Department of Veterans Affairs

Memorandum

Date: May 20, 2016

From: Dr. Michael Harris-Love, Clinical Research Center, DC VAMC

Subject: **Manuscript resubmission**

To: Editor and Peer Reviewers
PeerJ – Medicine

Dear Editor and Peer Reviewers:

Please accept the attached resubmitted manuscript, "Interrater reliability of quantitative ultrasound using force feedback among examiners with varied levels of experience," (#9967) for your consideration for publication in *PeerJ – Medicine.*

The authors have discussed the editor and reviewer reports, and revised the manuscript based on the provided feedback. The revisions are provided in the submitted tracked-changes and standard versions of the manuscript, and featured in the response letter appendix appended below.

In this revised manuscript, my co-authors and I report on the interrater reliability of force feedback scanning. Our initial findings suggest that this form of enhanced sonography may aid the reliability of morphometry measures across a range of examiner scanning forces, and perhaps allow for consistent performance among examiners with differing levels of experience.

Please note that all authors approve of the current version of the manuscript, agree with its resubmission to *PeerJ,* and do not have any conflicts of interest. Furthermore, all authors affirm authorship responsibility and report no financial disclosures or other conflicts of interest affecting the said work. This project was approved by the DC VAMC Research and Development Institutional Review Board (IRB; #01671). This manuscript has not been previously published and is not under review at any other scientific journal, and no external permissions are required to publish the tables or figures associated with our manuscript.

Thank you for facilitating the peer review of our work, and for considering our resubmitted work for publication in *PeerJ.*

Regards,

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Editor/Reviewer Comments & Author Response

Authorship

Authors Catheeja Michael Ismail, Paula Woletz, Valerie McIntosh, Bernadette Adams and Marc R Blackman still need to confirm their co-authorship using the email they received from *PeerJ*. Please ask them to check their spam folders.

The corresponding author has complied with this request. Some of the authors have not been successful in confirming their authorship upon following the previously provided link. We are actively working with the *PeerJ* editorial staff to resend the authorship invitation.

Tables

1) In addition to any tables embedded directly in your text manuscript, please also upload the tables in separate Word documents here <https://peerj.com/manuscripts/9967/files> as these will be used in production. [note: Tables should not be a .jpg or .pdf image of a table pasted into the Word document.]

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#1 and #2 completed.

Figures

1) Please use numbers to name your files, example: Fig1.eps, Fig2.png.

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4) Figures should be at least 900 by 900 pixels (without unnecessary white space around them).

#1 through #4 completed.

1a. Additional clarification is required on some aspects of the image acquisition process and how this was actually performed … (Editor + Reviewer #1)

1b. …the lack of difference between the levels of expertise … wasn't a main aim of the study. (Reviewer 2)

The authors largely agree with the critique as summarized above.

Reviewer #2's critique was based on the number examiners within each subgroup and the potential power issues introduced due to the modest number of examiners. It is important to point out that many clinical and technical papers concerning reliability feature a small number of examiners. This is – in part – due to pragmatic reasons, but it is also because the analyses regarding reliability studies are bolstered by the number of recorded observations. In the case of this study, the analyses are based on the 60 material thickness measures obtained by the examiners, and the additional 10 reference measures obtained using the KUKA LWR. Nevertheless, we do agree that the issue of examiner experience is secondary to the overall reliability of the manual force-control image acquisition method. While we demonstrate that each examiner (regardless of experience) attains good criterion-based reliability, we do not subject the *differences* among the subgroups to statistical analysis. Consequently, editing the 'purpose statement' at the end of the introduction section allowed for us to revise the hypothesis statement to more fully incorporate the priorities reflected in our statistical analyses (without changing the intent of the study). In addition, we were able to be responsive to the critique of Reviewer #1 by succinctly adding some additional detail concerning the methods used in the study throughout the manuscript.

Revised, Ln 90-108:
In this study, we determine the reliability of force-feedback image acquisition and morphometry over a range of examiner-generated forces using a muscle tissue-mimicking ultrasound phantom. We obtained reliability estimates for feedback-enhanced sonography using two methodological approaches. First, interrater reliability among the six examiners was determined based on material thickness measures obtained using manual force-feedback scanning and a series of applied force targets. Second, the criterion-based reliability of material thickness measures was determined by comparing the values obtained from each examiner using manual force-feedback scanning with the values obtained with robot-assisted force feedback scanning. We hypothesized that the manual force-feedback image acquisition method would yield reliable morphometry measures among the examiners, and in comparison to the criterion values obtained using robot-assisted image acquisition. In addition, we posited that the examiners would exhibit similar criterion-based reliability for morphometry measures, independent of experience level.

Revised, Ln 174-176:
Consequently, an *a priori* decision was made to use applied stress conditions during all scanning procedures in this study with target forces ranging from 1 N to 10 N, with image capture occurring at 1 N increments.

2. My main criticism that I believe need editing is that the section explaining the automated image acquisition needs to be improved. I suggest that the paragraph … should be prefaced with a sentence explaining what this process is required for (i.e., to create criterion referenced measures for comparison). (Reviewer 1)

Revised, Ln 139-239:
We appreciate the opportunity to address the concern raised by the Reviewer. Additional subheadings and paragraph breaks were incorporated to add clarity to the text within the Methods section. Also, procedural details were added to the subsections concerning the image acquisition methods:

Force Feedback Ultrasound Materials and Approach

All images used in this study were obtained via B-mode scanning using a portable ultrasound machine (SonoSite M-Turbo 1.1.2; SonoSite, Inc., Bothell, WA, USA) with a 13.6 MHz linear array transducer. The ultrasound machine was operated using its default gain levels and the "musculoskeletal" scanning factory preset. The transducer was fitted with a custom interface housing designed with SolidWorks software (version 2014 x64; Dassault Systèmes SolidWorks Corp., Waltham, MA, USA) that accommodated both the transducer and a load cell (Figure 1). This design allowed for the detection of examiner forces while ensuring unimpeded transducer contact with the scanned material. The ultrasound transducer interface housing was comprised of acrylonitrile butadiene styrene (ABS) and printed using an Objet500 rapid prototyping machine (Stratasys Ltd., Eden Prairie, MN, USA). Scanning force feedback was performed using a FC22 compression load cell (Measurement Specialties, Hampton, VA, USA) for axial force measurement. This load cell features a force detection capability up to 44.5 N ± 0.5 N with non-linearity, hysteresis, and repeatability characteristics of ± 1%. Applied forces detected by the load cell generated signals that were sent to a laptop computer (Latitude; Dell Corp., TX, USA) through a USB port via an Arduino Uno microcontroller (Arduino LLC; www.arduino.cc). Analog signals generated by the load cell were connected to the microcontroller analog output directly without an amplifier. The microcontroller sends the force signals to the computer as a series of serial strings by using the USB port as a virtual serial port. The graphical user interface (GUI) used during the force feedback scanning was developed with C++ programing language (Microsoft, Redmond, Washington, USA) to facilitate calibration of the load cell and allow for the viewing of real-time force values during data collection. The force-feedback transducer interface system was used during all manual and automated scanning featured in this study.

Clinical sonographers have been observed (Gilbertson & Anthony, 2013) applying variable axial forces when performing diagnostic ultrasound examinations at the abdomen with mean values ranging from 5 N to 14 N. These high forces are often required to manipulate the relative position of superficial anatomic structures in order to obtain optimal scans of deeper tissues. In contrast, practitioners using musculoskeletal quantitative ultrasound techniques often require minimal examiner forces which may be as low as 1 N in order to minimize tissue deformation during scanning (Ishida & Watanabe, 2012). Consequently, an *a priori* decision was made to use applied stress conditions during all scanning procedures in this study with target forces ranging from 1 N to 10 N, with image capture occurring at 1 N increments. The force targets were randomized for each examiner to minimize order effects on the scanning technique and the material deformation measures (VassarStats random number generator) (Lowry, 2004). A calibration adjustment was completed before each scan to account for the weight of the transducer, interface housing and components, and cord connecting the transducer to the ultrasound machine.

Manual force feedback image acquisition. Manual scanning of the ultrasound phantom by the six examiners was performed using an augmented transducer for the provision of real-time force feedback.

Each examiner began scanning following the positioning of the ultrasound phantom and application of water-soluble transmission gel. The examiners operated the ultrasound machine within view of the laptop computer with the GUI featuring the real-time force control levels. Examiners attempted to exert the targeted axial force through the transducer and onto the ultrasound phantom surface without incurring any pitch or roll of the device. Image capture occurred when the GUI on the laptop computer indicated attainment of the target force (± 0.5 N), and material thickness measurements were obtained using the Sonosite ultrasound machine digital caliper measurement function. Digital caliper measures were taken at the midpoint of the region of interest, within the simulated fascial planes of the ultrasound phantom, starting from the superior fascial plane to the inferior fascial plane. Each image capture and digital caliper measure was obtained three times. Every examiner repeated this process 10 times in order to acquire the images for each target force application condition (a 1 N to 10 N range using 1 N increments). The mean values obtained for the longitudinal images were used for the subsequent analyses. A total of 60 material thickness measures were acquired following the manual scanning procedures by the six examiners.

Robot-assisted image acquisition. Robot-assisted scanning of the ultrasound phantom by a bioengineer and sonographer was performed for the sole purpose of generating reference values for the criterion-based reliability analysis.

Automated image acquisition and transducer positioning were performed with the KUKA Light Weight Robot (LWR). The KUKA LWR (Kuka Inc., Augsburg, Bavaria, Germany) has multiple joints that are equipped with position and joint torque sensors (Archila Diaz, Suell & Noronha Castro Pinto, 2010). Each joint of this portable robot is driven by compact brushless motors via harmonic drives, which allow for 7 degrees of freedom with an estimated motion error of ± 0.05 mm. The total weight of the robot is approximately 16 kg, with a rated payload of 7 kg. The force-feedback transducer interface housing features an adapter that allowed for the external device and the transducer to be connected to the KUKA LWR end effector (Figure 2). This feature of the design allowed for the investigators to monitor the force imposed by the robotic arm, and maintain measurement consistency between the manual and robot-assisted scanning sessions. The gravity compensation mode of the robot was used to manually place the machine in close proximity to the transducer and ultrasound phantom. The position control mode was then selected after the robot was locked into the testing location.

The robot-assisted scanning session began following the positioning of the ultrasound phantom and application of water-soluble transmission gel. Scanning involving the KUKA LWR required the bioengineer to operate the robotic arm to position the augmented transducer on the ultrasound phantom surface. Using transducer and ultrasound phantom positioning similar to the manual image acquisition sessions, the bioengineer attempted to exert the targeted axial force through the transducer onto the ultrasound phantom surface by incrementally moving the robot arm using the KUKA LWR control panel. The bioengineer ceased the movement of the robotic arm and transducer when the GUI on the laptop computer indicated attainment of the target force (± 0.5 N).

The sonographer's tasks were coordinated with the efforts of the bioengineer. Once the bioengineer completed the positioning of the robotic arm and transducer, the sonographer (C.I.) initiated the image capture procedure. The sonographer operated the ultrasound machine (without manipulating the transducer) within view of the laptop computer with the GUI featuring the real-time force control levels. The sonographer confirmed the attainment of the target force (± 0.5 N) per the GUI on the laptop computer, verified that the image did not contain artifacts, and then captured the image within the field of view. Following each image capture, the sonographer used the Sonosite ultrasound machine digital caliper measurement function to obtain material thickness measures. In a similar manner to the manual scanning sessions, the image capture and digital caliper measures were obtained three times. The bioengineer and sonographer repeated this process 10 times in order to acquire the images for each target force application condition (a 1 N to 10 N range using 1 N increments). Following these scanning procedures, a total of 10 material thickness measures were acquired using the robot-assisted procedure to obtain the reference values used for the criterion-based reliability analysis.

3. … I believe it might be worth spending sometime on trying to figure out how this might have some transmission to practice. …from a clinical perspective, it doesn't seem to have the necessary links to its application. (Reviewer 2)

Ln 329-337:
Moreover, the range of quantitative ultrasound techniques vary from muscle thickness measures to identifying areas of hyperechoic tissue for biopsy site identification (Pillen et al., 2007). The latter technique may involve alteration of both the transducer orientation and the force exerted by the examiner. Also sonographers may apply high transient peak forces during clinical ultrasound examinations, which may yield serial images with different levels of tissue deformation (Gilbertson & Anthony, 2013). Consequently, feedback enhanced sonography may become an important component of the continual development of diagnostic ultrasound applications and capabilities.

Revised. Ln 408-413:
Furthermore, follow up investigations regarding the applied use of feedback-enhanced sonography should include morphology measures from individuals with musculoskeletal or neuromuscular disorders. This approach to ultrasound scanning and image capture may have utility for clinical assessment, or training investigators and practitioners who are new to quantitative ultrasound methods.

Revised. Ln 456-463:
The relatively low magnitude of error associated with the examiners' performance merits the continued development of this approach to diagnostic imaging in clinical and research settings. Future development efforts should also address if enhanced sonography, via the production of

force feedback accessory units or transducers with integrated sensors, can be adequately scaled to be viable within the clinical practice environment. This process would involve addressing the issues of cost and access, compatibility of the technology across an array of device models, and human factors design to ensure effective usage by practitioners.

4. Were the images manually recorded when the target forces were met, or was this process automated? (Reviewer 1)

Revised. Ln 224-234:

The sonographer operated the ultrasound machine (without manipulating the transducer) within view of the laptop computer with the GUI featuring the real-time force control levels. The sonographer confirmed the attainment of the target force (± 0.5 N) per the GUI on the laptop computer, verified that the image did not contain artifacts, and then captured the image within the field of view. Following each image capture, the sonographer used the Sonosite ultrasound machine digital caliper measurement function to obtain material thickness measures. In a similar manner to the manual scanning sessions, the image capture and digital caliper measures were obtained three times.

Ln 439-446:

Although the automated image capture method was facilitated by the use of the KUKA LWR to control the transducer position and force, the measurement of the resultant material deformation was measured in a conventional manner by an examiner. While this aspect of the measuring procedure introduces an additional source of error into the criterion-referenced scans, the robot-assisted method circumvents the psychomotor element associated with handling the transducer which constitutes the largest source of error in quantitative ultrasound imaging (Chadli et al., 2012; Gilbertson & Anthony, 2013; Harris-Love et al., 2014).

5. The number of sonographers may be too minimal to draw significant causational conclusions from. This may explain the lack of difference between the levels of expertise in the study. (Reviewer 2)

Revised - Abstract. Ln 44-50:

Methods: Sixty material thickness measures were acquired from a muscle tissue mimicking phantom using B-mode ultrasound obtained by six examiners with varied experience levels (i.e., experienced, intermediate, and novice)…

Added. Ln 385-391:

Based on our early findings, force feedback scanning may provide an effective means of obtaining consistent quantitative ultrasound values among examiners with varied experience levels. Nevertheless, it is important to note that the differences in material deformation values obtained by the subgroups were not subject to statistical analysis in this study. Additional investigative work is needed in the applied use of enhanced-sonography in clinical settings.

6. No mention of funding. It seems like a study which may not have been possible without associated funding. (Reviewer 2)

PeerJ website (Declarations → Required Statements):

This publication was partially supported by Award Number UL1TR000075 and UL1TR000101 from the NIH National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH), through the Clinical and Translational Science Awards Program (CTSA), and a VISN 5 Pilot Research Grant (VISN 5; VA Station: 688) - VHA/VA Capitol Health Care Network.

Ln 465-476 (Acknowledgements):

…in addition, we thank Dr. Kevin Cleary of the Sheikh Zayed Institute for Pediatric Surgical Innovation at Children's National Hospital in Washington DC for providing access to the KUKA Light Weight Robot.