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Lower limb muscle volume estimation from maximum cross-sectional area and muscle length in cerebral palsy and typically developing individuals

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Abstract

Background: Deficits in muscle volume may be a significant contributor to physical disability in young people with cerebral palsy. However, 3D measurements of muscle volume using MRI or 3D ultrasound may be difficult to make routinely in the clinic. We wished to establish whether accurate estimates of muscle volume could be made from a combination of anatomical cross-sectional area and length measurements in samples of typically developing young people and young people with bilateral cerebral palsy.

Methods: Full length lower limb MRI scans were obtained from the lower limbs of 21 individuals with cerebral palsy (14.7 ± 3 years, 17 male) and 23 typically developing individuals (16.8 ± 3.3 years, 16 male). The volume, length and anatomical cross-sectional area were estimated from six muscles of the left lower limb.

Findings: Linear regression analysis demonstrated that the product of anatomical cross-sectional area and length bore a strong and significant relationship to the measured muscle volume (R^2 values between 0.955 and 0.988). Analysis of Covariance demonstrated that the relationship between the length-ACSA product and volume was not significantly different depending on the subject group.

Interpretation: This study demonstrates that muscle volume may be estimated accurately in typically developing individuals and individuals with cerebral palsy by a combination of anatomical cross-sectional area and muscle length. 2D ultrasound may be a convenient method of making these measurements routinely in the clinic.

Key words: Cerebral palsy, lower limb, muscle volume, Magnetic Resonance Imaging

1 Introduction

Many studies have shown that children and adults with cerebral palsy (CP) have smaller muscle volumes normalised to body mass than their typically developing peers (Fry *et al.*, 2007; Malaiya *et al.*, 2007; Barber *et al.*, 2011; Noble *et al.*, 2014; Handsfield *et al.*, 2016). To date, there are few studies investigating longitudinal muscle growth in this patient group. Knowledge of muscle growth may provide valuable information for the design and timing of interventions. The paucity of longitudinal studies in the literature may in part be due to the expense and inconvenience of using 3D measurement tools such as MRI and 3D ultrasound (US).

Previous studies have reported that muscle volume (MV) can be estimated from measurements that could be made with a simpler and more convenient imaging technique such as 2D US (Esformes, Narici and Maganaris, 2002; Miyatani *et al.*, 2004; Infantolino *et al.*, 2007; Albracht, Arampatzis and Baltzopoulos, 2008; Park *et al.*, 2014). Measurements of muscle thickness (Miyatani, Kanehisa and Fukunaga, 2000; Miyatani *et al.*, 2004) or anatomical cross-sectional area (ACSA) (Morse, Degens and Jones, 2007; Albracht, Arampatzis and Baltzopoulos, 2008) have been used to estimate muscle volume. Albracht et al. (Albracht, Arampatzis and Baltzopoulos, 2008) and Morse *et al.* (Morse, Degens and Jones, 2007) reported strong linear relationships between muscle volume and the product of ACSA and muscle length in quadriceps and triceps surae muscles. Only one study to date has estimated muscle volume from 2D measurements in individuals with CP. Park *et al*. measured muscle thickness and ACSA at 25% of the tibial length of the medial and lateral gastrocnemius in children with CP using 2D US (Park *et al.*, 2014). They found an R^2 value 0.903 for the medial and 0.858 for the lateral gastrocnemius muscle volume when comparing the measured (by MRI) with estimated (the product of tibial length and ACSA from 2D US) values. However, Park *et al.*, did not include TD individuals in their study and only the heads of gastrocnemius were investigated. It is currently not known whether strong relationships exist between ACSA and MV for other lower limb muscles in young people with CP.

To enable the estimation of muscle volume from *2D* measurements to be compared with 3D measurements, a 'form factor' is required to create an accurate estimation of muscle volume (Albracht, Arampatzis and Baltzopoulos, 2008). This form factor accounts for the non-uniform cross section of the muscle along its length. Without correcting for the non-linear shape of the muscle through use of a form factor the product of ACSA and muscle length will result in an overestimation of muscle volume. This correction factor is required if the estimated muscle volume is to be compared with muscle volume measured using a full 3D technique such as MRI or 3D ultrasound. Therefore,

investigation of the form factor is required to enable accurate comparison with other clinical measurements.

The aim of this study was to investigate the relationship between volume, ACSA, and the product of ACSA and length for multiple muscles in TD young people and young people with CP using MRI. We hypothesise that there are strong linear relationships between muscle volume and ACSA and the product of ACSA and muscle length. We hypothesis that a greater degree of variance in muscle volume will be explained by the product of ACSA and muscle length compared to ACSA alone and that muscle volume can be accurately estimated by utilising a form factor.

2 Methods

The local research ethics committee granted approval for this study (11/LO/1520,10/Y0804/83, 05/Q0704/46). All participants gave informed consent prior to data collection. This study was a convenience sample of individuals attending clinics at our university hospital, with consecutive patients that met the inclusion criteria invited to participate in the study. Individuals aged 10 – 23 years, with a diagnosis of bilateral CP, Gross Motor Function Classification System (GMFCS) levels I-III, who met the safety requirements of Magnetic Resonance Imaging (MRI) were invited to take part in this study. Patients who had undergone surgery, serial casting or botulinum toxin injections to the lower limbs within the previous year, or could not understand instructions in English were excluded from the study. TD subjects were recruited from friends and family of staff and students at our university hospital. The inclusion criteria for the TD subjects were: age 10 – 23 years, no neurological or musculoskeletal condition, and no previous surgery to the lower limbs. 21 individuals with bilateral CP (14.7 years, SD 3 years, 10.2 to 23.1 years, 17 male, GMFCS level I [n=5], II [n=11], and III [n=5]) and 23 of their TD peers (16.8 years, SD 3.3 years, 10.6 to 23.2 years, 16 male) took part in this study. Muscle volume to body mass ratio data from 10 out of 21 of the participants with CP and 10 out of 23 of the TD participants have been previously reported in a study comparing mean lower limb muscle volumes between individuals with CP and their TD peers (Noble *et al.*, 2014).

1.1. *Data collection*

MRI data was acquired on 1.5T and 3.0T Achieva systems (Philips Medical Systems, Best, The Netherlands), with a quadrature body coil. MRI images of both lower limbs of all subjects were acquired with contiguous transverse slices from above the iliac crest to below the calcaneum. All subjects lay supine on the scanner bed with their feet resting against a wooden footplate giving an approximate plantarflexion angle of 25°.

Ten subjects with CP and twelve TD subjects were scanned using a 1.5T system using a three point Dixon sequence (TE/TR=4.6/13 ms, echo time shift = 1.53 ms (120 ^{o} echo phase shift), 20^{o} flip angle, 0.9 x 0.9 mm in-plane voxel size, number of averages = 2, 5 mm slice thickness) with a quadrature body coil. Eleven subjects with CP and eleven TD subjects were scanned in a 3.0T system using a three point mDixon sequence (TE/TR=2.11/5.2 ms, echo time shift = 0.76 ms (120 ^{o} echo phase shift), 10^{o} flip angle, 0.9 x 0.9 mm in-plane voxel size, number of averages = 2, 5 mm slice thickness) were acquired of both lower limbs. Analyses were performed on the left lower limb for all subjects except for one subject with CP, for whom the right lower limb was used due to missing MRI data for the left lower limb.

1.2. Image analysis

Manual segmentation of six muscle bellies (medial gastrocnemius (MG), soleus (SOL), tibialis anterior (TA), rectus femoris (RF), semimembranosus (SM) and semitendinosis (ST)) was performed in Osirix (version 5.8.2; Pixmeo, Geneva, Switzerland) (Rosset, Spadola and Ratib, 2004).

1.3. Volume calculation and estimations

Data processing was performed offline using a commercial software package (MATLAB 8.6.0, The MathWorks Inc., Natick, MA, USA, 2015b). The volume of each MRI slice was calculated by multiplying the cross-sectional area (CSA: calculated by multiplying the number of pixels by pixel area) with the slice thickness (ST). Muscle volume was calculated by summing the volume of each slice (CSA x ST) along the length of the muscle belly (Equation 1). The product of the ACSA (the maximal CSA) and muscle length was computed using equation 2. Muscle belly length (ML) was taken as the straight line distance between the most proximal and most distal ends of the muscle.

Eq. 1

Where, MV = muscle volume, n = the number of slices, CSA = cross-sectional area and ST = slice thickness.

Eq. 2

1.4 Statistical Analysis

An Analysis of Covariance (ANCOVA) was performed to see if the relationship between MV and the product of ACSA and length (Eq. 2) was different between the subject groups. To investigate the strength of the linear relationships between $product_{ACSA\_ML}$ and *MV*, linear regression analysis was performed. . To investigate whether $product_{ACSA\_ML}$ was a better estimator of MV copared to ACSA alone, we used a 2-tailed t-test of Fischer's transformation to evaluate whether the proportion of variation in muscle volume was significantly different when using only ACSA or $product_{ACSA\_ML}$.

The muscle form factors (FF) were calculated as the inverse of the gradient of the line of best fit in a linear model and the offset to correct for a significant intercept in the relationship between $product_{ACSA\_ML}$ *and MV*. Estimated muscle volume was then calculated using Equation 3. The regression analysis was then repeated with the intercept forced through zero to acquire the best possible estimate of muscle volume. All statistical analyses were performed using SPPS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

$$((\mathrm{ACSA} * \square\square) - \square\square\square\square\square\square) * \mathrm{FF} \qquad \text{Eq. 3}$$

3 Results

The results for the relationship between $product_{ACSA\_ML}$ and *MV* are given in Figure 1. The ANCOVA did not reveal a significant interaction between the subject groups and $product_{ACSA\_ML}$ for any of the six muscles (MG: $P = 0.498$. SOL: $P = 0.056$. TA: $P = 0.910$. RF: $P = 0.361$. SM: $P = 0.344$. ST: $P = 0.940$.). Since there was no significant different between the subject groups, the data was pooled for subsequent analyses. Table 1 summarises the mean and standard deviations for all measurements for each group individually and for the pooled data. Table 2 summarises the linear regression results for ACSA and MV together with the results of the 2-tailed t-test of Fischer's transformation.

The results of the regression analysis between $product_{ACSA\_ML}$ and *MV* for all six muscles are shown in Table 3. R^2 varied between 0.955 and 0.988 and the standard error of the estimate (SEE) varied between 15.7 and 59.4 cm^3. The intercept was not significantly different from zero all muscles except for the soleus. The FF and Offset for accurate estimation of MV are given in Table 3 together with the results of the linear regression coefficient and SEE for MV_{est} and MV.

		MV (cm3)			$Product_{ACSA\_ML}$ (cm^3)			ACSA (cm^2)			ML (cm)		
		TD	CP	Pooled	TD	CP	Pooled	TD	CP	Pooled	TD	CP	Pooled
MG	Mean	237	124	183	203	376	293	14.9	9.7	12.4	25.0	20.2	22.7
	SD	57	58	80	94	95	129	2.4	3.4	3.9	3.7	3.5	4.3
SOL	Mean	428	255	346	865	548	714	26.3	18.4	22.5	32.6	28.7	30.8
	SD	107	123	143	195	261	277	4.4	6.3	6.6	3.6	5.1	4.8
TA	Mean	135	68	104	259	130	198	8.7	5.1	7.0	29.0	24.8	27.0
	SD	41	22	47	86	47	95	2.0	1.3	2.5	4.0	3.7	4.4
RF	Mean	268	153	216	448	257	362	14.2	9.6	12.1	37.6	26.1	32.4
	SD	80	65	93	137	108	156	3.5	3.6	4.2	30.6	3.1	23.2
SM	Mean	209	115	165	341	187	269	13.1	7.7	10.6	25.9	23.7	24.8

	SD	57	55	74	90	87	117	2.8	2.8	3.8	2.8	3.7	3.4
ST	Mean	192	86	143	315	150	238	10.6	6.6	8.8	29.0	20.9	25.2
	SD	70	50	81	131	94	141	3.5	3.0	3.8	3.6	6.2	6.4

Table 1 : Mean and standard deviation (SD) for muscle volume (MV), estimated muscle volume ($Product_{ACSA\_ML}$), maximum anatomical cross-sectional area (ACSA), and muscle length (ML) for the TD and CP groups and for the pooled data including subjects from both groups.

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	R^2	SEE (cm^3)	SEE (%)	*P*-value
MG	0.894	26.60	14.54	<0.001
SOL	0.903	45.06	13.03	<0.001
TA	0.965	9.02	8.71	<0.001
RF	0.823	39.49	18.29	<0.001
SM	0.827	30.78	18.64	<0.001
ST	0.894	26.60	18.63	<0.001

Table 2: R^2 and SEE for the regression model based on ACSA and *P*-values for the 2-tailed Fischer's transformation.

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	R^2	*P*	SEE (cm^3)	Gradient	*P*	Intercept	*P*
MG	0.985	<0.001	15.7	1.593	<0.001	2.153	0.719
SOL	0.955	<0.001	59.4	1.889	<0.001	60.653	0.014
TA	0.973	<0.001	16.0	1.981	<0.001	-7.508	0.205
RF	0.988	<0.001	17.5	1.676	<0.001	-0.146	0.983
SM	0.978	<0.001	17.6	1.571	<0.001	4.843	0.479
ST	0.977	<0.001	21.5	1.728	<0.001	-8.512	0.211

Table 3: Linear regression results for MV and $product_{ACSA\_ML}$ including the linear regression coefficient, SEE, gradient, and intercept for the regression line.

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	Gradient	FF	Intercept	R^2	SEE	% SEE
MG	1.59	0.628	0	0.998	9.77	5.34
SOL	1.89	0.529	60.65	0.993	31.09	8.99
RF	1.98	0.505	0	0.998	8.70	4.03
SM	1.68	0.597	0	0.997	10.45	6.21
ST	1.57	0.637	0	0.994	13.75	9.63
TA	1.73	0.579	0	0.995	9.30	8.99

Table 4: Gradient and intercept of the linear regression equation of MV and product$_{ACSA_ML}$, from Table 3 and the form factor (FF). Linear regression coefficient and SEE for the corrected estimated musde volume against MV. % SEE calculated relative to the pooled group mean volume (MV) for each muscle.

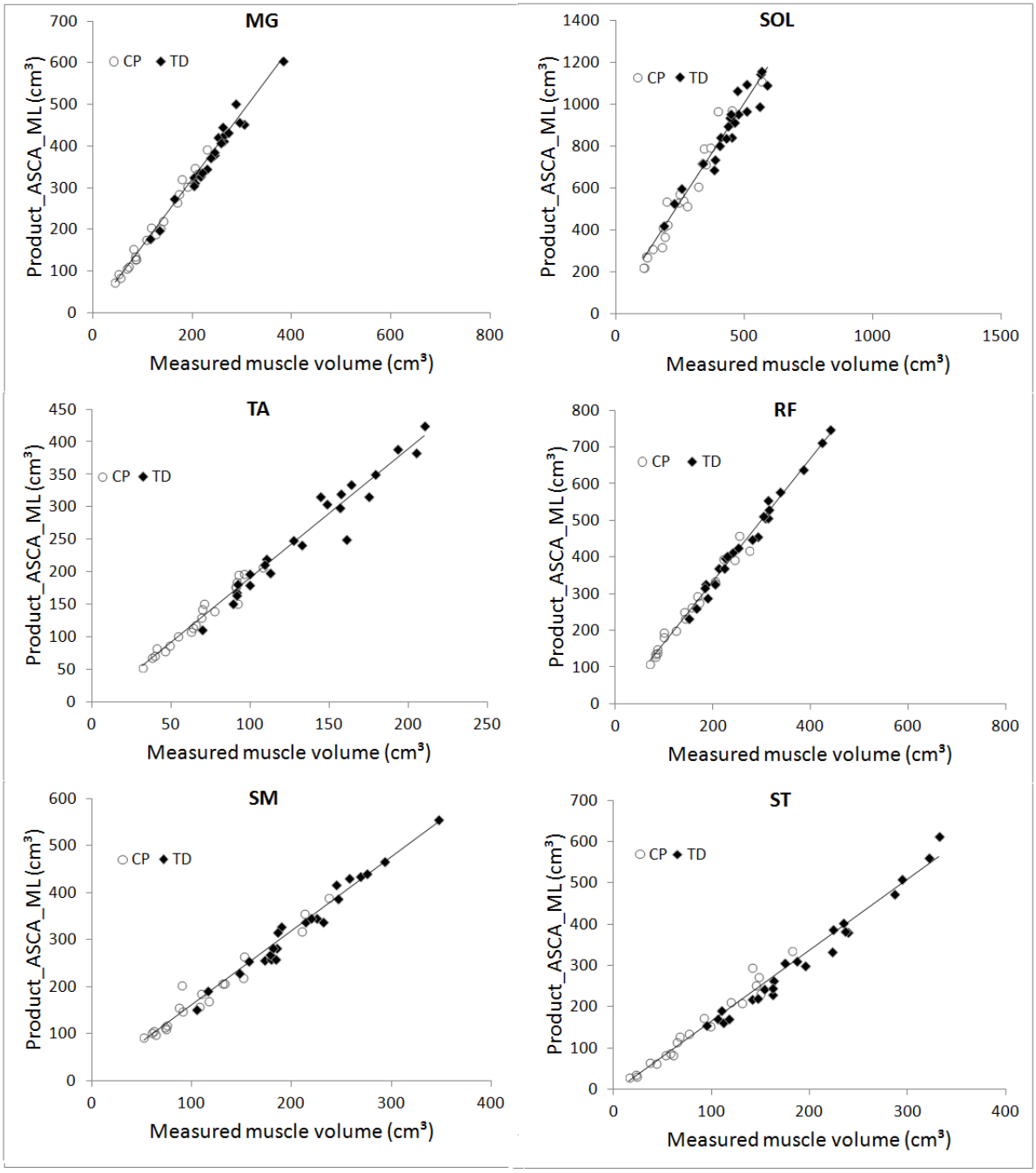

Fig. 1: Regression analysis for the product$_{ACSA_ML}$ (calculated using equation 2) and *MV* for (A) medial gastrocnemius, (B) soleus (C) Tibialis anterior, (D) Rectus femoris, (E) Semimembranosus and (F) Semitendinosis. The regression line shown is the one for the data pooled for TD subjects and subjects with CP.

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152 **4 Discussion**

We investigated the relationship between volume and the product of ACSA and length in multiple muscles in young people with cerebral palsy and their TD peers. We found strong and significant relationships between these variables that were not dependent on subject group. Our results are similar to those reported by Albracht *et al.* (Albracht, Arampatzis and Baltzopoulos, 2008) for typically developing individuals, and stronger than those reported by Park *et al.* (Park *et al.*, 2014) for the heads of gastrocnemius in children with cerebral palsy. The results of Park *et al.* may be explained by their estimation of CSA at 25% of the tibial length from the knee rather than of the ACSA. Although we could not find a significant difference in the relationship between *MV* and $product_{ACSA\_ML}$ between subject groups, the results for the soleus were close to significance. This suggests that there may be some alterations in the shape of the soleus in young people with CP in this complex multipennate muscle.

ACSA alone has been considered as a predictor of muscle volume by previous authors (Cotofana *et al.*, 2010) . However, this single variable does not appear to explain a large amount of the variance in muscle volume in TD adults. Since muscles differ in length and the inter-variation in muscle length may be even greater in subjects with CP, it is unlikely that ACSA alone is a good predictor of muscle volume. In our dataset a greater proportion of the variance of muscle volume was explained by $product_{ACSA\_ML}$ in comparison with ACSA for all muscles (Table 3). This suggests that muscle length should be included when estimating muscle volume from 2D measurements.

The product of ACSA and ML results in an overestimation of muscle volume. This is not a problem when comparing to data estimated in the same way suing these 2D measurements; however it is an issue for comparing to muscle volume measured using 3D techniques such as MRI or 3D ultrasound. This can be corrected for by utilising a FF and offset as shown in Equation 3. The offset for all muscles except for SOL was zero as the intercept in the regression model was not significantly different to zero for these muscles. The %SEE values expressed relative to the mean of VM varied between 4.03 and 9.63% for all muscles (see Table 4). These values are similar to Albrecht *et al.* who reported RMS values between 4 and 7% for the triceps surae muscle based on a shape factor in healthy individuals (Albracht, Arampatzis and Baltzopoulos, 2008). The form factor values are similar for the different muscles, suggesting that it might be possible to use a common form factor for different muscles. These results suggest that muscle volume can be accurately estimated from the product of maximum ACSA and muscle belly length through utilising form factor, to enable a comparison with muscle volumes measured utilising traditional 3D techniques.

Study limitations

The purpose of estimating MV from 2D measurements is to save time during data analysis and image segmentation. In this study maximal ACSA was obtained by segmenting all slices of the muscle. In

practice, locating the position of the maximal ACSA within a muscle will introduce variability into the dataset and further investigation is required to standardise the location at which ACSA is measured within each muscle to reduce this source of measurement variability and to avoid delays during data collection, for example when using 2D ultrasound, while the largest ASA of the muscle is investigated.

This study incorporates a wide range of muscle sizes due to the wide range in age of the participants and the pooling of data from CP and TD individuals. This large heterogeneity favours high correlations and further investigation of the ability to estimate muscle volume in a more homogenous sample is required.

Clinical implications

Our results suggest that estimates of muscle volume in clinical and research studies could be made by the application of a simple equation with just two measurements and a form factor, with an offset also required for the soleus (equation 3). This has implications for large research studies where the estimation of muscle volume by the segmentation of multiple slices may be time-consuming. It also has implications for the estimation of muscle volume with alternative, and perhaps more clinically-convenient, imaging methods such as 2D ultrasound imaging. Here, some caution must be applied as the pressure of the ultrasound probe on the skin surface may deform the local muscle cross-section and the length of the muscle belly would need to be estimated from a tape measure placed over the skin surface (guided by ultrasound) rather than from a direct linear measurement from the most proximal position of the muscle belly to the most distal. Considering these sources of potential error in estimating muscle volume using 2D US, further validation studies utilizing 2D ultrasound is required.

4 Conclusions

This study found that muscle volume can be accurately estimated from measurements of ACSA and muscle length obtained during MRI imaging. Since these measurements can be routinely performed using 2D US, this method may prove to be highly applicable and practical for clinical and research applications.

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6 Conflict of interest

The authors declare to have no conflict of interest.

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