, a large polypeptide linking the thick filaments and the Z-lines, determines passive properties of muscles at longer muscle length (e.g. Horwits, 1999; Wang et al., 1991). In addition, tendon also contributes to the compliance of the whole muscle–tendon unit, even at low forces experienced by resting muscles (Herbert et al., 2002; Murakoa et al., 2002). So, while the muscles in multiple sclerosis may undergo changes in contractile properties as reported by earlier studies (de Haan et al., 2000; Kent-Braun et al., 1997), the current results indirectly suggest that intramuscular and tendinous structures that determine passive stiffness of muscle are not altered in people with multiple sclerosis, at least in those who are ambulant and do not have clinical signs of contracture. This interpretation is consistent with data from a recent study by Malisoux et al. (2007). The authors found that long-term reduced neuromuscular activity due to spinal cord injury did not change the passive characteristics of single muscle fibers when compared with those in able-bodied subjects.

Three of seven subjects with multiple sclerosis (subjects 1–3, see Table 1) had clinical evidence of spasticity (1–2/4 Ashworth Scale). Although the notion that spastic muscles are associated with increased muscle stiffness has gained wide clinical support, passive properties of gastrocnemius in these subjects were not different from those of age-and-sex-matched controls. There are no directly comparable studies but our observations are in agreement with some recent studies on spastic muscles in other neurological conditions, although the methods differed. Burne et al. (2005) found no increase in passive joint resistance in spastic muscles after stroke. Gallana et al. (2005) studied 11 stroke patients with clinical evidence of spasticity and found seven stroke subjects had normal ankle stiffness. The remaining four subjects had increased stiffness.

One shortcoming of our study was that only people with multiple sclerosis at Disease steps 1–3 were investigated. In this first study we chose, for practical reasons, to measure passive muscle properties in patients with little disability. In subsequent studies we will investigate the passive muscle properties of people with more disability and clinical evidence of contracture.

Another limitation of the study was that the current model allowed us to focus on the passive properties of gastrocnemius, which crosses both ankle and knee joints. There may well be more marked changes in the properties of single-joint structures crossing the ankle, such as soleus. To check this possibility we compared the raw torque at full dorsiflexion when the knee is at 100° – when the contribution from gastrocnemius is assumed to be minimal. The results showed that the mean maximal measured ankle torques were 8.1 (3.1) N m and 6.6 (1.9) N m for the subjects with multiple sclerosis and the controls respectively. The mean difference (1.5 N m; 95% CI = −0.6–3.7 N m) was not significant statistically (p = 0.15). This, and the similarity in ankle range of movement between the two groups, indicate that passive properties of single-joint structures (presumably mainly soleus) in this group of people with multiple sclerosis are not different from the controls.

In summary, based on a combination of ultrasound with our recently developed method, we showed that passive mechanical properties of gastrocnemius in people with multiple sclerosis who are ambulant but without clinical signs of contracture do not differ from those in neurologically normal people. We speculate that standing and locomotion may help maintain the passive properties of gastrocnemius in people with multiple sclerosis. In addition, these activities may have prevented the weakness–disuse–weakness cycle which eventually leads to muscle and joint contracture and changes in muscle properties associated with immobilization (Gracies, 2005).

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