REDUCTION OF MAGNETIC RESONANCE IMAGING PROCESSING TIME FOR THE ASSESSMENT OF LEG MUSCLE VOLUME IN CHILDREN WITH CEREBRAL PALSY

by

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ABSTRACT

Cerebral palsy (CP) is a movement disorder associated with substantially reduced muscle volume, especially in the lower extremities. A criterion method used to assess muscle volume is magnetic resonance imaging (MRI); however, the processing procedures can be extremely labor intensive. The aim of this study was to determine the proportion and location of magnetic resonance images needed to accurately estimate leg muscle volume in children with CP. To address this aim, the volume of individual leg muscles was assessed in 13 children with spastic CP (4-11 years) using MRI. Muscle volume from the full image set (FIM) was compared to 1-image (1IM) and 3-image (3IM) subsets. Results from 13 subjects and 10 muscles in the leg are presented. Muscle volumes from FIM and 1IM were strongly correlated for the peroneus brevis ($r^2 = 0.97$), gastrocnemius ($r^2 = 0.80$), flexor hallucis longus ($r^2 = 0.79$), tibialis anterior ($r^2 = 0.78$; all $p < 0.001$), flexor digitorum longus ($r^2 = 0.74$; $p = 0.001$), tibialis posterior ($r^2 = 0.71$, $p = 0.001$), extensor digitorum longus ($r^2 = 0.69$, $p = 0.001$) and peroneus longus ($r^2 = 0.62$, $p = 0.001$). Muscle volumes from FIM and 1IM were moderately correlated for the extensor hallucis longus ($r^2 = 0.44$, $p = 0.013$), and soleus ($r^2 = 0.42$, $p = 0.016$). The relationships between FIM and 3IM vs. between FIM and 1IM were stronger for all muscles ($r^2 = 0.78$ to 0.95, all $p < 0.001$). The results indicate that total volume of the leg muscles can be estimated with as few as 3 magnetic resonance images in children with CP.

Chapter 1

BACKGROUND INFORMATION

Cerebral palsy (CP) is a movement disorder caused by a non-progressive lesion in the brain[18] associated with underdevelopment of skeletal muscles. It is the most common childhood disorder[1] with prevalence in the United States and around the world ranging from 1.5 to more than 4 children per 1,000 live births[3, 4, 27, 5, 33]. Classification of CP is based on the patterns of movement dysfunction exhibited, such as spasticity (hypertoned muscles), dyskinesia (uncontrollable movements), and ataxia (deficient balance and coordination)[8]. Moreover, the limbs affected with cerebral palsy are indicated in the diagnosis. A classification of hemiplegia is made when half the body is involved; diaplegia refers to involvement of the lower extremities; and quadriplegia refers to involvement of all four limbs[19]. In this study, we looked at children with spastic CP, the most common type of cerebral palsy.

Children with CP have significantly weaker muscles due to deficits in motor unit activation[28] and loss of muscle volume[17, 12]. When compared to typically developing (TD) children, ambulant children with spastic CP produce only 52% of the force in a maximal contraction[32]. Furthermore, the structure of the skeletal muscle is affected by spasticity[13], which in turn affects the lower limbs of children with CP significantly more than their TD counterparts[11]. Obtaining measurements of muscle volume of the leg in children with spastic CP could help determine changes in strength and the effects of interventions.

Moreover, muscle volume is thought to relate to functional walking ability in children with spastic CP. Riad and collegues[28] investigated the relationship of muscle volume and concentric muscle work of the thigh and leg, in children with spastic cerebral palsy. They quantified the volume of the muscles considered important for walking, and then related those volumes to the concentric muscle work during walking. The study found that both the affected and non-affected limbs had a direct correlation between the muscle volume ratio and concentric work ratio. Furthermore, almost all of the muscles in the affected thigh and leg had smaller volumes and smaller concentric work ratios than the non-affected limb. Their findings suggest that changes in muscle volume and concentric work occurred due to both primary deviations and compensatory mechanisms.

Muscle volume not only correlates with concentric work[28], and muscle strength[6, 7,18, 23], but also with joint torque. Fukunaga[14] and colleagues conducted a study with healthy university students and student-athletes, in which they found muscle volume to be a major determinant of joint torque in the upper arm. The investigators hypothesized that since muscle force is linearly related to its cross-sectional area (CSA), maximal joint torque would be a function of muscle volume. The results showed that the joint torque to muscle volume ratio were the same for both the students and student-athletes, thus supporting their hypothesis.

Several techniques have been used to assess muscle volume in vivo, with magnetic resonance imaging (MRI) considered a gold standard. Additionally, MRI provides accurate estimates of interstitial adipose tissue and subcutaneous adipose tissue[21]. Thus, using MRI to assess muscle volume can help to identify adipose tissue infiltration, a recurring phenomenon in children with CP[16].

Furthermore, using cross-sectional scans provides more accurate estimates in contrast of longitudinal scans. Using the forearms of seventeen cadavers, Eng[9] and colleagues calculated muscle volume values using MRI analysis and the weight of dissected muscles. The results exhibited an excellent agreement between the weighted and MRI based muscle volumes, when all the 43 forearm muscles were grouped. However, MRI-based measurements had relatively small errors in some muscles (7.75 – 9.8%) and larger errors for other muscles (17.2 – 21.6%), when the muscles were considered individually[9]. The muscles that resulted in inaccurate MRI-based measurements presented a high surface area-to-volume ratio..

Other imaging methods have been used to assess muscle volume. For example, Fukunaga and colleagues[14] estimated muscle volume using ultrasound, and compared it to muscle volume values obtained through MRI. To obtain muscle volume using ultrasound, a muscle volume index equation (MVI_{ULT}) was first calculated by multiplying fiber length (FL) and the square of muscle thickness (MT^2). This resulted in the equation $MVI_{ULT} = L \times (MT^2)$. Then, a prediction equation for muscle volume (MV_{ULT}) was created based on regression analyses, the previously mentioned MVI_{ULT}, and anthropometric measures (body height, body weight, and circumference of upper arm). The results indicated that the muscle volume values from the prediction equation (MV_{ULT}) were more strongly correlated with the values of MR images (MV_{MRI}), than the values from the index equation (MVI_{ULT}). The findings of this study show that the prediction equations for muscle volume obtained by ultrasound are more accurate than those obtained by previous studies based only on anthropometry[29, 22]. However, this study acknowledges that MRI remains the most accurate method.

Measurements from dual-energy X-ray absorptiometry (DXA) can also be used to quantify muscle volume or muscle mass. Modlesky[25] developed a mathematical model using DXA measurements to estimate mid-thigh muscle mass. The study focused on TD children and children with quadriplegic CP. Fat-free soft tissue mass estimated using DXA ($FFST_{DXA}$) was compared to muscle mass estimated using MRI ($muscle_{MRI}$). Even though the mathematical model based on DXA resulted in valid estimates of muscle mass for the TD children, muscle mass for children with CP was overestimated by 15%. Such a discrepancy relates to the lower ratio of muscle and fat-free soft tissue mass ($muscle_{MRI}/FFST_{DXA}$) that the children with CP present, in contrast with the TD children. This study shows that unless appropriate prediction equations are developed, other imaging techniques do not necessarily provide accurate estimates of muscle volume from MRI, particularly in children with CP. Even though other studies have used MRI to assess muscle volume in the upper limbs[2], and other populations with upper-motor neuron (UMN) injuries[24], few studies[9] have attempted to estimate leg muscle volume in children with spastic CP.

Even though quantification of muscle volume through MRI has proved very accurate, there are limitations to it such as the high cost, radiation and limited access to MRI machines[15]. Likewise, it is a very time consuming to process the magnetic resonance images once they are obtained. To reduce the analysis time and improve the efficiency of the MRI technique, studies have estimated muscle volume from a single image. Morse and colleagues[26] estimated the volumes of the muscles that constitute the quadriceps in young men. To quantify muscle volume, they used cross-sectional images at 40%, 50%, and 60% of the femur length, and found that the most accurate predictor was the single image located at 60% of femur length from the distal end

(SEE = 10%). However, no studies have attempted to predict muscle volume of the leg of children with CP with as few as 1 or a limited number of magnetic resonance images.

Lastly, this study attempts to quantify the muscle volume for each of the ten individual muscles using manual processing. Riad[28] showed that measurements of muscle volume based on MRI analysis are reliable, even when selection of muscle boundaries is not fully automated. It is the goal of the current study to utilize manual segmentation of MRI scans to predict the total volume of all muscles in the leg of children with spastic CP using 1 or 3 images, which represents approximately 3 and 10 % of all images, respectively.

Chapter 2

MATERIALS AND METHODS

2.1 Subjects

Children (n = 13) between 4-11 years old, with a diagnosis of spastic hemiplegic or diplegic CP and between I and III on the Gross Motor Function Classification Scale (GMFCS) were recruited from the AI duPont Hospital for Children in Wilmington, DE. A physician assistant assessed pubertal development and gross motor function. Institutional Review Boards at both the University of Delaware and AI duPont Hospital for Children approved the study. Furthermore, written consent was granted by the parents, as well as written assent by the children, if able to do so, before any testing happened.

2.2 Anthropometrics

Children had their height and body mass measured while wearing a t-shirt and shorts. No braces or shoes were worn during the measurements. The height of children with CP was measured using a stadiometer (Seca 217; Seca GmbH & Co. KG., Hamburg, GER). Their body mass was measured using a scale (Detecto 6550, Cardinal Scale, Webb City, Missouri).

2.3 MRI analysis

Magnetic resonance imaging (1.5 T; GE, Milwaukee, WI) was used to assess the volume of the muscles in the nondominant leg. Participants were immobilized

from the waist down using the BodyFIX (Medical Intelligence, Schwabmunchen, Germany). A three-plane localizer was used to identify the region of interest. Axial T1-weighted images were collected from the tibia plateau to the malleolar articular surface (TR 750, TE = 14,field of view = 12 cm, 0.5 cm thick separated by 0.5 cm of spacing; Figure 1) using a semiflex long bone array coil (ScanMed, Omaha, NE). The volumes of individual muscles in the leg were determined using custom software developed using Interactive Data Language; Research Systems, Inc, Boulder, CO).

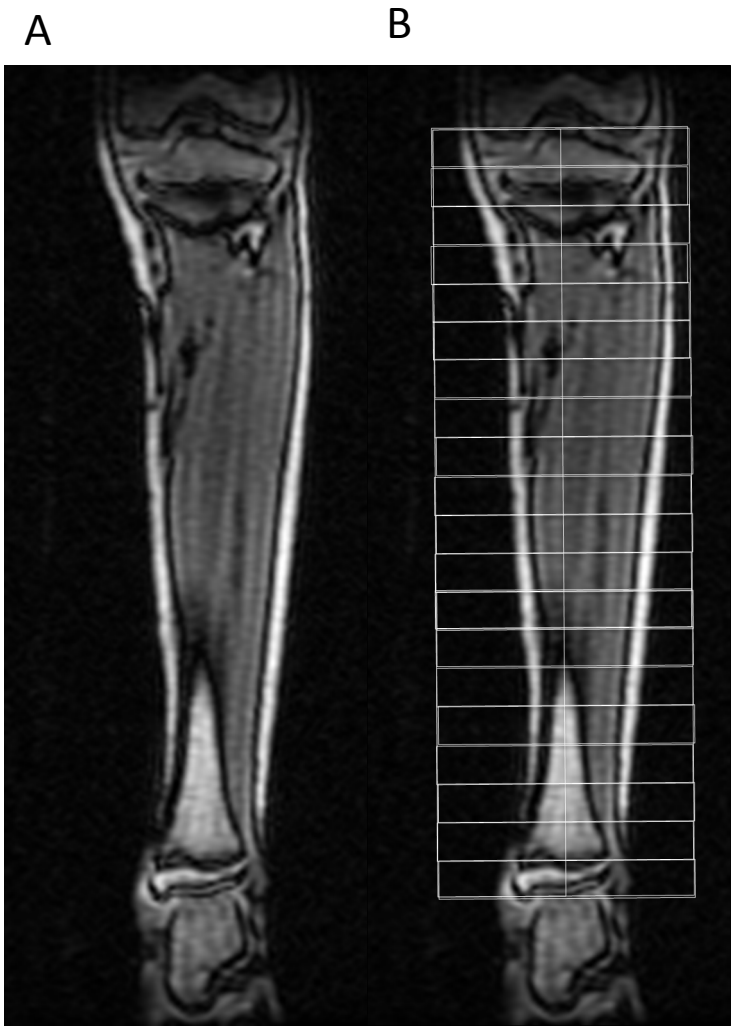

Figure 1: Coronal magnetic resonance image (A) used to identify the region of interest. Images (0.5 cm separated by 0.5 cm) representing the region of interest (B) extended from the tibia plateau to the malleolar articular surface of the tibia.

Using in-house custom software developed with Interactive Data Language (Research Systems, Inc, Boulder, CO), individual muscles in each raw image were traced over the muscle boundary, labeled appropriately, filtered using a median filter, and segmented into muscle non-muscle tissue using a fuzzy clustering algorithm [29]. Muscle volume was calculated for each image and the volumes in the full set of images were summed (FIM). Muscle volumes calculated using the image representing the center of a muscle (1IM) and three images distributed throughout a muscle (3IM) were compared to FIM.

2.4 Statistical Analysis

Data was analyzed using GraphPad (GraphPad Software, Inc, La Jolla, CA) with an α level set at 0.05. The agreement between volume and image subsets (1IM and 3IM) was assessed using regression analysis.

Chapter 3

RESULTS

Presented are results from 13 children with CP and 10 muscles constituting the leg: tibialis posterior (TP), tibialis anterior (TA), gastrocnemius, soleus, flexor digitorum longus (FDL), flexor hallucis longus (FHL), peroneus longus (PL), peroneus brevis (PB), extensor digitorum longus (EDL), and extensor hallucis longus (EHL).

Table 1: Characteristics of children with cerebral palsy (CP)

	CP (n = 13)
Age (y)	7.8 ± 2.3
Sex (m/f)	5/8
Tanner Stage (1/2/3)	
Pubic hair	9/3/1
Breast/Testicular-Penile	9/4/0
Height (m)	1.19 ± 0.13
Height (%)	19 ± 21
Body mass (kg)	24 ± 9
Body mass (%)	30 ± 30
BMI (kg/m^2)	16.5 ± 3.3
BMI (%)	48 ± 34
Gross Motor Function Classification (I/II/III)	5/7/1

Values are means ± SD

Muscle volumes from FIM and 1IM were strongly correlated for the peroneus brevis ($r^2 = 0.97$, $p < 0.0001$; Figure 5C), the gastrocnemius ($r^2 = 0.80$, $p < 0.0001$; Figure 3A), flexor hallucis longus ($r^2 = 0.79$, $p < 0.0001$; Figure 4C), and tibialis anterior ($r^2 = 0.78$, $p < 0.0001$; Figure 2C). Muscle volumes were fairly correlated for the flexor digitorum longus ($r^2 = 0.74$, $p = 0.0002$; Figure 4A), tibialis posterior ($r^2 = 0.71$, $p = 0.0003$; Figure 2A), extensor digitorum longus ($r^2 = 0.69$, $p = 0.0005$; Figure 6A), and peroneus longus ($r^2 = 0.62$, $p = 0.0015$; Figure 5A). Extensor hallucis longus ($r^2 = 0.44$, $p = 0.0129$; Figure 6C), and soleus ($r^2 = 0.42$, $p = 0.0162$; Figure 3C) were weakly correlated.

The relationships between FIM and 3IM were stronger for all muscles ($r^2 = 0.78$ to 0.95, all $p < 0.0001$; Figures 2B, 2D, 3B, 3D, 4B, 4D, 5B, 5D, 6B, and 6D).

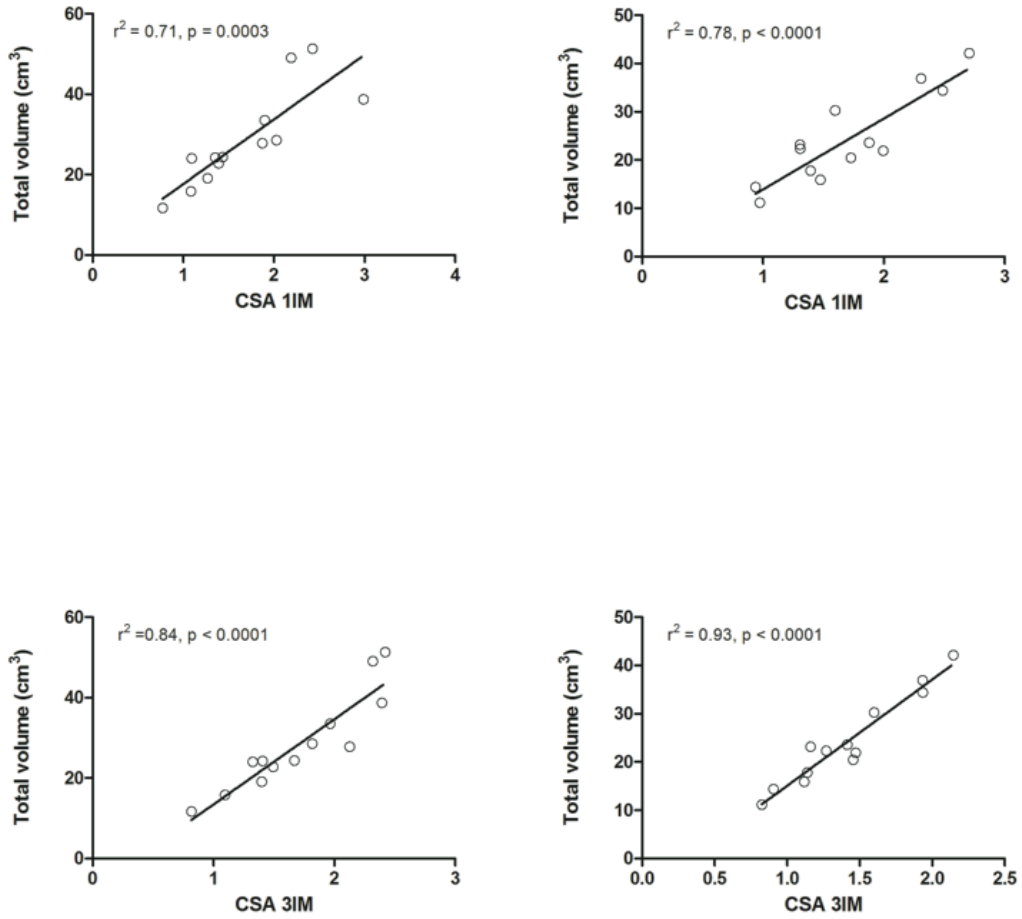

Figure 2: Scatter plots show the relationships between the volume of a full set of images for tibialis posterior (A and B) and tibialis posterior (C and D), compared to the average cross-sectional area of 1-image (CSA 1IM) and the average CSA of 3 images (3IM).

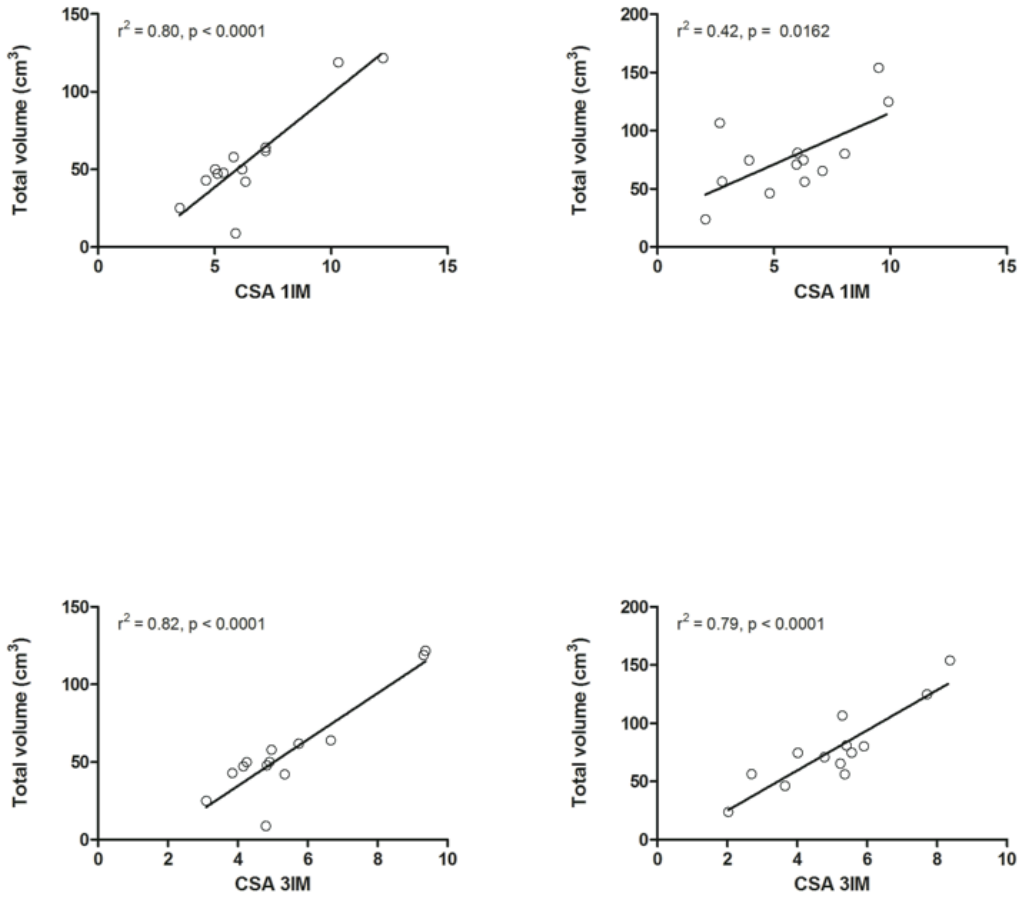

Figure 3: Scatter plots show the relationships between the volume of a full set of images for gastrocnemius (A and B) and soleus (C and D), compared to the average cross-sectional area of 1-image (CSA 1IM) and the average CSA of 3 images (3IM).

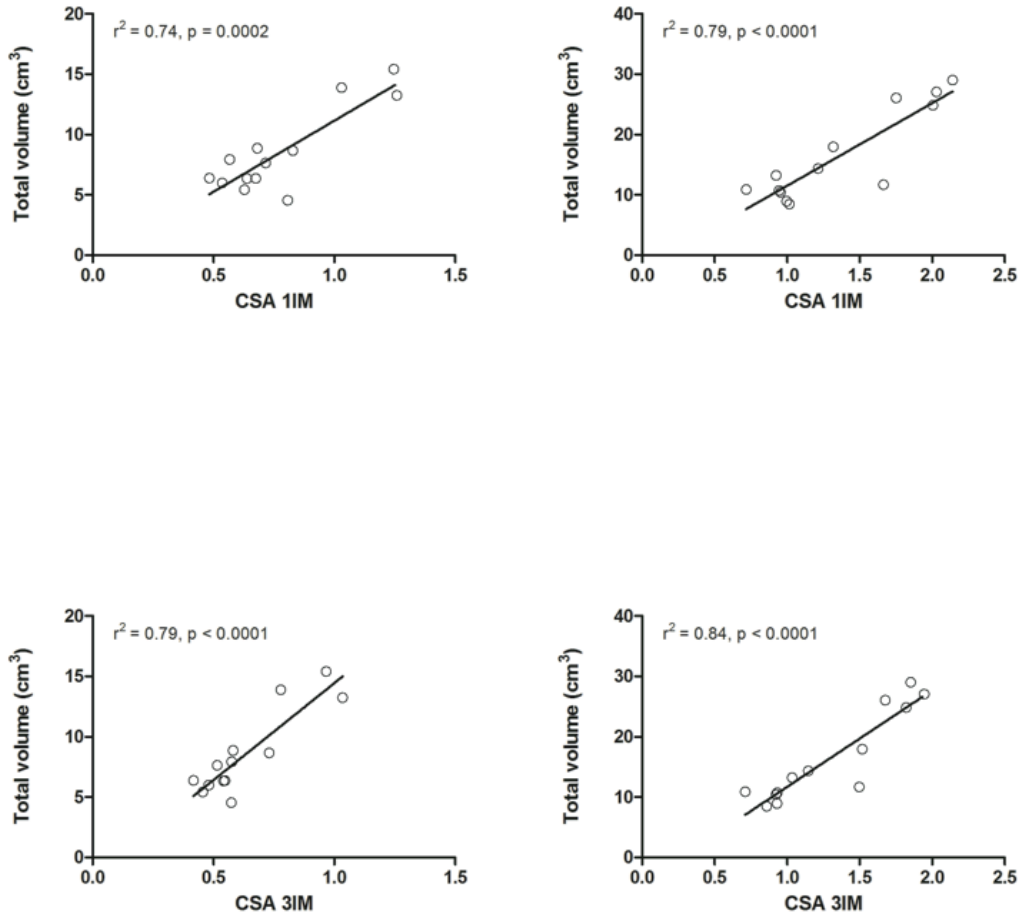

Figure 4: Scatter plots show the relationships between the volume of a full set of images for flexor digitorum longus (A and B) and flexor hallucis longus (C and D), compared to the average cross-sectional area of 1-image (CSA 1IM) and the average CSA of 3 images (3IM).

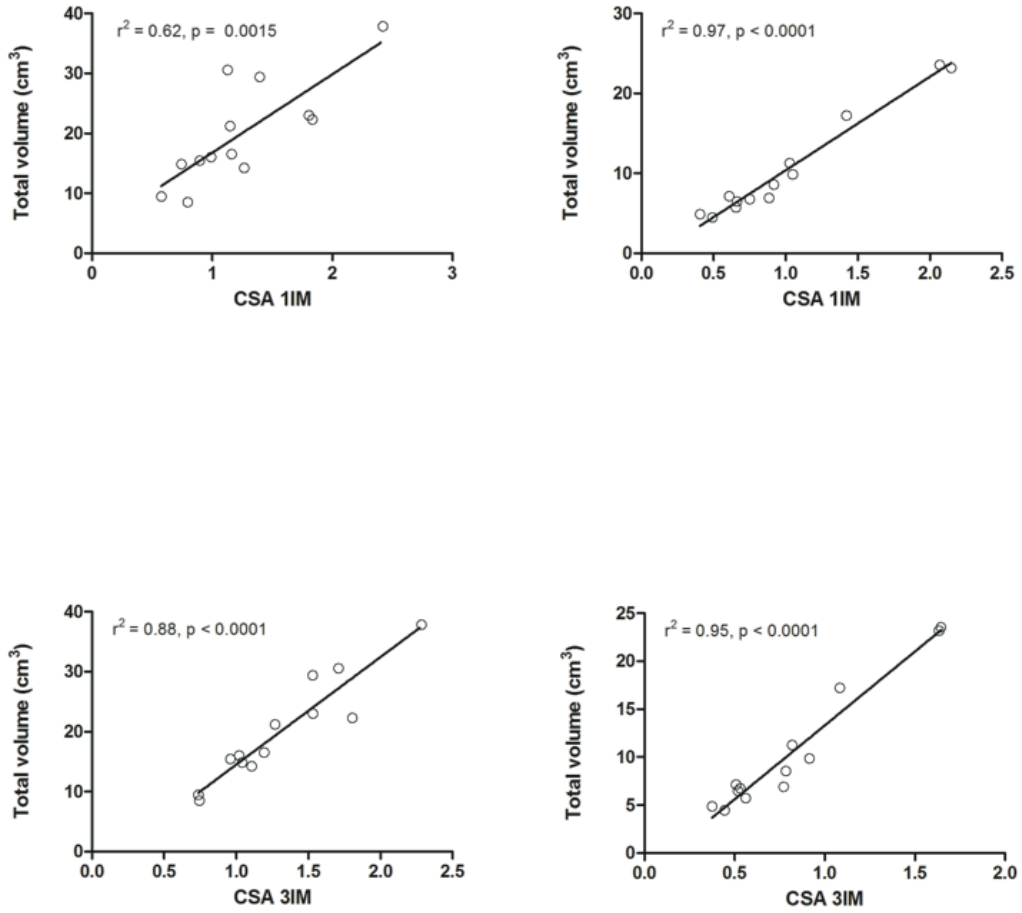

Figure 5: Scatter plots show the relationships between the volume of a full set of images for peroneus longus (A and B) and peroneus brevis (C and D), compared to the average cross-sectional area of 1-image (CSA 1IM) and the average CSA of 3 images (3IM).

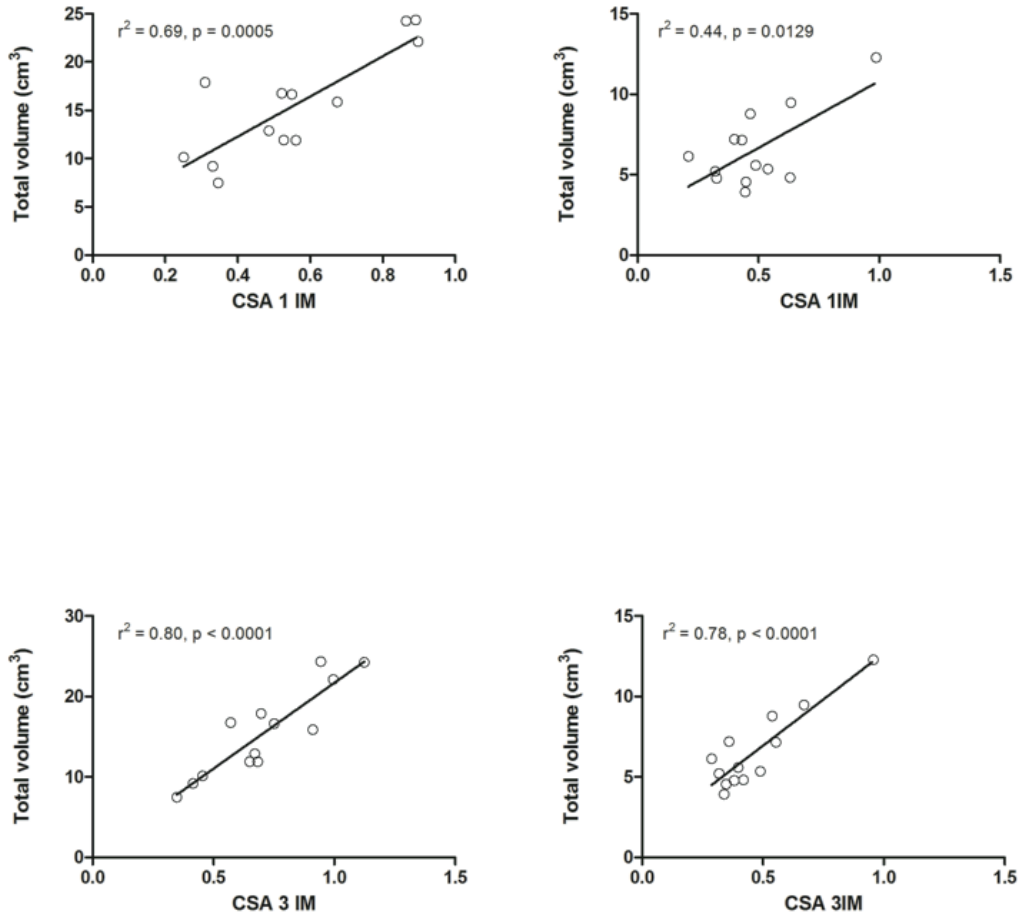

Figure 6: Scatter plots show the relationships between the volume of a full set of images for extensor digitorium longus (A and B) and extensor hallucis longus (C and D), compared to the average cross-sectional area of 1-image (CSA 1IM) and the average CSA of 3 images (3IM).

Table 2: Summary of Results

Muscle	1 IM	3 IM
Tibialis Posterior	$r^2 = 0.71$, $p = 0.0003$	$r^2 = 0.84$, $p < 0.0001$
Tibialis Anterior	$r^2 = 0.78$, $p < 0.0001$	$r^2 = 0.93$, $p < 0.0001$
Gastrocnemius	$r^2 = 0.80$, $p < 0.0001$	$r^2 = 0.82$, $p < 0.0001$
Soleus	$r^2 = 0.42$, $p = 0.0162$	$r^2 = 0.79$, $p < 0.0001$
Flexor Digitorum Longus	$r^2 = 0.74$, $p = 0.0002$	$r^2 = 0.79$, $p < 0.0001$
Flexor Hallucis Longus	$r^2 = 0.79$, $p < 0.0001$	$r^2 = 0.84$, $p < 0.0001$
Peroneus Longus	$r^2 = 0.62$, $p = 0.0015$	$r^2 = 0.88$, $p < 0.0001$
Peroneus Brevis	$r^2 = 0.97$, $p < 0.0001$	$r^2 = 0.95$, $p < 0.0001$
Extensor Digitorum Longus	$r^2 = 0.69$, $p = 0.0005$	$r^2 = 0.80$, $p < 0.0001$
Extensor Hallucis Longus	$r^2 = 0.44$, $p = 0.0129$	$r^2 = 0.78$, $p < 0.0001$

Chapter 4

DISCUSSION

The results indicate that the total volume of the leg muscles can be estimated with as few as 3 magnetic resonance images in children with CP. This is important because the assessment of individual muscle volume using MRI is very time consuming. If the current finding is confirmed with a large sample, image processing using the current protocol can be reduced from approximately 5 hours to less than 1 hour. Moreover, it is very challenging for children with CP to stay still during an MRI scan because they may have cognitive issues, spasticity or a strong startle reflex. If the number of MR images needed to accurately assess muscle volume could be reduced, from approximately 30 to 3, the time it takes to collect images could also be reduced. Thus, this project could potentially make the assessment of the leg muscles in children with CP using MRI a more efficient and comfortable method.

Lastly, the high level of sensitivity in the assessment of muscle volume through MRI shown by the CSA 3IM predictions allows detection of subtle changes in muscle quality. Therefore, a more accurate monitoring of the changes in muscle architecture and volume due to spasticity could help both researchers and practitioners to design better treatments more targeted to specific muscles.

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