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Panoramic ultrasound: a novel and valid tool for monitoring change in muscle mass

Jessica M. Scott[1]*, David S. Martin[2], Robert Ploutz-Snyder[1], Timothy Matz[3], Timothy Caine[2], Meghan Downs[4], Kyle Hackney[5], Roxanne Buxton[4], Jeffrey W. Ryder[1] & Lori Ploutz-Snyder[1]

[1]*Universities Space Research Association, Houston, TX, USA;* [2]*KBRwyle, Houston, TX, USA;* [3]*MEI Technologies, Houston, TX, USA;* [4]*University of Houston, Houston, TX, USA;* [5]*North Dakota State University, Fargo, ND, USA*

Abstract

Background The strong link between reduced muscle mass and morbidity and mortality highlights the urgent need for simple techniques that can monitor change in skeletal muscle cross-sectional area (CSA). Our objective was to examine the validity of panoramic ultrasound to detect change in quadriceps and gastrocnemius size in comparison with magnetic resonance imaging (MRI) in subjects randomized to 70 days of bed rest (BR) with or without exercise.

Methods Panoramic ultrasound and MRI images of the quadriceps and gastrocnemius muscles were acquired on the right leg of 27 subjects (26 male, 1 female; age: 34.6 ± 7.8 years; body mass: 77.5 ± 10.0 kg; body mass index: 24.2 ± 2.8 kg/m^2; height: 179.1 ± 6.9 cm) before (BR-6), during (BR3, 7, 11, 15, 22, 29, 36, 53, 69), and after (BR+3, +6, +10) BR. Validity of panoramic ultrasound to detect change in muscle CSA was assessed by Bland–Altman plots, Lin's concordance correlation coefficient (CCC), sensitivity, specificity, positive predictive value, and negative predictive value.

Results Six hundred ninety-eight panoramic ultrasound CSA and 698 MRI CSA measurements were assessed. Concordance between ultrasound and MRI was excellent in the quadriceps (CCC: 0.78; $P < 0.0001$), whereas there was poor concordance in the gastrocnemius (CCC: 0.37; $P < 0.0006$). Compared with MRI, panoramic ultrasound demonstrated high accuracy in detecting quadriceps atrophy and hypertrophy (sensitivity: 73.7%; specificity: 74.2%) and gastrocnemius atrophy (sensitivity: 83.1%) and low accuracy in detecting gastrocnemius hypertrophy (specificity: 33.0%).

Conclusions Panoramic ultrasound imaging is a valid tool for monitoring quadriceps muscle atrophy and hypertrophy and for detecting gastrocnemius atrophy.

Keywords Panoramic ultrasound; Magnetic resonance imaging; Hypertrophy; Atrophy; Disuse

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**Correspondence to: Jessica Scott, PhD, Exercise Physiology and Countermeasures, Mail Code SK, NASA Johnson Space Center, 2101 NASA Parkway, Houston, TX 77058, USA. Phone: 281-483-8398, Fax: 281-483-4181, Email: jessica.m.scott@nasa.gov*

Introduction

Muscle mass loss affects patients with chronic diseases such as cancer, heart failure, and chronic obstructive pulmonary disease and millions of apparently healthy adults over the age of 70.[1–7] Moreover, muscle atrophy can develop independent of disease and aging through immobilization and reduced physical activity.[8] Assessment of muscle cross-sectional area (CSA) is used clinically to assess lean tissue mass[9] and has been shown to independently predict survival, the risk of treatment failure, hospital re-admission, and cancer therapy-induced toxicity.[2,3,10] Importantly, recent findings suggest that skeletal muscle measurements assessing change in muscle size over time may improve prognostication over a single time point assessment.[11–13] The strong association between reduced muscle size and morbidity and mortality, together with the urgent need for interventions that can increase muscle size, creates a compelling rationale to examine simple techniques that can monitor bidirectional change in skeletal muscle CSA.

Current muscle mass screening and monitoring guidelines recommend the use of computerized axial tomography (CT) or magnetic resonance imaging (MRI).[14,15] Evaluation of muscle CSA with these tools requires specialized equipment and is time-consuming and expensive, and repeated measurements with CT are not considered safe given the high radiation dose.[16] Accordingly, complementary tools are required to efficiently monitor change in muscle CSA. Ultrasonography, like MRI, makes clear distinctions between muscle and subcutaneous fat tissues and is a technique that is safe (no ionizing radiation) and portable.[17,18] To date, although conventional ultrasound has been used to assess the thickness of small individual muscles,[19–21] to accurately characterize and monitor change in muscle size, it is imperative to quantify the entire muscle CSA.[22,23]

Advances in ultrasound technology and the development of panoramic scanning allow quick and automatic construction of cross-sectional images of muscles. Our group recently reported that panoramic ultrasound images can be reliably assessed for individual thigh and calf muscle groups and that compared with MRI, panoramic ultrasound is a valid technique to evaluate muscle CSA.[24] However, whether panoramic ultrasound could be used to quantify muscle atrophy and/or hypertrophy is unknown. Therefore, as a prespecified substudy of a randomized trial investigating the efficacy of exercise training to mitigate bed rest (BR)-induced deconditioning, we examined the validity of panoramic ultrasound to detect changes in quadriceps and gastrocnemius CSA in comparison with MRI in subjects undergoing 70 days of BR with or without exercise.

Methods

Subjects

Twenty-seven subjects (26 male, 1 female; age: 34.6 ± 7.8 years; body mass: 77.5 ± 10.0 kg; body mass index (BMI): 24.2 ± 2.8 kg/m^2; height: 179.1 ± 6.9 cm) completed 70 days of BR. In brief, subjects were recruited and screened according to standard National Aeronautic and Space Administration Flight Analogs Project procedures.[25] Briefly, subjects with a history of cardiovascular disease, a BMI outside of 21–30, or musculoskeletal injury that could affect exercise performance or expose the subject to an increased risk of injury were excluded from the study. To simulate spaceflight, subjects were confined to 6° head down tilt BR for the entire 70 days,[26,27] including personal hygiene activities. Diets were eucaloric and strictly controlled (55% carbohydrate, 30% fat, and 15% protein). Eighteen subjects were randomly assigned to exercise training, and nine remained sedentary. All study procedures were reviewed and approved by National Aeronautic and Space Administration Johnson Space Center and University of Texas Medical Branch institutional review boards. All subjects signed a written informed consent prior to the initiation of any study-related procedures.

General procedures

Both MRI and ultrasound images were acquired on the right leg in the morning before (BR-6), during (BR3, 7, 11, 15, 22, 29, 36, 53, 69), and after (BR+3, +6, +10) BR. The quadriceps including vastus medialis, vastus intermedius, vastus lateralis, and rectus femoris and gastrocnemius including medial gastrocnemius and lateral gastrocnemius were assessed (*Figure* 1A–1C). During both ultrasound and MRI scanning, subjects lay in a relaxed and identical position with feet strapped into a MRI-compatible footplate.[28] For the purposes of this investigation to compare MRI and ultrasound images, oil-filled capsules visible on MRI images were taped to the skin at each ultrasound template slice.

Image acquisition

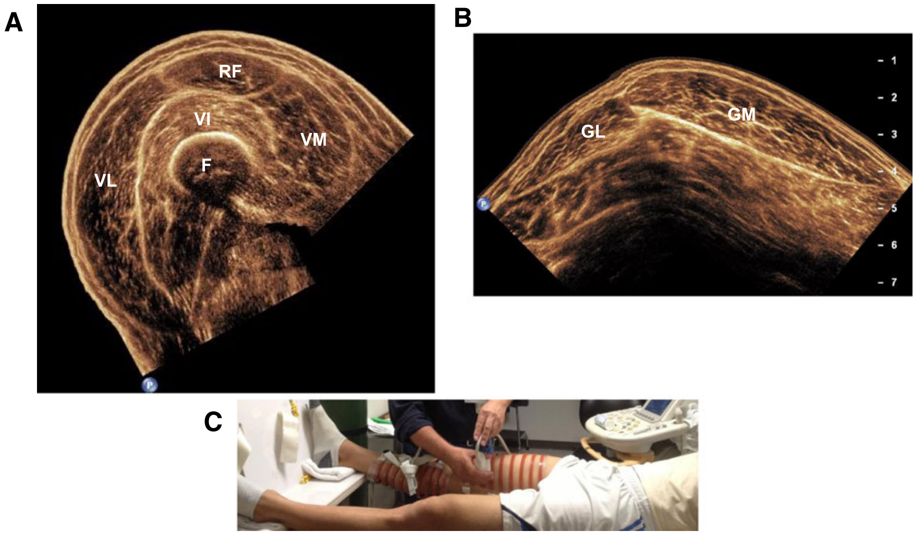
As previously described, B-mode axial-plane ultrasound (iE33, Phillips, USA) images were acquired with a 9 MHz linear array probe (60 mm width) in panoramic mode by a trained sonographer.[24] Depending on subject leg length, one of three thighs and one of three calf templates were used (small, medium, or large). Templates consisted of five to eight 2 cm slices with a 1 cm gap between slices with four straps to fix the template in place and slid easily onto subjects' legs.[24] To ensure that the ultrasound template placement was the same at each time point, the distance from the footplate to the ultrasound template was measured during the first session and reproduced at subsequent sessions. A consistent, minimal pressure was applied with the probe to the skin to avoid compression of the muscle, and transmission gel was applied to improve acoustic coupling. No visually identifiable muscle compression could be detected on the scans. Total scanning time to acquire upper and lower leg images was approximately 40 min.

Axial spin-echo T2-weighted MRI images were acquired from the level of the ankle mortise to the iliac crest while subjects lay supine in a 3T scanner (Signa Horizon LX, General Electric, USA). Images of the upper and lower leg were collected by using a repetition time of 2000 ms, echo time of 51 ms, slice thickness of 10 mm, and a gap between slices of 10 mm. A matrix size of 512 × 512 was used for all scans, and the field of view was varied to maximize in-plane resolution for each scan.

Image analysis

MRI and ultrasound images from all subjects (ultrasound: MATLAB, Mathworks, USA; MRI: IMAGEJ, National Institutes of

Figure 1 Sample ultrasound muscle images of one slice of (A) quadriceps, (B) gastrocnemius, and (C) ultrasound template set-up. Images were acquired in one motion in order to capture all quadriceps muscles [vastus medialis (VM), rectus femoris (RF), vastus lateralis (VL), vastus intermedius (VI)] and both gastrocnemius muscles [gastrocnemius medialis (GM), gastrocnemius lateralis (GL)]. The femur (F) is also visible in the thigh.



Health, USA, version 1.42) were manually traced as previously described.[18,24,29] This is a highly reliable technique with inter-experimenter reliability (coefficient of variation) of 2.4 to 4.1% and intraclass correlation coefficient of 0.963 to 0.991 for panoramic ultrasound and inter-experimenter coefficient of variation of 2.8 to 3.8% and intraclass correlation coefficient of 0.946 to 0.986 for MRI.[24] The average of analysed slices was used to calculate CSA.[24,29]

Statistical analysis

All statistical analyses were performed by using by STATA, IC software (v 14.1, StataCorp LP, College Station, TX) setting two-tailed alpha to reject the null hypothesis at 0.05. Our purpose was to compare the validity of panoramic ultrasound vs. the reference MRI for detecting change in muscle CSA; therefore, subjects' pre-BR (BR-6) ultrasound and MRI data were subtracted from each longitudinal measure collected during (BR3, 7, 11, 15, 22, 29, 36, 53, 69) and after (BR+3, +6, +10) BR for these analyses. Data from the two groups were combined for these analyses, thereby increasing the variability of change among the entire subject pool.

We present the results of 95% limits of agreement in Bland–Altman plots by using bootstrapped standard error estimates to accommodate the multiple measurements within subjects. Bland–Altman plots display the difference between MRI and ultrasound CSA measures along the *Y*-axis vs. the range of the average of MRI and ultrasound observations along the *X*-axis, with the average and 95% limits of agreement.[30] The concordance in absolute change in CSA from BR-3 measured by ultrasound and MRI was assessed by Lin's concordance correlation coefficient (CCC),[31] also with bootstrapped standard errors to adjust for the longitudinal experimental design. A CCC value of 1 indicates perfect agreement; values $<$0.5 were considered to be poor agreement, values between 0.5 and 0.7 to be moderate agreement, and values $>$0.7 to be excellent agreement.[32] Additionally, MRI and ultrasound change scores were dichotomized into atrophy or hypertrophy, enabling us to examine accuracy of ultrasound in assessing directional change compared with the clinical reference of MRI. Sensitivity was defined as the percent of true muscle atrophy observations (per MRI reference) that ultrasound identified; specificity was defined as the percent of true muscle hypertrophy observations that ultrasound identified. Positive predictive value was defined as the number of true atrophy (per MRI reference) cases divided by the number of ultrasound-estimated atrophy cases, which includes true atrophy and falsely estimated atrophy observations. Negative predictive value was defined as the ratio of true hypertrophy cases divided by ultrasound-estimated hypertrophy cases, which includes true hypertrophy and falsely estimated hypertrophy observations.

Results

All ultrasound and MRI images were of high quality and were included in the analysis. Two subjects did not complete BR +10 testing, and one subject did not complete BR+6, resulting in analysis of 698 ultrasound CSA measurements and 698 MRI CSA measurements. Bland–Altman analyses indicated that ultrasound and MRI measuring techniques were in close agreement for the quadriceps and gastrocnemius (*Figure* 2A and 2B). The mean-of-all difference lines were near 0, indicating no systematic deviation between the measured values of the two techniques. Furthermore, the limits of agreement indicated that 95% of all measured differences lie within 5 cm^2 for the quadriceps and 3 cm^2 for the gastrocnemius. There was excellent agreement between ultrasound and MRI in the quadriceps (CCC: 0.78; $P < 0.0001$; *Figure* 3A). In contrast, there was poor agreement between ultrasound and MRI in the gastrocnemius (CCC: 0.37; $P < 0.0006$) (*Figure* 3B). Ultrasound demonstrated high sensitivity and specificity in the quadriceps and high sensitivity and low specificity in the gastrocnemius (*Table* 1).

Discussion

The principal new findings from this study are that panoramic ultrasound imaging is a valid tool for monitoring quadriceps muscle atrophy and hypertrophy and that panoramic imaging can be used to detect gastrocnemius atrophy. This promising tool provides, for the first time, a low-cost, radiation-free, and portable approach to monitoring change in leg muscle size.

Data from a growing number of studies indicate that assessing change in muscle mass may improve prognostication over a single time point assessment.[11–13] For example, in 123 patients with ovarian cancer, Rutten *et al.*[33] reported that a decrease in skeletal muscle mass during neoadjuvant chemotherapy was an important prognostic factor for overall survival (hazard ratio: 1.77, 95% CI: 1.02–3.09, $P = 0.043$), whereas a single time point assessment revealing low muscle mass did not predict overall survival. Similarly, median overall survival was significantly associated with change in muscle CSA ($P = 0.04$), but not muscle CSA at baseline ($P = 0.49$), in 35 patients with non-small cell lung cancer.[13] Thus, monitoring skeletal muscle CSA over time may be critical for improving prognostication and enabling the implementation of appropriately timed nutrition,[34] exercise,[35] and/or pharmacological[36] interventions.

Evaluation of muscle CSA with current imaging techniques (i.e. dual-energy X-ray absorptiometry, MRI, CT) is time-consuming, expensive, may involve exposure to low-dose radiation, and requires large, specialized equipment.[16] Moreover, although CT scans are often readily available for patients with cancer, the widely applied analysis of one slice

Figure 2 Bland–Altman plot of the difference between MRI and ultrasound measures of (A) quadriceps and (B) gastrocnemius.

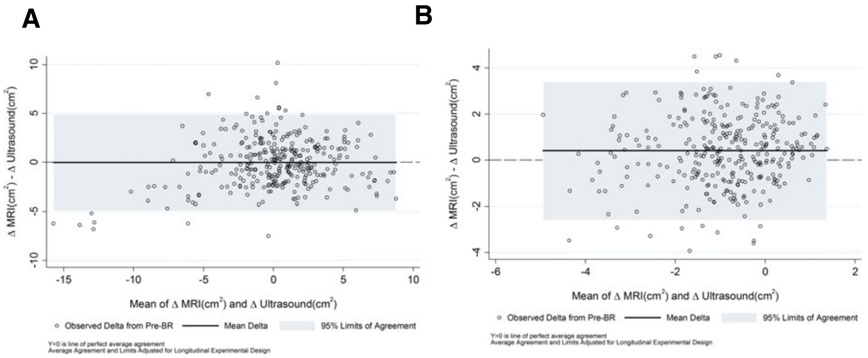


Figure 3 Concordance plot of the difference between MRI and ultrasound measures of (A) quadriceps and (B) gastrocnemius.

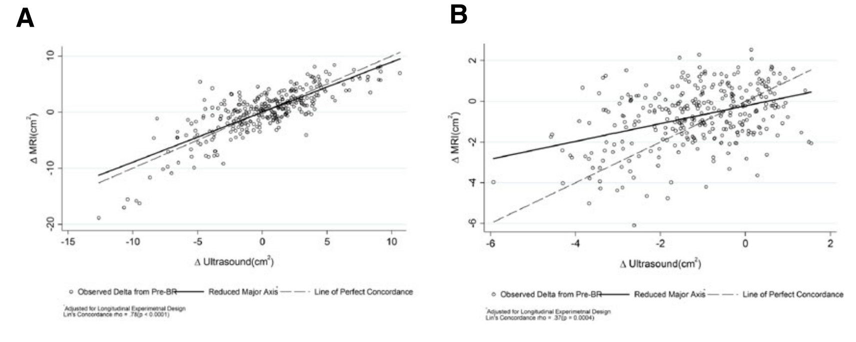


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Table 1 Sensitivity, specificity, positive predictive value, and negative predictive value of panoramic ultrasound

	Sensitivity	Specificity	PPV	NPV
Quadriceps	73.7%	74.2%	66.7%	80.0%
Gastrocnemius	83.1%	33.0%	72.5%	47.9%

PPV, positive predictive value; NPV, negative predictive value.

at the third lumbar vertebra[16,37] may only have utility for large group comparisons[37] and has limited applicability to functional muscle groups.[38] Quadriceps muscle size, strength, and endurance are recognized as underlying much of the decreased exercise capacity and increased risk of morbidity and mortality in patient populations.[39] The role of the quadriceps has also been well characterized with respect to performance of tasks of everyday living, and functionally relevant thresholds have been developed.[40] Calf muscle size and function are also important contributors to balance, and low calf muscle size and strength are associated with disabling falls.[41] Accordingly, quantifying change in leg muscle CSA by using a simple technique may have significant clinical utility.

Recent findings from our group,[24] and others,[18,23,42] indicate that panoramic ultrasound is a promising method to measure leg muscle CSA. Of import, all studies to date have evaluated the validity of panoramic ultrasound at one time point[23] or assessed hypertrophy with exercise training in a single muscle.[42] In the current study, we developed a procedure whereby repeated panoramic ultrasound measurements of quadriceps and gastrocnemius muscles could be acquired, a far more relevant measurement for both clinical and research settings.[16] In particular, we utilized leg templates to (i) ensure precise ultrasound probe placement; (ii) assist the sonographer with maintaining a continuous medial to lateral motion thus limiting acquisition errors; (iii) acquire multiple CSA slices across the leg to decrease measurement error[43]; and (4) allow comparison of scans over time.

Findings from the present investigation indicate that there is high concordance between MRI and panoramic ultrasound for quadriceps muscles, a finding that was not extended to the gastrocnemius. This disparity may, in part, be due to the smaller muscle size in the gastrocnemius than in the quadriceps, where a change in the smaller muscle results in a greater relative difference. We meticulously measured ultrasound template placement and acquired MRI images at anatomical landmarks; however, a 1 mm error in placement could result in large variances in distal gastrocnemius muscle CSA. Additionally, the distal quadriceps slices were approximately 50 cm^2, and previous research has shown that the larger surface of the thigh may allow for more accurate and repeatable muscle scanning.[23] We also examined the ability of ultrasound as a diagnostic tool to detect muscle atrophy and hypertrophy where they are defined simply as a muscle decreasing or increasing in size without regards to the magnitude of change. The calf measurement was sensitive with an 83% likelihood of correctly identifying atrophy and lower accuracy (33%) in identifying hypertrophy. For the quadriceps, a different pattern was observed: Ultrasound showed both a specificity and sensitivity of 74% suggesting that it is equally useful in identifying atrophy and hypertrophy. Thus, panoramic ultrasound is a valid and accurate tool for monitoring quadriceps muscle atrophy and hypertrophy, and it can accurately identify gastrocnemius atrophy.

Limitations

The limitations of our study require consideration. First, our study population consisted of healthy subjects ranging from small muscle CSA to large muscle CSA; however, the ultrasound field of view in patients with a high BMI (>30 kg/m^2) may not be sufficient to accurately quantify leg muscle CSA. Previous studies have shown that a high amount of subcutaneous adipose tissue limits border definition.[44,45] Second, whether lower body muscle CSA assessed by ultrasound correlates to the clinical standard of whole body muscle mass or clinical outcomes is unknown. Prospective trials investigating the relationship between lower body muscle CSA and total body muscle mass across the age continuum and in clinical settings are needed. Third, the feasibility of acquiring muscle CSA in the clinical setting is unknown. However, the ultrasound templates were designed to easily don and remove, and acquisition time could be reduced by acquiring CSA of only the upper or lower leg to accommodate patient comfort. Moreover, given the importance of lower leg muscle for activities of daily living,[39,40] future research should assess whether a single slice of the mid-quadriceps could provide incremental prognostic information beyond a single slice at the third lumbar vertebra from CT imaging. Fourth, among the compartments that can be distinguished with ultrasound are muscle and subcutaneous adipose tissue. We did not assess subcutaneous adipose tissue; future studies are required to examine the validity and reliability of analyzing subcutaneous adipose tissue with ultrasound. Finally, we assessed muscle quantity, whereas the functional capabilities of muscle are a reflection of both quantity and quality. Muscle quality may be altered as a result of muscular infiltration of non-contractile elements such as intramuscular adipose and fibrous tissue.[46] Several investigations have found that evaluation of muscle quality by using ultrasound echogenicity may reflect increased adipose and/or fibrous tissue within muscle[47] and that echogenicity is related to muscle strength.[48,49] It is foreseeable that images obtained from panoramic imaging could be used to evaluate both muscle quantity and quality. Accordingly, a novel area for future work is to examine the feasibility and clinical utility of combining panoramic imaging and evaluation of echo intensity.

Conclusions and implications for practice and research

Loss of muscle mass is a major contributor to the morbidity and mortality of numerous patient populations.[1] As such, techniques that can monitor change in skeletal muscle size are of utmost importance. Our findings have several important implications for application and future research. First, ultrasound is a safe (no ionizing radiation) and portable technique that can be used at the bedside and in remote environments. To this end, panoramic ultrasound is currently being used to monitor leg muscle size in astronauts during long duration spaceflight, an environment where extensive muscle atrophy may occur.[50] Second, acquisition of panoramic images is a straightforward technique that could be used at primary care centres. After several ultrasound training sessions on the ground, astronauts are adept at acquiring panoramic images in microgravity. Third, our results indicate that panoramic ultrasound imaging is a valid and feasible tool for assessing change in upper leg muscle size and that ultrasound can detect calf muscle atrophy. Additional research is required to assess applicability and feasibility of panoramic ultrasound in clinical populations. To this end, external and prospective validation of these findings in other cohorts is imperative in order to assess the utility of panoramic ultrasound to reflect whole body mass, detect change in muscle size for risk stratification, and for the design and optimization of interventions.

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Conflict of interest

None declared.

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