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Intracellular-to-total water ratio explains the variability of muscle strength dependence on the size of the lower leg in the elderly

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ABSTRACT

Bioelectrical impedance spectroscopy (BIS) can assess intracellular water (ICW) and total water (TW) in limbs. This study aimed to examine whether BIS can explain a part of the inter-individual variation of the muscle size-strength relationship in older adults. We analyzed the data of 79 participants aged 64–86 years. The maximal voluntary isometric torques of dorsiflexion and plantar flexion on the right side were measured. The anterior and posterior muscle thickness (MT) in the right lower leg was assessed using ultrasonography. The length of the right lower leg (L) was measured, and the ICW-to-TW ratio (ICW/TW) in the right lower leg was obtained using BIS. The MT was multiplied by L to represent an index of muscle volume (MV). Correlation and stepwise regression analyses were performed. The anterior and posterior MT × L significantly and positively correlated with the muscle torque of dorsiflexion and plantar flexion (r = 0.710 and 0.649, respectively, P < 0.001). In the stepwise regression analyses, ICW/TW was selected as a significant predictor of muscle torque independent of MT × L (P < 0.05) for both dorsiflexion and plantar flexion. Electrical parameters of BIS (membrane capacitance, characteristics frequency, and phase angle) in the lower leg also significantly correlated with muscle torques. In addition, the skeletal muscle mass index (appendicular lean mass/height^2) was also associated with ICW/TW (P < 0.001). The present results suggest that ICW/TW explains the interindividual variations of the muscle size-strength relationship.

1. Introduction

The term *sarcopenia* was originally created and defined by Rosenberg as the age-related loss of muscle or lean mass (Rosenberg, 1989). Mitchell et al. (2012) reviewed the literature and found that the skeletal muscle mass (SMM) in the elderly decreased by approximately 0.4% per year in comparison with that in young adults. The rate of decrease declined more steeply at a certain older age (range, 50–65 years) than at a younger age, but the longitudinal study that assessed this in older adults (≥65 years) aged 5 to 12.2 years showed that the decrease rate was still up to approximately 1% (Mitchell et al., 2012).

Conversely, longitudinal studies with the elderly showed that muscle strength decreased by approximately 3% every year (Mitchell et al., 2012). In the cohorts where muscle size and strength were measured at the same time (*e.g.*, the Baltimore Longitudinal Study and Health ABC study), the rate of decrease in muscle strength was two to four times as high as that in muscle size (Ferrucci et al., 2012a; Goodpaster et al., 2006). Muscle size, determined using either mid-thigh muscle cross-sectional area (CSA) measured on computed tomography (CT) or leg and arm lean soft tissue mass measured on dual-energy X-ray absorptiometry, did not explain the strong association of muscle strength with mortality (Newman et al., 2006). In the In-CHIANTI study, calf skeletal muscle CSA was also not a significant risk factor of mortality in community-dwelling older adults after adjustment for potential confounders, although physical function (*e.g.*, gait speed) was confirmed to be a powerful predictor of mortality (Cesari et al., 2009).

Although the ratio of skeletal muscle strength to mass is relatively constant during development from childhood to adulthood, the strength-to-mass ratios have great heterogeneity between individuals in older adults (Ferrucci et al., 2012b). Moritani and deVries's studies

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revealed that muscle strength is not solely dependent on muscle size (Moritani and Devries, 1979; Moritani and Devries, 1980). Clark and Manini, therefore, coined the term “dynapenia,” defined as the age-related loss of muscle strength (Clark and Manini, 2008). On the basis of many studies in the late 1990s and through the 2000s, international working groups have re-defined sarcopenia as an age-related loss of muscle mass and loss of strength and/or physical function to connect a diagnostic condition to a subject's future health outcomes (Cruz-Jentoft et al., 2010; Fielding et al., 2011; Studenski et al., 2014; Chen et al., 2014).

The mechanisms of the interindividual variations of muscle size-strength relationships are diverse, from “neural factors” and “neuromuscular factors” to “factors in muscle tissues” (Manini and Clark, 2012).

In terms of “factors in muscle tissues,” about three-quarters of muscle tissue is water *in vivo*. Azzabou et al. used nuclear magnetic resonance (NMR) imaging with water T2 maps and fat fraction quantified using the three-point Dixon technique and found that water T2 mean values and the heterogeneity index, as well as fat fractions, were significantly higher in the elderly than in young adults (Azzabou et al., 2015). NMR is, however, difficult to apply in a large-scale study or in a clinical setting for sarcopenia screening. Water in muscle tissues is divided into intracellular water (ICW) and extracellular water (ECW) fractions. The muscle cell membrane acts as a capacitor in bioelectrical impedance spectroscopy (BIS) (Giaever and Keese, 1993); thus, BIS can obtain information on the ratio of intracellular water (ICW) to total water (TW) in the limbs (Bartok and Schoeller, 2004). Recent studies (electrical impedance myography by Rutkove et al.) that used rodent models found that bioelectrical impedance can estimate information on myofibers *in vivo* (Arnold et al., 2017; Kapur et al., 2018). In addition, previous studies indicated that electrical parameters measured using BIS are good biomarkers of muscle mass or function (Yamada et al., 2017a; Yamada et al., 2010; Yamada et al., 2014; Siglinsky et al., 2018; Taniguchi et al., 2017; Yamada et al., 2013; Yamada et al., 2017b).

Ultrasonography is widely available and easily operated at bedside or at regular health checkups, without any radiation exposure, and can be used to assess the muscle thickness (MT) in each site (Abe et al., 2011; Kawakami et al., 1998). The first research on assessing the size-strength relationship of human muscle *in vivo* was also conducted using ultrasonography by Ikai and Fukunaga (1968). Ultrasonography has the advantage of being able to take pictures not obtainable using BIS. We hypothesized that the combination of BIS and ultrasonography may be a good solution for assessing muscle quantity and quality in the clinical setting, and the ratio of ICW/TW, measured using BIS, can partly explain the heterogeneity of the size-strength relationship in older adults. The primary aim of the present study was to examine whether BIS can explain a part of the interindividual variation of the muscle size-strength relationship in older adults. In addition, the secondary aim was to confirm that the electrical parameters (membrane capacitance [Cm], characteristic frequency [fc], and phase angle [φ]) obtained with BIS correlated with single-joint muscle strength in the older adult population, which have been examined in a recent previous study with the complex multi-joint task of jumping muscle power in adults aged 26–76 years (Yamada et al., 2017b).

2. Methods

2.1. Subjects

For this study, 82 community-dwelling older adults were recruited. One potential participant had a chronic nerve injury to his right leg, and two participants had joint instability; these three were excluded from the study. Therefore, the present study included 79 subjects aged 64–86 years (40 women and 39 men). Height was measured without shoes. Body weight and composition were assessed using a standing-posture 8-electrode multi-frequency bioelectrical impedance analysis (MC-980, TANIA, Tokyo, Japan) with the subjects dressed in light clothing. The appendicular lean mass (ALM) was obtained using a previously developed and cross-validated equation (Yamada et al., 2017c). The skeletal muscle mass index was calculated as ALM divided by height squared (ALM/Ht^2, kg/m^2). A previous study in Japan indicated that for sarcopenia, the skeletal muscle mass index cutoffs were 6.8 and 5.7 kg/m^2 from the dataset of 1624 men and 1368 women aged 18–40 years, respectively (Yamada et al., 2017c). This study protocol was approved by the ethics committee of Waseda University and conducted in laboratories at Waseda University (2016-311).

2.2. Bioelectrical impedance spectroscopy

Bioelectrical impedance was measured using a logarithmic distribution of 256 frequencies ranging from 4 to 1000 kHz (SFB7, ImpediMed, Pinkenba, QLD, Australia) with disposable tab-type monitoring electrodes (2 × 2 cm; Red Dot, 3 M, St. Paul, MN) (Yamada et al., 2017a; Siglinsky et al., 2018; Yamada et al., 2013). Before the test, the system was checked with a series of precision resistors provided by the manufacturer. Current injection electrodes were placed on the dorsal surface of the right hand, proximal to the second and third metacarpal-phalangeal joints, and on the dorsal surface of the right foot, proximal to the second and third metatarsal-phalangeal joints. Sensing electrodes were placed on the right articular cleft between the femoral and tibial condyles (“knee”) and on the anterior surface of the ankle between the protruding portions of the tibial and fibular bones (“ankle”; Fig. 1) (Yamada et al., 2010). “Impedance measurements were obtained with the subjects in a relaxed supine position on a padded bed, arms slightly abducted from the body, forearms pronated, and legs slightly apart. Room temperature was adjusted to maintain a thermoneutral environment. The BIS measurement was taken after 5–10 min of rest to avoid the immediate (1–2 min) effect of the transition from a standing to a supine position on the shift in body fluid from the extremities to the thorax, as well as the slow phase of this shift that continues for up to 3–12 h” (Yamada et al., 2013). The resistance of the extracellular water compartment (R_0) and that of the total water compartment (R_∞) for the lower leg were determined by extrapolation after fitting the spectrum of bioimpedance data to the Cole-Cole model using the supplied software. The resistance of the intracellular water compartment (R_{ICW}) was calculated as $1/[(1/R_\infty) - (1/R_0)]$. The segmental ECW and ICW in the lower leg were calculated using the following equations (Bartok and Schoeller, 2004): ECW = $\rho_{ECW} \times L^2/R_0$ and ICW = $\rho_{ICW} \times L^2/R_{ICW}$, where ρ represents factors for extracellular (ρ_{ECW} = 47 Ωcm) and intracellular resistivities (ρ_{ICW} = 273.9 Ωcm), respectively; L is the segmental length, R_0 is the segmental extracellular resistance, and R_{ICW} is segmental intracellular resistance. The volume of TW was calculated as the sum of ECW and ICW, and the ratio of ICW divided by TW (ICW/TW) was calculated for the right lower leg. According to a previous study, the electrical parameters (Cm, fc, and φ) in the lower leg were also obtained from the Cole-Cole model (Yamada

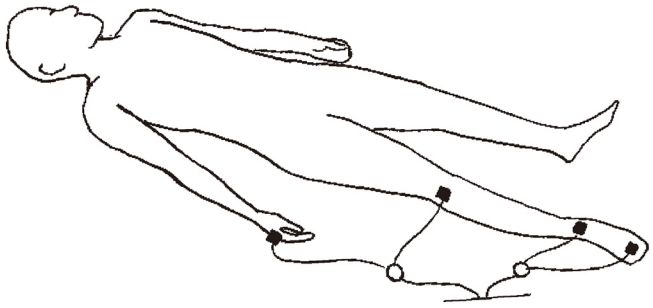

Fig. 1. Schema of the measurement of segmental multi-frequency bioelectrical impedance spectroscopy for the right lower leg (Yamada et al., 2010) (permission from original publisher obtained).