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Multi-modal magnetic resonance elastography for noninvasive assessment of ovarian tissue rigidity *in vivo*

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Abstract

For centuries, physicians have relied on touch to palpate tissue and detect abnormalities throughout the body. While this time-tested method has provided a simple diagnostic exam for large, superficial abnormalities, it does not permit quantifiable measurements of stiffness in deeper, small organs. Advances in noninvasive imaging to measure tissue rigidity represent important extensions of manual palpation techniques. Tissue fibrosis occurs with age in many organs; in the ovary, it is thought to be a marker of polycystic ovary syndrome (PCOS) and age-related idiopathic infertility, although quantitative assessment of fibrosis in this deep, abdominal tissue has not been possible. We used noninvasive methods to quantify ovarian tissue rigidity and clarify the role of tissue stiffness in reproductive health. With proper validation against accepted standards, noninvasive imaging techniques may become the quantitative counterpart to interior probing palpation methods and invasive (surgical) diagnoses, with applications across many clinical settings, including evaluation of adolescent and young adult ovarian function.

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Keywords

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1. Introduction

Characterization of ovarian tissue rigidity is critical for understanding organ function and diseases such as polycystic ovary syndrome (PCOS) [1]. Unlike the breast or liver, however, the ovary is not typically biopsied for the diagnosis of PCOS, and clinicians must rely on external palpation to detect ovarian tissue abnormalities. Moreover, the ovary is not a regenerating tissue system, and biopsy of the ovarian tissue is thus not an option in young, normally cycling women. Noninvasive measures of ovarian function and rigidity would make it possible to more quantitatively assess mechanical properties of the ovary and diagnose diseases such as PCOS. Moreover, non-invasive measures of ovarian function in adolescents would be far superior to invasive techniques, especially those that require transvaginal probes.

Quantitative methods to measure the mechanical properties of deep, abdominal, soft tissues such as the ovary are still in their infancy [2]. Tissue size, heterogeneity, depth, and porosity present challenges when attempting to accurately assess the material properties of a tissue. Tissues are complex materials and contain fluid—up to 90% or more of total weight—which greatly influences their properties and renders most tissues nearly incompressible ($\nu \approx 0.50$) [3]. Because of their solid-fluid nature, tissues are more accurately characterized in the frequency domain using viscoelastic material models [4]. Stiffness is measured and reported as the storage modulus (E' or G') in the frequency domain. Young's modulus (E) and shear modulus (G) are related by the Poisson ratio for isotropic homogeneous materials [$E=2G*(1+\nu)$], typically using a factor of 3 for soft materials such as tissues. Borrowing from characterization of traditional heterogeneous materials [5–7], contact or indentation-type measurement methods have been applied to tissues [8–11] to characterize spatially resolved properties. However, this indentation-type methodology is only applicable to *in vitro* studies and therefore represents a quantifiable, but micro-scale, palpation test that is not amenable to clinical assessment of the ovaries.

MRE is a novel technique that has been used to acoustically probe internal organs, such as the breast and liver, for early detection of cancer and cirrhosis [12]. This method combines mechanical wave propagation methods with magnetic resonance imaging (MRI). During MRE, a low-frequency sound wave (60–120 Hz) is sent into the body through a driver that is placed on the body, pointing towards the area of interest. The sound wave displaces the tissue and the tissue displacements are then measured via MRI and transformed into an equivalent stiffness image, or elastogram. MRE, like MRI, is noninvasive and well accepted by patients [2]. MRE can have up to sub-millimeter to millimeter resolution given the robust algorithm package capable of reducing artifacts and directional filtering of shear waves to eliminate shear wave interference. The resolution of MRE is typically one-fifth to one-half the resolution of the MRI image depending partially on the vibrational frequency of the acoustic wave. MRE represents a technological link between what has been accomplished previously with *in vitro* imaging and the ability to detect tissue abnormalities through

traditional palpation. The ability to detect tissue stiffness abnormalities *in vivo*, which are measured as hard or soft domains on MRE, can provide important additional prognostic information and insight into the overall health of an individual patient.

Though imaging methods to date have been restricted to assessment of the larger organs such as the liver and lungs, recent developments in driver and software technology are making it possible to penetrate deeper to analyze organs like the ovary. To date, MRE results have not been quantitatively validated by established mechanical characterization methods and have not been applied specifically to assess ovarian rigidity. Our goal was to investigate MRE as a quantitative biomaterial characterization method that could be applied clinically to assess rigidity of the ovary *in vivo*. We first performed a rigorous validation of MRE on gels and tissues and then compared the results to those of *in vitro* studies using bovine ovaries. Finally, we examined the ability of MRE to distinguish between healthy and PCOS ovaries *in vivo*.

2. Materials and Methods

2.1. Animal tissue collection

Bovine ovaries were isolated from heifers (<2 years of age) following kosher slaughter from the Aurora Packing Company in Aurora, IL. The ovarian tissue was immediately stored at 4°C and transported by automobile to Northwestern University (1 hour).

2.2. Human tissue collection

Using an institutional review board (IRB)-approved, HIPAA-compliant protocol, 7 women were selected and gave consent to undergo clinical testing with MRE (see Supplementary Information). Each subject underwent multiple MRE scans to determine interscan variability.

2.3. Agar hydrogel sample processing

Granulated agar (Fisher BioReagents, Waltham, MA) was mixed with DDI water at 2.25 wt % for MRE, nanoindentation, and bulk experiments. The gels were cured using the liquid setting in a standard autoclave for 1 hour.

2.4. Bulk material characterization of gels

RSA III dynamic mechanical analysis (DMA) (TA Instruments, New Castle, DE) was used to test the tensile and compressive viscoelastic properties (E', E'') of the agar hydrogel samples (phantoms). For rheometry, a series of 5 agar gels specimens were cut using a cylindrical die and tested for shear viscoelastic properties (G', G'') using a Physic MCR-300 (Anton Paar, Graz, Austria). Specimens were preloaded with 0.2 N to ensure proper contact before samples were subjected to testing. The details of this protocol are included the Supplementary Information.

2.5. Nanoindentation

Indentation testing was performed using a Triboindenter (Hysitron, Minneapolis, MN) and a 100 μm radius spherical tip with a dynamic oscillatory load [4] of 1.0 μN at 10–200 Hz, at a

sufficiently large contact depth of between 1.5 and 2 μm. For bovine ovary samples, nanoindentation tests were performed at 3 different sites on each ovary to test for heterogeneities: the cortex, the medulla, and the corpus luteum. At each site, a series of 5 different sites were tested (10 data points per site), sufficiently spaced by 50–200 μm. During testing, samples were partially submerged in Dulbecco's phosphate-buffered saline to prevent dehydration. For nanoindentation testing, a universal surface energy term, similar in value to those defined for the agar hydrogels, was used to correct stiffness values to account for work of adhesion (see Supplementary Information).

2.6. Magnetic resonance elastography

Measurements of internal ovarian stiffness were obtained using MRE by determining a circular region of interest within the ovary margins to ensure that the surrounding tissue was not included in the stiffness measurement. This is a conservative approach that sacrifices the outer cortex region of the ovary and only captures information on the interior region. Images were taken with a field view of 275 mm × 400 mm and were acquired on a 141 × 256 matrix, yielding anatomic images with 1.9 mm × 1.5 mm resolution, corresponding to elastograms of 1.3 cm × 1.0 cm. Stiffness was computed using the MRE software package [13] (See Supplementary Information for more details on the stiffness extraction method).

2.7. Statistical analysis

Samples were compared using two-tailed Student's t-tests. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Validation of MRE in agar hydrogel phantoms

We first compared MRE, nanoindentation testing, and bulk mechanical methods applied to agar hydrogels, a common tissue mimic, using a suite of testing methods covering all strain modes (tension, compression, shear) and a wide range of probing volumes. We observed considerable agreement between MRE and bulk mechanical measurements (≈15% error) (Figure 1, left), thereby validating MRE against the standard testing methods. The minor variations in observed stiffness values can be attributed to testing differences, such as strain mode (tension/compression), sample geometries, or sample variation. Nanoindentation results on the agar hydrogels, corrected using a version of the Johnson-Kendall-Roberts (JKR) model [14, 15] (Figure 1, right), match those of the bulk methodologies, especially for compression (≈8% error).

3.2 Assessment of bovine ovarian stiffness

The cow ovary closely phenocopies human tissue in terms of size. Because ovaries from young women are rarely removed and never excised for research purposes, we used bovine ovaries as our proxy of human ovarian tissue. Two bovine ovaries were probed with nanoindentation methods. For *in vitro* MRE measurements, 3 pairs of bovine ovaries were embedded in an agar gel matrix, a standard method used to suspend tissue in a hydrated environment. Figure 2 shows a comparison of measurements from each technique and

demonstrates the ability of nanoindentation to test local regions of a structure and resolve stiffness values.

We probed three regions of each ovary, but the results showed only one statistical outlier: the corpus luteum in ovary 1. We observed that the exterior cortex had statistically uniform mechanical properties, even in areas proximal to noticeable follicle structures. The lack of variation in stiffness of the interior features demonstrates that the ovary was fairly homogeneous, with the exception of a dominant corpus luteum, and the normal tissue was therefore extremely compliant (~ 100kPa or lower).

3.3 Comparison of ovary stiffness in human PCOS ovaries and matched controls

We next used MRE to explore differences *in vivo* in human ovaries of women with diagnosed PCOS [16] and age-matched controls. Representative MRI and elastograms from participants in the study are shown in Figure 3a, and illustrate the variability in tissue stiffness that exists naturally within the abdomen. This variability created noise and made isolation of the ovary difficult in practice because the organ is not perfectly isolated and lies underneath layers of air-filled bowel, fat, and other tissue structures. Despite this challenge, we found that patients with a diagnosis of PCOS had stiffer ovaries than those of age-matched controls (Figure 3b,c; $p<0.05$; two-sided student's t-test).

4. Discussion

In this paper, we compared established technologies and MRE to measure tissue material properties *in vitro*, and explored the ability of MRE to distinguish between healthy and diseased (e.g., PCOS) ovaries *in vivo*. MRE results were comparable to those of bulk material characterization methods on a standard engineering material, thereby validating MRE as an accurate and appropriate method to characterize hydrated materials. Studies of bovine ovaries *in vitro* showed some agreement between MRE and nanoindentation, though the magnitudes differed. These discrepancies are likely attributable to differences between interior probing (MRE) and surface probing (nanoindentation) methods, as well as loading mode differences, in which localized hydration state, surface adhesion and nonlinearities present in tissues can significantly influence results. Nanoindentation revealed some statistical variation inside the bovine ovary, in the case of the corpus luteum, and while MRE did not capture discrete variation, it was able to detect variations within an individual ovary. Localized stiffness variations provide evidence of slight heterogeneity within an overall fairly compliant and homogeneous tissue. Using the validated MRE stiffness measurements, our preliminary clinical results are the first published evidence of ovary stiffening in PCOS patients compared with healthy controls. These results provide the first *in vivo* validation of the hypotheses generated from previous *in vitro* studies regarding biomechanical regulation mechanisms within the ovary and the relationship between ovary stiffness and the presence of ovarian cysts in PCOS [17, 18].

4.1 MRE, nanoindentation testing, and bulk mechanical methods are comparable in agar hydrogel phantom testing

Nanoindentation techniques, both quasi-static and dynamic, have achieved similar moduli compared to traditional bulk methods for a wide range of polymer types [19–22]. Indentation-type characterization methods are commonly chosen for heterogeneous materials and can be tailored to a wide range of material types. Most often, contact-based methodologies resolve higher stiffnesses or moduli for soft materials, attributed to adhesion effects, surface confinement, and non-linear viscous effects [15, 23]. Aside from these effects, indentation-type testing has proven to be a consistent methodology for determining relative stiffness of a variety of material types [15, 22] and has unique spatial capabilities for mapping or isolating heterogeneity within materials [24, 25]. Adhesion effects have been well studied and are defined by the surface energies of the tip and sample and measured through pull-off experiments [15]. In our study, the agreement between MRE, nanoindentation and several bulk mechanical testing procedures applied to standardized agar samples demonstrates that MRE may be useful for probing the local stiffness of soft materials with complex geometries without the need for physical contact with the region of interest.

4.2 MRE and nanoindentation assess bovine ovary stiffness at different resolutions

In contrast to the controlled agar samples (phantoms), the nanoindentation stiffness results for the ovary samples were approximately an order of magnitude higher than the MRE results (140 kPa vs 13 kPa). In MRE, the regions of interest (ROI) are deliberately chosen as smaller than the ovary to avoid artifacts from the surrounding gel (see Supplementary Information); as such, the cortex material is excluded from the measurements, providing an underestimation of ovary stiffness. Additionally, nanoindentation tests of soft and irregular samples have been shown to overestimate moduli due to non-ideal sample geometry factors —such as surface curvature, tilted sample surface, and non-linear response—and tip-sample adhesion effects [11, 14, 26, 27]. The unique inherent challenges with tissue samples arise because of the need for physical contact to determine stiffness, a significant drawback in this particular case. The current challenges facing indentation techniques on ultra-soft materials —especially machine sensitivity, non-linear behavior, and adhesion effects—have slowed efforts to develop it as a standard method for assessing tissue stiffness in general. Nevertheless, while nanoindentation overestimated absolute values of the stiffnesses compared to shear-based methods, the technique produced results comparable to bulk compression (Figure 1 and Supplementary Information) and provided high spatial resolution and accurate relative differences in moduli.

In the case of soft tissues, the compliance of the sample approached the sensitivity limit of the instrumentation and noise was significant. Within the nanoindentation results, we observed compliant medulla and cortex regions as well as significant stiffening in the dominant corpus luteum structure in ovary 1, the only region that passed a two-sample t-test. Although some heterogeneity may exist, the current level of noise complicated this differentiation. Nanoindentation did show that primary structures, such as in ovary 1, were significantly stiffer than other regions of the ovary. MRE resolved some stiffness variations within the ovary as shown in the enlarged view of ovary 2; however, MRE did not match the

spatial resolution capabilities of nanoindentation. Of course, what MRE lacks in spatial resolution must be weighed against its unique capabilities as an noninvasive *clinical* tool and its relative simplicity, features that make it an attractive diagnostic method for evaluating tissues such as the ovary, where biopsy is not possible and palpation is the only method available for assessment of tissue abnormalities.

4.3 Study limitations

Limitations of the study include that it is a pilot study with low sample numbers, and used a prototype MRE system (acoustic driver, pulse sequence, and reconstruction software). We found that depth penetration of the acoustic waves were patient-specific in some cases, yielding low mathematical confidence. We explicitly rejected some exams based on poor image quality, indicating several areas were protocol development is needed. Optimization of the system and protocol are currently in progress.

5. Conclusions

The advent of *in vivo* imaging technologies such as MRE has opened up the possibility for diagnostic and prognostic testing—specifically for diseases related to tissue stiffness—that is less invasive, less expensive, and more accurate and/or reliable. Our studies provide an initial demonstration of MRE for measuring tissue material properties *in vivo*; in particular, the capacity for deep probing of tissues such as ovaries. MRE represents a major improvement on current palpation techniques, which are generally skill driven and less quantitative. The need for non-invasive assessments of reproductive function is becoming increasingly important as the obesity epidemic changes ovarian function in adolescents where more interventional imaging techniques such as transvaginal sonography is not as appropriate.

The non-invasive MRE method also potentially expands the amount of the body available for probing without the need for biopsy, which is not an option for tissues such as the ovary. The technological advance of MRE not only provides us with a new tool that will permit a greater understanding of ovarian biology, but also offers new opportunities to noninvasively and quantitatively assess other internal organs for early fibrotic changes and evaluate the efficacy of new treatments for fibrotic diseases. Improvements in non-invasive assessment may impact patient outcomes as well as overall quality of care by allowing for earlier, more precise diagnosis and collection of additional data that can refine prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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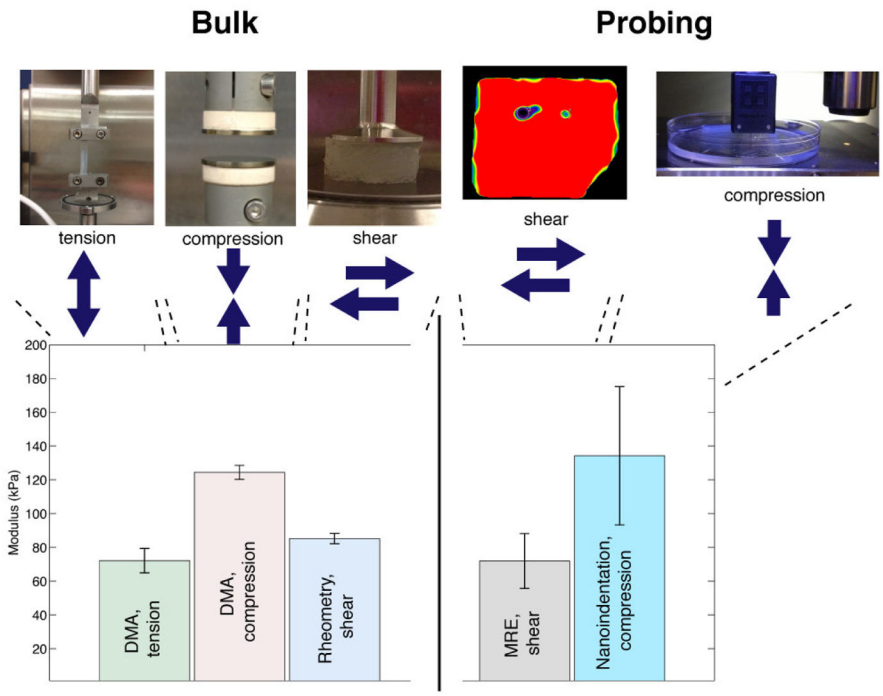

Figure 1.

Comparison of elastic stiffness of an agar hydrogel using five different material characterization methods: three bulk methods (left) and two localized methods (right). Due to the incompressible nature of most isotropic hydrated materials, such as hydrogels and tissues, their shear modulus (G) is approximately 1/3 of the tensile or compressive modulus (E) [E=2*G*(1+nu)]; the conversion of the measured G to E is shown for easier comparison. Results are displayed for an agar gel at 2.25 wt% and averaged across a broad frequency range (1–100 Hz). Error bars displayed represent standard deviations. MRE results on the agar gel are taken from the gel phantoms used in the *in vitro* experiments (see also Fig. 2) and are visualized as the red portion of the image above. Nanoindentation results were corrected for tip adhesion effects using a Johnson, Kendall and Roberts model (JKR model) (see Supplementary Information).

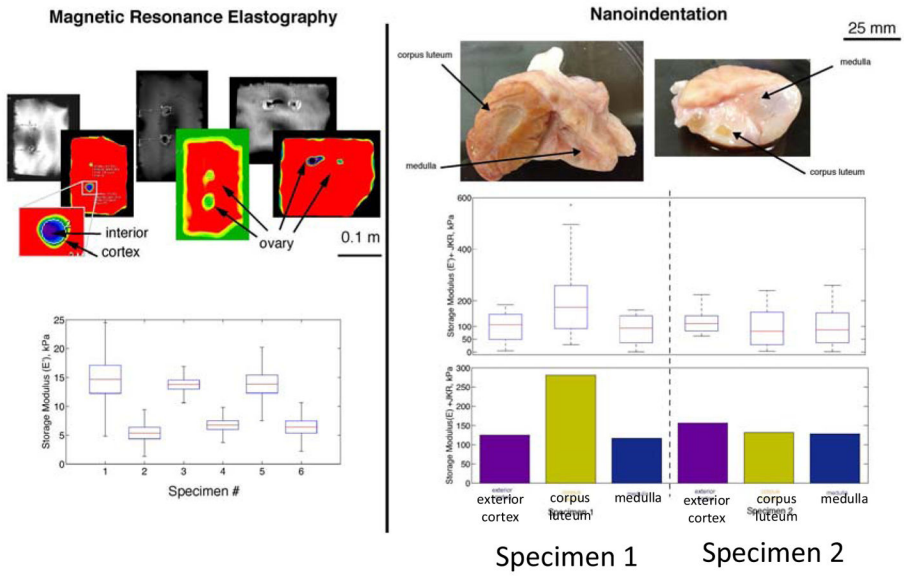

Figure 2.

Comparison of probing/local measurements of stiffness in bovine ovaries suspended in agar hydrogel phantoms (matrices), using magnetic resonance elastography (MRE) and nanoindentation. Colorized MRE elastographs are scaled from min/max results of individual phantoms to visualize heterogeneity; quantified results for E′ (where E′=3G′) for the defined regions of interest (ROI) are shown as box and whisker plots for ovaries 1 through 6. The results illustrate heterogeneity within the ovary structure and a stiffened corpus luteum in ovary 1. For nanoindentation, the results are displayed as box-and-whisker plots (above) on a logarithmic scale and a simple average (below) on a linear scale. Resolving heterogeneity within the ovary was difficult with MRE, but this method was able to probe interior features and did not require a free surface for testing as is needed with nanoindentation.

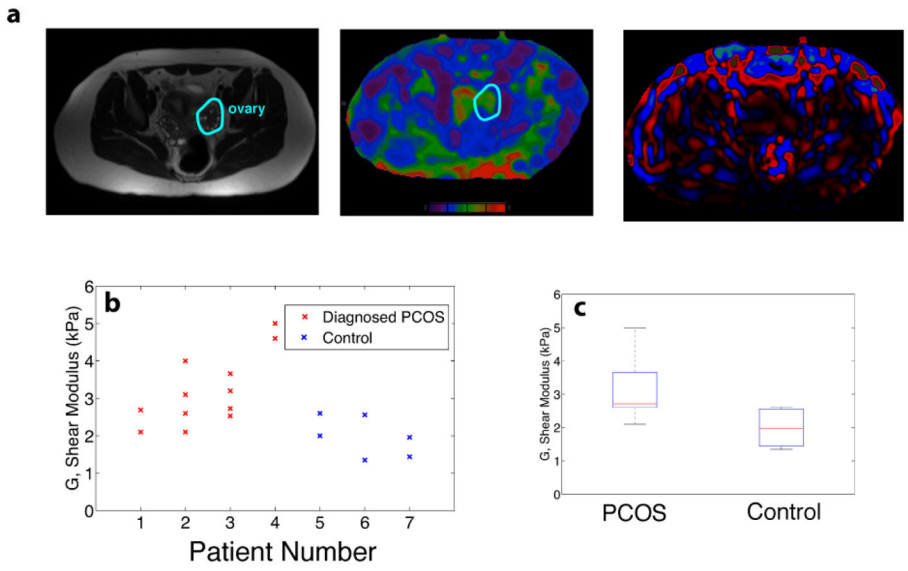

Figure 3.

In vivo magnetic resonance elastography (MRE) studies were performed on seven clinical patients, four of whom had a previous diagnosis of PCOS. (a) T-2 anatomical images were cross-referenced with colorized MR elastograms (0–8 kPa, purple-red respectively) to identify a region of interest (ROI). The ROI was used to measure the shear stiffness, G′ (kPa). (b,c) However, results demonstrate an overall higher stiffness in the ovaries of women diagnosed with PCOS versus age-matched controls. MRE wave images are shown as last color image.