Radiofrequency Echographic Multi Spectrometry (REMS) for the assessment of muscle strength

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ABSTRACT

Objective: Due to the limitations of available methods for muscle strength evaluation, there is a need to develop more effective ways to quantify muscle function and performance in individuals suffering from musculoskeletal diseases. This study investigated the relationship between handgrip strength and a novel parameter derived from ultrasound scans of the forearm obtained using Radiofrequency Echographic Multi Spectrometry (REMS) technology. Estimations of muscle strength were performed in two study groups: healthy subjects and individuals affected by sarcopenia.

Methods: A total of 58 Caucasian volunteers (30 healthy individuals and 28 subjects affected by sarcopenia) were recruited. A handgrip strength test was used to measure the Maximum Voluntary Contraction (MVC) of each subject's dominant arm. Transversal echographic scans of the forearm were performed using an EchoStation device (Echolight S.p.a., Lecce, Italy) equipped with a 40 mm linear probe. A dedicated segmentation algorithm was designed and optimized for automatic identification of the ulnar and radius muscle profiles. The correlation between MVC values and REMS-based estimations of MVC (MVCREMS) was established using a linear regression approach.

Results: MVCREMS showed excellent correlation with the MVC taken as ground truth. A high correlation value (r=0.95) was found in the overall population, and the corresponding values in the healthy and pathological subgroups were r=0.90 and r=0.83, respectively ($p<0.0001$).

Conclusion: This technique allows reliable estimation of muscle strength in both pathological and healthy subjects, and is a valid alternative to conventional handgrip tests for use in primary care. In the future, this technique might help to enhance the assessment, screening and prevention of musculoskeletal diseases.

KEYWORDS

Sarcopenia diagnosis, Radiofrequency Echographic Multi Spectrometry (REMS), forearm, muscle strength.

Introduction

Musculoskeletal disorders characterized by decline of connective tissue, joints, bone and muscle compartments are the main contributors to disability of the locomotor system. Although cellular ageing is a common cause, musculoskeletal disorders can also have other causes, such as progressive inflammation and neurological changes, that affect individuals of all ages [1].

Sarcopenia, a main contributor to the burden of musculoskeletal conditions, is a pathological muscle condition characterized by progressive loss of muscle mass, strength and physical performance. While ageing is responsible for this muscle mass degeneration, which increases drastically above the age of 65 [2], sarcopenia can also occur in younger individuals, in whom it is secondary to a systemic condition characterized by an inflammatory response, organ failure, hormonal dysfunction and/or malignancy (induced by cardiovascular diseases, diabetes, renal insufficiency and cancer) [3].

Globally, the prevalence of severe sarcopenia is reported to range from 2% to 9% [4], and it is predicted to soar to 200 million people in the next 40 years due to population ageing [5].

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Sarcopenia considerably increases the propensity for falls and in turn bone fractures, mainly at the hip and radius, which are linked to extremely poor outcomes, such as declining physical mobility, hospitalization, decreased quality of life, increased morbidity and mortality, and growing healthcare costs [6-8]. Sarcopenia and osteoporosis are now recognized as equally significant risk factors for bone fractures, given that both loss of appendicular muscle mass and loss of bone density contribute to musculoskeletal fragility. As a result of the intrinsic muscle-bone relationship, subjects at risk of osteoporosis may develop osteosarcopenia, where both pathologies coexist, worsening the pathogenesis of fragility syndrome. It is estimated that individuals with sarcopenia have a 5- to 10-fold higher risk of developing osteoporosis and vice versa [9].

Furthermore, increasing clinical evidence shows that from 30% to 50% of subjects with distal radius and hip fractures are also affected by sarcopenia [6,10-12].

Although sarcopenia is recognized as a clinical entity, no standardized diagnostic and clinical protocols exist for its diagnosis, with the result that it often remains underdiagnosed. A further challenge is to improve methods for accurate identification of individuals at high risk of sarcopenia and osteosarcopenia, who might benefit from a therapeutic or preventive intervention [13]. Currently, tools for predicting muscle and bone status are limited to separate evaluations of these tissue compartments. While Magnetic Resonance Imaging (MRI) and computed tomography (CT) techniques are considered reference methods for measuring muscle quality for the purpose of diagnosing sarcopenia, they are limited by their high costs, lack of portability, and radiation exposure (in the case of CT). Clinicians prefer to use dual X-ray absorptiometry (DXA) for assessing muscle health due to its ability to estimate lean body mass and appendicular lean mass, which however are not reliable predictors of adverse outcomes. Moreover, DXA is limited by radiation exposure and measurement variability across manufacturers [3]. Handgrip strength, knee flexion/extension, and gait speed are commonly used to assess muscle strength and physical disability. Yet, cost-effective techniques for the early diagnosis of sarcopenia are lacking, and there is also an urgent need to find a single prognostic tool that can effectively identify musculoskeletal disorders by correlating different muscle and bone compartments.

To date, relevant clinical evidence has proven the diagnostic validity of the ultrasound-based Radiofrequency Echographic Multi Spectrometry (REMS) technology for the diagnosis of osteoporosis and prediction of fracture risk [14-16]. Interestingly, REMS can be also used in the assessment of muscle status. In this regard, the purpose here was to estimate upper limb muscle strength by developing a dedicated algorithm based on REMS ultrasound scans at the forearm. In particular, we investigated the correlation between muscle strength measured using the handgrip test versus a novel REMS-based parameter in healthy and pathological subjects affected by sarcopenia.

Methods

Study population

A total of 58 Caucasian volunteers (male and female), comprising 28 subjects identified by the clinician as affected by sarcopenia (including sarcopenia secondary to pathological conditions) and 30 healthy individuals, all aged between 34 and 48 years, were recruited for this study. Sarcopenia evaluation was carried out by means of various tools, from screening questionnaires to radiographic imaging, MRI, CT, DXA, BIA (Bioelectrical Impedance Analysis) and muscle strength (measurement of handgrip strength). The study was performed in accordance with the ethical principles of the Declaration of Helsinki and consent was obtained from all the participants.

Handgrip strength measurement

Handgrip strength was measured using an electronic hand dynamometer (EH101, Camry, Guang Dong, China) according to the instruction manual (Figure 1). Patients, using their dominant arm, were asked to squeeze the dynamometer to allow measurement of the Maximum Voluntary Contraction (MVC). This test involves use of the hand and forearm muscles. For each subject, the maximum value out of three tests was included in the analysis.

REMS acquisition of the upper limb

REMS scans were performed using the EchoStation device (Echolight S.p.a., Lecce, Italy), equipped with a 40 mm linear transducer probe operating at a nominal frequency of 10 MHz. The scans were performed with the patient in a supine resting position with the elbow joint fully extended. The linear probe was placed transversely at the proximal third of the forearm, between the styloid process and the head of the radius. During the scan, the operator followed the manufacturer's instructions, adjusting the scanning depth in such a way as to place the ulna and radius in boxes displayed on the ultrasound image. Each acquisition was monitored by a dedicated progress bar, and all REMS datasets were anonymized before analysis.

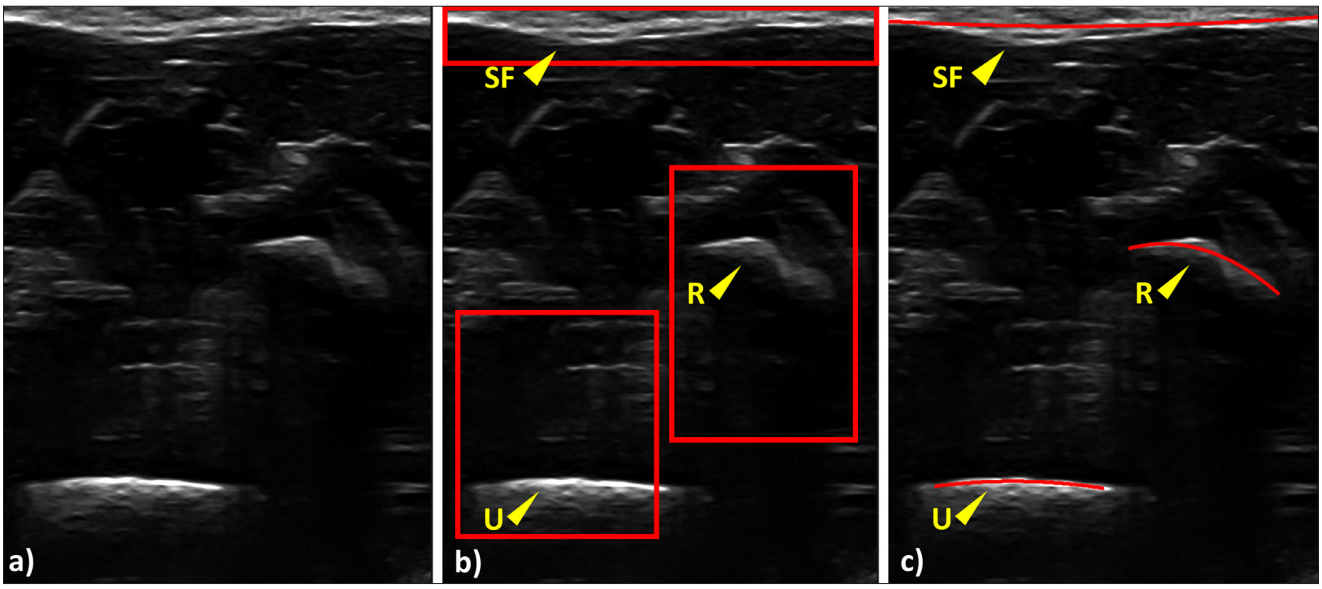
Data analysis

Imaging parameters were optimized for the identification, on the B-mode echographic images, of two regions of interest (ROIs): the ulnar and radius muscles. To this end, the ulnar bone and radius bone profiles, as well as the corresponding subcutaneous layer, were taken as the muscle boundaries. We segmented the two muscle ROIs through their boundaries, which in turn had been obtained using an ad hoc automatic segmentation algorithm based on the REMS approach previously developed for the lumbar spine [17]. In particular, raw radiofrequency signals were filtered to reduce acquisition noise and converted to grey-scale images by computing the signal envelope with the Hilbert transform (Figure 2, a). The subsequent segmentation process was designed to identify and analyze features of interest in the medical images, and the various steps ensured that the analysis was accurate and efficient.

In particular, subcutaneous fat, and the ulnar and radius bone ROIs were sought in the red boxes, whose positions have

Figure 1 Handgrip strength test. The figure shows the hand dynamometer that was used in the study.

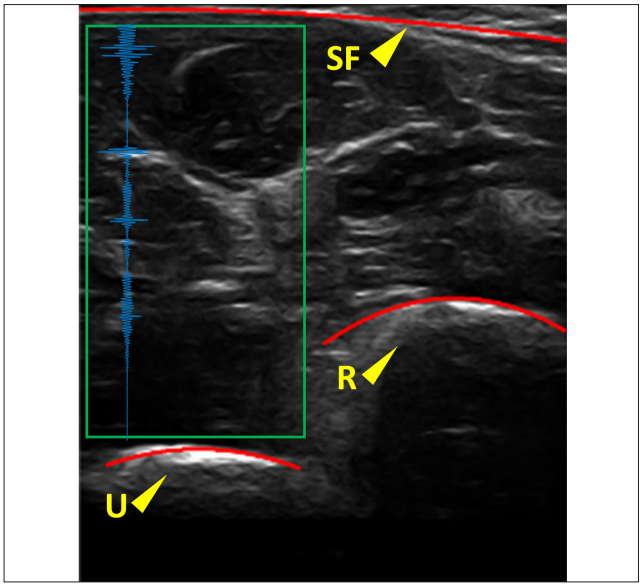
Figure 2 Image analysis: a) B-mode echographic image created from the Hilbert transform of the raw radiofrequency signals; b) identification of the region with the highest probability of containing the subcutaneous fat layer (SF) and the ulnar (U) and radius (R) bones; c) identification of the brightest structures, including ulna, radius and subcutaneous fat layer within the ROI and interpolation with a quadratic polynomial function.



been heuristically identified as the ones with the highest probability of containing them (Figure 2, b). The red boxes also appeared on the screen during the image acquisition phase, and the operator had been instructed to ensure that the structures of interest were placed within them.

Brightness masking was applied to the image within the ROIs to improve the quality and to remove any unnecessary background noise. Then, contrast enhancement and image smoothing were applied to increase the visibility of the features of interest in the image and to reduce any image artefacts. Moreover, histogram equalization, i.e., adjustment of the intensity levels of the image, was used to improve contrast and the visibility of features. Thresholding was then applied to convert ROIs from greyscale to black-and-white images. Lastly, a quadratic polynomial interpolation was fitted to the remaining pixels, so as to identify the profile of the subcutaneous fat, ulnar and radius bone (red lines in Figure 2, c). We identified the region between the fat layer and the ulnar bone as the ulnar muscle ROI (Figure 3). Images were visually checked for possible segmentation errors. Within the ROIs, REMS features, based on radiofrequency spectral analysis, and imaging features, based on gradients, co-occurrence matrices, pixels and histogram values, were computed on a sub-ROI rectangular sliding window, moving across the main ROI in horizontal and vertical directions. A linear modelling approach was used to establish a relationship between REMS spectral and imaging features considered together as covariates, and MVC values as the target variable. Through a leave-one-out approach for model selection, the number of covariates was further reduced to obtain the highest correlation between true MVC and MVCREMS values. A t-test was used to assess the difference in the anthropometric characteristics between the two groups. Correlations between true MVC versus MVCREMS were investigated by using the Pearson correlation coefficient (r) and calculating the slope of the regression line. For all statistical analyses, a p-value <0.05 was considered statistically significant.

Figure 3 MVC measurement through REMS features. Transversal ultrasound image of the forearm depicting the ulna (U), radius (R) and subcutaneous fat layer (SF) in red and the ROI used for feature extraction in green. The underlying raw ultrasound signal (i.e., the so-called radiofrequency signal) is depicted in blue for one line of sight.



Results

Study population

As shown in Table 1, anthropometric characteristics of the two groups were found to be appropriately balanced, with no observable differences between them. However, as expected, a significant difference was observed for both MVC and MVCREMS between healthy and pathological subjects.

Correlation between MVC and MVCREMS

The first scatterplot (Figure 4, a) shows the true MVC (ground truth) and the REMS-predicted MVCREMS (REMS-

based algorithm) measurements analyzed in the overall population, which resulted in a Pearson correlation coefficient of r=0.95 (p<0.0001). After stratifying the population into the two subgroups, the healthy group showed a correlation of r= 0.90 (Figure 4, b), and in a similar fashion, a significant correlation of r = 0.83 was observed between the MVC and the corresponding MVCREMS in the pathological group (Figure 4, c) (all with p < 0.0001).

Table I Anthropometric characteristics of the participants.

	HEALTHY SUBJECTS (N=30)	PATHOLOGICAL SUBJECTS (N=28)	*p*-VALUE
Age (years)	40.6 ± 3.0	41.1 ± 3.4	ns
Weight (kg)	71.9 ± 8.4	69.8 ± 8.4	ns
Height (cm)	171.7 ± 6.5	172.2 ± 5.8	ns
BMI (kg/m$^{2)}$	24.5 ± 3.3	23.5 ± 2.8	ns
True MVC (kg)	44.5 ± 6.7	25.8 ± 6.8	p<0.0001
MVC_{REMS} (kg)	43.6 ± 6.8	26 ± 7.8	p<0.0001

Values are presented as mean ± standard deviation; the difference is significant with p<0.0001 or not significant (ns) with p>0.05 between healthy and pathological subjects (t-test). **BMI**, body mass index; **MVC**, maximum voluntary contraction; **ns**, not significant.

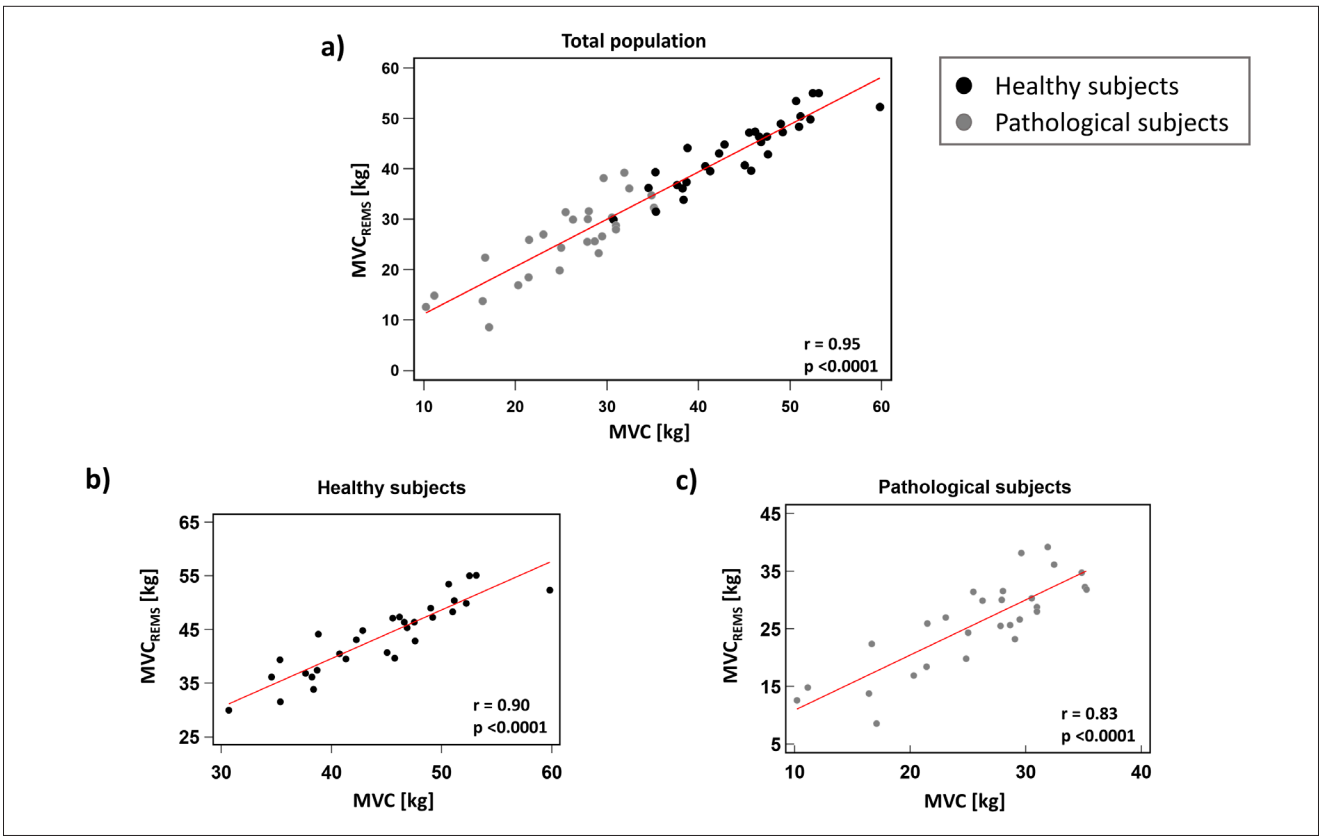
Discussion and conclusion

REMS is a versatile diagnostic tool: a previously developed algorithm applied to axial reference sites (e.g., lumbar spine and femur) could be refined and specifically tailored to assess the muscle status of the upper limb in healthy and pathological populations. In this study, we were able to show that REMS can estimate the muscle strength of the dominant forearm by using, as predictors, features derived from automatic analysis of echographic datasets acquired at this anatomical site.

The European Working Group on Sarcopenia in Older People recommended, among others, the handgrip strength test as a screening method in clinical routine practice as it is a valid predictor of muscle disability and closely correlates with other muscle districts, including the lower limbs [18]. Here, the proposed REMS-based approach showed a high correlation with dynamometric measures derived from the handgrip test in both groups, confirming that this method is suitable in primary care and represents a reliable alternative to the handgrip test. It is worth noting that although, in the literature, handgrip strength [19,20] evaluation is one of the diagnostic criteria for the identification of mobility limitation and sarcopenia, it may present some limitations, since sarcopenia evaluation involved different modalities and tools.

As expected, a clear distinction was observed between the subgroups, reflecting the functional muscle strength status of the two categories. Indeed, the pathological group showed low MVC compared with the higher MVC values that typically characterize normal muscle strength [21-23].

Figure 4 Correlation analysis of the MVC measured by handgrip test (MVC) and MVCREMS (MVC predicted using the REMS-based algorithm): a) total population; b) healthy subjects; c) pathological subjects. Pearson correlation coefficient was r=0.95 for the total population, r=0.90 for healthy subjects (black dots), and r=0.83 for pathological subjects (grey dots) with p< 0.0001 for all groups. The slope of the regression lines for each graph were 0.94, 0.91 and 0.96, respectively.



The strength of the correlation between the two methods was found to be slightly lower in the pathological subjects (r=0.83) than in their healthy counterparts (r=0.90), a difference that may be explained by a greater dispersion of data points presumably due to the patients' clinical histories and clinical factors.

Given its non-invasiveness, portability, inexpensiveness, operator-independence and user-friendliness, REMS could be a valid alternative to other imaging techniques (e.g., DXA, CT, MRI) for assessing muscle strength and sarcopenia.

The muscle mass reduction typical of sarcopenia is caused by a reduction in the number of myofibers, which also become hypotrophic, together with marked fat infiltration (myosteatosis) [24]. In this regard, the REMS approach has the advantage of being able to automatically visualize, localize and identify atrophy in affected muscles, since hyperechogenicity reflects muscle alterations that are strong predictors of poor function and physical performance in underlying musculoskeletal pathologies, including sarcopenia [25].

Past reports evaluated the association between handgrip strength and ultrasound-measured morphological features of the ulna and radius, but found poorer correlation outcomes than those of the present study [26-28]. This proof-of-concept study implemented a new REMS-based methodology that aims to target all populations affected by musculoskeletal disorders. The performance of the REMS model in distinguishing between patients with normal and poor muscle strength will be verified in further studies, also in comparison with other imaging techniques (e.g., MRI). Because it is currently not clear which is the best anatomical site for sarcopenia diagnosis, dedicated investigations focusing on other muscle districts (e.g., rectus femoris) are ongoing, with the aims of reliably predicting total skeletal muscle mass and accurately screening categories at risk of sarcopenia. Once thoroughly refined, REMS will provide a dual assessment of muscle and bone health status, paving the way for the development of an integrated approach that, through a single safe and efficient US scan, will provide a comprehensive musculoskeletal examination.

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The Conflict of Interest Statement: *Conversano F. and Casciaro S. owns stocks of Echolight Spa. All remaining authors have no competing interests to declare.*