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Dynamic and Quasi-Static mechanical testing for characterization of the viscoelastic properties of human uterine tissue

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Abstract

Ultrasound elastography is envisioned as an optional modality to augment standard ultrasound B-mode imaging and is a promising technique to aid in detecting uterine masses which cause abnormal uterine bleeding in both pre- and post-menopausal women. In order to determine the effectiveness of strain imaging, mechanical testing to establish the elastic contrast between normal uterine tissue and stiffer masses such as leiomyomas (fibroids) and between softer pathologies such as uterine cancer and adenomyosis has to be performed. In this paper, we evaluate the stiffness of normal uterine tissue, leiomyomas, and endometrial cancers using a EnduraTEC ElectroForce (ELF) system. We quantify the viscoelastic characteristics of uterine tissue and associated pathologies globally by using two mechanical testing approaches, namely a dynamic and a quasi-static (ramp testing) approach. For dynamic testing, 21 samples obtained from 18 patients were tested. The testing frequencies were set to 1, 10, 20, and 30 Hz respectively. We also report on stiffness variations with pre-compression from 1–6% for testing at 2, 3, and 4% strain amplitude. Our results show that human uterine tissue is both dependent on percent pre-compression and testing frequencies. For ramp testing, 20 samples obtained from 14 patients were used. A constant strain rate of 0.1% was applied and comparable results to dynamic testing were obtained. The mean modulus contrast at 2% amplitude between normal uterine tissue (the

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Conflict of interest statement

None of the authors have any financial or personal relationships with other people or organizations that could have inappropriately influenced or biased the work.

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background) and leiomyomas was 2.29 and 2.17, and between the background and cancer was 0.47 and 0.39 for dynamic and ramp testing, respectively.

Keywords

elastography; elasticity imaging; Young's Modulus; viscoelasticity; uterus; cervix

Introduction

Ultrasound elastography has become a popular imaging technique for mapping tissue stiffness (Ophir *et al.*, 1991). Tissue deformation for elastography is divided into two main groups: quasi-static and dynamic (Fatemi & Greenleaf, 2002). In quasi-static methods, tissue is compressed slowly and at least two frames of data, before and after the deformation (Ophir *et al.*, 1999), or a data loop during the deformation are acquired (Varghese 2009). Local displacements are estimated by comparing these data frames over small gated regions. Deformations can be applied using the transducer itself, either freehand or with mechanical devices. Strain computed from the displacement gradient is related to the stress distribution, if available, and resulting Lamé parameters calculated via elasticity equations (Sarvazyan *et al.*, 2011). However, the stress distribution is generally not available and modulus reconstruction is performed by solving the inverse problem (Barbone & Bamber, 2002). In many clinical applications, strain distributions are used to determine tissue stiffness as a qualitative surrogate marker of elasticity; i.e., low strain indicates high stiffness while large strain indicates a low stiffness region.

Mechanical testing has been used to quantify differences in elastic moduli and spatial distribution of Young's modulus for different tissue types (Krouskop *et al.*, 1998; Mazza *et al.*, 2007, DeWall et al. 2012). Detection and characterization of uterine masses causing abnormal uterine bleeding have been evaluated with elastography (Hobson *et al.*, 2007; Omari *et al.*, 2012), and its role for differential diagnosis of endometrial pathologies investigated by several research groups. Significant differences in endometrial stiffness have been reported for patients with atrophic endometrium confirmed with pathology (Preis *et al.*, 2011). A pilot study using transvaginal real-time ultrasound elastography confirmed benign etiology based on the presence of an endometrial strip in the elastogram (Neale *et al.*, 2011). To determine effectiveness of ultrasound elastography for differentiation of abnormal uterine bleeding etiology, the elastic or modulus contrast between normal uterine tissue and stiffer masses such as leiomyomas and between softer pathologies such as uterine cancer and adenomyosis is essential (Omari *et al.*, 2012).

Human cervical and uterine tissue studies to quantify elastic and viscoelastic properties were conducted in our laboratory. Kiss *et al.*, (2006) measured the complex modulus in *ex-vivo* cervical and uterine hysterectomy samples using dynamic testing. Small compressions, 1–2%, were applied over a wide frequency range spanning 0.1–100 Hz. Modulus values for cervical and uterine tissue increased monotonically from approximately 30 kPa to 90 kPa with an increase in testing frequency. Leiomyomas exhibited modulus values that ranged from 60–220 kPa.

Bauer *et al.* (2007) utilized an aspiration device for *in-vivo* cervical evaluations, to evaluate physiological and biomechanical changes through gestation for detecting pregnant women at risk of cervical incompetence. For *in-vivo* studies their stiffness parameter values varied from 0.065 to 0.315 bar/mm, while softening parameter values ranged from 0.05 to 0.19. *Ex-vivo* testing results ranged from 0.11 to 0.29.

Myers *et al.* (2008) performed ramp loading tests on cervical ring sections under three different testing modes: load-unload cycle, unconfined ramp-relaxation, and confined ramp-relaxation. Ramp testing is a quasi-static approach which subjects the sample to a constant strain rate over a large applied deformation, with the stress and strain measured continuously. Each specimen was first loaded under unconfined compression to a 15% axial strain and unloaded to 0% strain at a constant strain rate of 0.1% per second over three cycles. Their results indicated that cervical stroma has a nonlinear time-dependent stress response with varying degrees of conditioning and hysteresis depending on its obstetric background. Cervical tissue obtained from women who were never pregnant was significantly stiffer than women who underwent a pregnancy.

DeWall *et al.* (2010) quantified viscoelastic properties of normal human cervix through a range of pre-compressions (1–6%), compression amplitudes (2%, 3%, 4%), and testing frequencies (1, 10, 20, 30 Hz). This study revealed lower modulus values, by an order of 10, than those previously reported by Kiss *et al.* (2006). The storage modulus increased monotonically from approximately 4.7 kPa to 6.3 kPa over the pre-compression range of 1–6% at a testing frequency of 1 Hz. The material's damping ($\tan\delta$) remained fairly constant (~ 0.35) over this range. However, with an increase in the mechanical testing frequency both the storage modulus and damping increased (DeWall *et al.*, 2010; Kiss *et al.*, 2006).

In this paper, mechanical testing methods for global stiffness measurements of human uterine tissue are described. We compare results obtained using two mechanical testing techniques namely dynamic and ramp testing of normal uterine tissue, leiomyomas, and carcinoma.

Mechanical Testing of Human Uterine Tissue

Soft tissue behavior has been characterized to be anisotropic, viscoelastic and nonlinear. However, under certain simplifying assumptions, such as low strain and rapid load application, soft tissue can be assumed to be linear, elastic, and isotropic (Krouskop *et al.*, 1998; Wells & Liang, 2011). Uterine and cervical tissues are viscoelastic. Transient properties such as creep and relaxation are illustrated in Figure 1 to depict differences between elastic and viscoelastic materials.

Characterization of biological tissue stiffness can be performed globally or locally (Omari, 2014; DeWall *et al.*, 2012). In order to characterize linear viscoelastic properties, the complex Young's modulus (E^*) is generally estimated. In this study, both dynamic and ramp loading tests using an EnduraTEC ElectroForce (ELF) (Bose Corporation, ElectroForce Systems Group, Eden Prairie, MN, USA) system, shown in Figure 2, were performed for global stiffness estimation of uterine specimens. Normal, fibroid, and cancerous uterine specimens were obtained from UW Hospital and Clinics (Madison, WI)

pathology lab following a hysterectomy procedure on patients. The protocol for sample acquisition was approved by the University of Wisconsin Institutional Review Board (IRB). Patient consent was obtained prior to acquisition of excised samples.

Samples were transported to the elastography lab in the Wisconsin Institute for Medical Research (WIMR), in a small container immersed in isotonic saline solution. Samples were kept refrigerated prior to testing, and were mechanically tested within a few hours of excision. Samples were brought to room temperature, cut to approximately a cubic centimeter in dimension, measured using dial or digital calipers for precision measurements. After mechanical testing, the samples were placed in formalin and returned to the UW pathology laboratory for histological analysis. A total of 41 uterine (non-cervical and non-fundus) samples were tested. Samples were tested parallel to the fiber directions. A pathologist determined the pathology state of tissue prior to testing. For pathological tissue, the fibroid or the endometrial cancer occupied most of the cube (especially the top portions where compression is applied).

Global stiffness characterization

For global estimation of the complex Young's modulus (E^*), a compressive load was applied to a volume of material typically 1 cm^3 . Stress was measured based on the applied force and pre-compression sample surface area. Strain was measured based on sample deformation, calculated from the change of height versus original height of the sample. Mineral oil was used to coat the lower and upper platen (1.5 cm radius Teflon®) prior to tissue placement. This was done to ensure free-slip boundary conditions.

Dynamic Testing

Let strain $\varepsilon(t)$, be varying sinusoidally in time t with a frequency f , and ε_o is the peak-to-peak strain amplitude, then

$$\varepsilon(t) = \varepsilon_o e^{i2\pi ft} \quad (1)$$

The stress $\sigma(t)$, will also be sinusoidal with a peak-to-peak stress amplitude of σ_o , however it will lead the strain by a phase angle δ

$$\sigma(t) = \sigma_o e^{i(2\pi ft + \delta)} \quad (2)$$

The relationship between stress and strain can be expressed using the Boltzmann superposition integral:

$$\sigma(t) = \int_{-\infty}^t E(t-\tau) \frac{d\varepsilon(\tau)}{d\tau} d\tau \quad (3)$$

To obtain the complex modulus E^* we can substitute equations (1) and (2) into (3) and take the Fourier transform. We then obtain after simplification:

$$\sigma(\omega) = E^*(\omega)\varepsilon(\omega) \rightarrow E^*(\omega) = \frac{\sigma(\omega)}{\varepsilon(\omega)} = \frac{\sigma_0}{\varepsilon_0} (\cos(\delta) + i\sin(\delta)) = E_s + iE_l \quad (4)$$

where E_s is the storage modulus (capability of the material to store energy during a loading cycle), and E_l is the loss modulus (energy lost during each cycle). The loss factor is the tangent of the phase shift ($\tan\delta$), determined from the ratio of E_l to E_s .

Unconstrained uterine samples were tested under applied sinusoidal strain from the constant amplitude driver attached to the upper platen, as shown in Figure 2. Resulting load cell voltages were detected and converted to force values. Dynamic mechanical analysis (DMA) software WinTest™ (Bose Corporation, ElectroForce Systems Group, Eden Prairie, MN, USA), uses the force and displacement values to calculate the complex modulus. The block diagram in Figure 3, describes the protocol utilized for dynamic testing of uterine tissues using the ELF.

After the test conditions are entered and contact point determined, the load cell was zeroed before initiating any measurements. In order to stabilize tissue and ensure removal of creep, a constant pre-compression of 1% was used to ensure contact. Then the upper platen was lowered to the mean level, at a rate of 0.2 mm/s. The platen dwells at the mean level for about 15 seconds, then a “pre-cycle” of 15 seconds duration was performed. A sinusoidal compression was then applied to the sample at the desired frequency and displacement and force noted. If tissue was tested at more than one frequency, the upper platen returns to the mean position and another pre-cycle performed before initiating the second measurement. Using displacement and force amplitudes as well as sample dimensions, the DMA software, calculates the Young’s modulus.

The Young’s moduli $|E^*|$, and loss factors $\tan\delta$ were measured. The DMA software on the ELF system utilizes the initial area (A_o) and height (h_o) of the sample to compute the stiffness measures. These are based on the assumption that the material is incompressible. A correction factor (Hobson M.A., 2008), to account for height and surface area changes of the sample was used, after data acquisition. The correction factor is shown in equation (9).

$$CF = \frac{A_o h_f}{h_o A_f} = \left(1 - \frac{\text{mean level compression}}{100}\right)^2 \quad (9)$$

where h_f and A_f are the final height and surface area of the sample, respectively.

We quantify the viscoelastic properties of human uterine tissue at different testing frequencies of 1, 10, 20, and 30 Hz respectively. The impact of pre-compression on the storage modulus of cervical tissue has been previously reported (DeWall *et al.*, 2010). The effect of pre-compression on Young’s modulus for human uterine tissue, however, has not yet been reported. We report results on the changes in pre-compression percentages from 1–6% at 2, 3, and 4% strain amplitude.

Ramp Testing

Here tissue samples were subjected to a constant strain rate for a large applied deformation. Let S be the strain rate. Then the strain $\varepsilon(t)$ can be defined as:

$$\varepsilon(t) = \begin{cases} S_t & \text{for } t \geq 0 \\ 0 & \text{otherwise} \end{cases} \quad (5)$$

By substituting in Boltzmann's superposition integral (3), we obtain:

$$\begin{aligned} \sigma(t) &= \int_{-\infty}^t E(t-\tau) \frac{d\varepsilon(\tau)}{d\tau} d\tau = \int_0^t E(t-\tau) S R d\tau = S R \int_0^t E(t-\tau) d\tau = -S R \int_0^t E(U) dU \dots \\ \sigma(t) &= S R \int_0^t E(U) dU \end{aligned} \quad (6)$$

Using Leibniz' rule:

$$\frac{d}{dx} \int_a^b F(x, t) dt = \int_a^b \frac{\partial F(x, t)}{\partial x} dt + F(x, b) \frac{db}{dx} - F(x, a) \frac{da}{dx} \quad (7)$$

We can therefore simplify (6) to the following:

$$\frac{d\sigma(t)}{dt} = S E(t) \quad (8)$$

Samples tested included human normal, fibroid, and cancerous uterine specimens. Three consecutive ramp tests were performed on each sample; the first two ramp tests were discarded and used only for preconditioning. The third ramp test data was used to calculate the Young's modulus. Preparation of the samples was described in the previous section. The test setup differs since once the contact point is established, the upper platen remains in contact with the sample prior to the test start up. Parameters that are fed into the WinTest™ software include the strain rate in mm/sec and the final deformation position. For ramp tests, we maintained a strain rate of 0.1%, for compression in the range 0–15%; i.e., the final position was at 15% of the sample's height. At the end of the loading stage, the sample was unloaded and relaxed to its initial position. This step was repeated 3 times. Advantages of ramp testing lie in the ease of performing measurements and amount of time required for the measurement.

Results

Dynamic Testing

Samples from 18 female patients were dynamically tested. Women who underwent hysterectomies due to abnormal uterine bleeding were candidates, and were approached to participate in this study. A total of 21 samples were tested, including 18 normal specimens, 2 fibroids, and 1 cancer. Normal samples as specified in this study included uterine tissue, without masses or other abnormalities.

Figures 4 and 5 show the effect of changes in the percent pre-compression, for a mechanical testing frequency of 1 Hz and 2% amplitude, on the magnitude of the complex modulus, $|E^*|$, and loss factor, $\tan \delta$, for normal uterine tissue, fibroids, and the carcinoma. For example, if the test was done using compressions between 4–6%, the mean compression denotes 5% of the height of the sample, with dynamic testing amplitude of 2%.

In order to investigate whether the strain amplitude would have an effect on stiffness changes, the percent amplitude was varied as follows: 2%, 3%, and 4%. The mechanical testing frequency was kept at 1 Hz. Figure 6 shows the percent pre-compression versus the complex Young's modulus magnitude at three compression amplitudes for normal uterine samples. No significant changes ($p > 0.01$) in stiffness levels were observed in Fig. 6, as the strain amplitude was varied. Therefore, 2% strain amplitude was considered sufficient for testing uterine tissue samples.

We also evaluated different mechanical testing frequencies for evaluating dynamic mechanical properties, as shown in Fig. 7. The magnitude of the Young's moduli versus the percent pre-compression at 4 different testing frequencies for normal, fibroid, and cancerous uterine samples are shown in Figure 7a, 7b, and 7c, respectively. The strain amplitude was kept the same at 2%.

Since strain and modulus contrast are correlated, determination of the modulus contrast using mechanical testing can provide an indicator of the elastographic contrast in strain images. The magnitude of the modulus contrast $|C^*|$ can be calculated as follows:

$$|C^*| = \frac{|E_{FIB}^*|}{|E_{NORM}^*|} \text{ or } |C^*| = \frac{|E_{CA}^*|}{|E_{NORM}^*|} \quad (10)$$

where $|E_{FIB}^*|$, $|E_{CA}^*|$, and $|E_{NORM}^*|$ are the magnitude of the Young's modulus for uterine fibroid, cancer and normal tissue, respectively.

Figure 8 shows the modulus contrast levels between normal uterine tissue and uterine leiomyomas, as well as, normal uterine tissue and the uterine carcinoma. The strain amplitude and mechanical testing frequency was set to 2% and 1 Hz, respectively. Figure 8 shows that $|C^*|$ was 2.29 between leiomyomas and normal uterine tissue and 0.47 between carcinoma and normal uterine tissue. This indicates that the cancerous uterine tissue was softer than normal myometrium for the tested sample. Cervical cancer is stiffer than normal cervical tissue (Su et al., 2013). However, only one sample was tested in this paper.

Ramp Testing

Human uterine tissue was also tested quasi-statically by applying a constant strain rate of from 0.1% to 15%. The number of samples tested was 20, obtained from 14 patients who underwent hysterectomies at UW Hospitals and Clinics. The 14 normal uterine tissue specimens exhibited no masses within the specimen itself, however, this determination was not based on pathology. Additionally, 4 uterine fibroids, and 2 uterine carcinomas were also assessed with mechanical testing. Figure 9a, 9b, and 9c present the stress-strain curves for the ramp tests performed on normal uterine tissue, leiomyoma, and carcinomas, respectively. The top portion of the curve denotes the loading stage of the test, while the bottom curve denotes the unloading stage of the test.

The stress-strain plots clearly indicate uterine tissue as viscoelastic because of the hysteresis that is clearly visualized in Fig. 9. Elastic materials tend to rebound back to their equilibrium position immediately after the removal of the applied strain. On the other hand, viscoelastic materials show an energy loss during the unloading stage. Fibroid tissue tested present with

the highest stress levels, while carcinoma sample indicate the lowest stress level. The energy dissipated or lost was the area enclosed between the loading and unloading curves. Note that the normal uterine tissue and fibroid tissue show similarity in the energy dissipated, while the carcinoma sample exhibited the least energy loss. These results corroborate our previous results obtained from dynamic testing of samples, when the mean loss factor was compared.

Discussion

Dynamic testing results indicate a monotonic tissue stiffening as the pre-compression was increased. However, the stiffer the tissue the larger the increase in the Young's modulus magnitude with percent pre-compression ($p < 0.001$). The loss factor did not significantly ($p > 0.01$) change with percent pre-compression or with the type of tissue tested. Although we have limited data for fibroid and cancerous tissue, our results indicate that uterine tissue and fibroids have similar energy loss. On the other hand, the loss factor for cancerous tissue was half that of normal and fibroid tissue.

For dynamic testing, the mechanical testing system showed consistent erroneous results with large fluctuations for a testing frequency of 20 Hz. These results could be due to internal errors or to tissue resonances while generating the applied strain loads at that frequency. Excluding the results obtained at 20 Hz, the results for the variation in the frequency versus the variation in the % pre-compression show a monotonic increase in stiffness as the % pre-compression increases as well as an increase in tissue stiffness with testing frequency. Results obtained at the higher mechanical testing frequencies can also be utilized to evaluate the expected tissue modulus and contrast for dynamic elastography and methods that track shear wave velocities to estimate the shear modulus. However, at a 1 Hz mechanical testing frequency the stiffness values between normal and pathological tissue were more separated than at higher frequencies ($p < 0.001$) for all uterine tissue types.

The results presented in this paper, were compared to that described in Kiss *et al.* (2006), they reported a monotonic increase in the Young's modulus magnitude as a function of frequency. However, modulus values measured were higher than values reported in this paper for both normal uterine samples and fibroids. This could be due to the use of different testing conditions such as the amount of pre-compression applied to the sample. Another reason for the differences in stiffness values could be due to the over processing of the tissue samples as they undergo testing at the large range of testing frequencies (0.1 to 100 Hz), which could have resulted in tissue hardening in Kiss *et al.* (2006). On the other hand in the mechanical testing frequency range from 1 Hz to 30 Hz, similar trends in the increase of $|E^*|$ were noted in both studies.

To analyze hysteresis loops for ramp testing, we calculated the magnitude of the Young's modulus using equation (9), by computing the slope of the stress-strain curve at specific strain levels and dividing by the strain rate. We approximate the Young's modulus magnitude in the range from 1–8%, which are compared to our pre-compression values and compression amplitude of 2% used with dynamic testing. Since the stress/strain data was noisy, we do not directly calculate the ratio of stress to strain. Finding piecewise slopes by fitting the data to a line using a least squares fit was utilized. Compression values of 1–3%,

2–4%, 3–5%, 4–6%, 5–7%, and 6–8% were approximated. Figure 10-a shows the results of the Young's modulus magnitude versus the percent pre-compression at 2% strain amplitude obtained with dynamic testing ($p < 0.001$). Figure 10-b shows the contrast of the fibroid with respect to the background (normal uterine tissue) as well as that of a carcinoma with respect to the background.

Our results show an increase in tissue stiffness as the % pre-compression was increased, which is comparable to the dynamic testing results. The only difference being that ramp testing provided higher Young's modulus estimates. This was expected since tissue was tested in a quasi-static approach at a constant strain rate. Modulus contrast values obtained, however, are comparable especially at lower compression rates (1–3%, 2–4%). $|C^*|$ for leiomyomas versus normal uterine tissue was 2.17, while that for the carcinoma versus normal tissue was 0.39.

Conclusion

Human uterine tissue and its pathologies exhibit viscoelastic behavior with compression. The Young's modulus and loss factor are measured for tissue tested dynamically. Uterine leiomyomas ($n=4$) are shown to be stiffer than normal tissue and the single carcinoma specimen was softer than normal tissue. Results show a dependence of the Young's modulus on pre-compression applied to tissue prior to mechanical testing, where a monotonic increase was observed. Human uterine tissue also showed monotonic mechanical testing frequency dependence. The dynamic tests showed no significant dependence on the compression amplitude applied. For quasi-static testing at 0.1% strain rate, our testing results were comparable, in terms of the modulus contrast to that obtained with dynamically tested uterine tissue. The contrast ratio between the normal uterine tissue (background) and leiomyoma was greater than 2 and between the background and carcinoma to be less than 0.5 at low pre-compression rates.

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Figure 1.

Original un-deformed state of the material is shown in the top row, while (a) Creep and recovery, and (b) relaxation and recovery are shown for elastic and viscoelastic material. Stress is denoted by (σ) and strain by (ϵ) vs. time t .

Figure 2. EnduraTEC ELF 3200 Mechanical Testing System (MTS). The zoomed in area shows the upper platen (U), the lower platen (L), and a 1000g load cell (C).

Figure 3. Block diagram illustrating the steps involved in using the EnduraTEC ELF 3200 for testing uterine tissue samples.

Figure 4. Magnitude of the complex modulus $|E^*|$ versus the percent pre-compression for dynamically tested samples. The mechanical testing frequency was 1 Hz and the strain amplitude was 2%. NORM: normal uterine tissue. FIB: fibroids. CA: cancerous.

Figure 5.

The loss factor, $\tan \delta$, versus the percent pre-compression for normal tissue, fibroids, and cancerous uterine tissue. Testing was performed using a 2% strain amplitude and 1 Hz mechanical testing frequency. NORM: normal tissue, FIB: fibroids, and CA: carcinoma.

Figure 6.

Young's modulus $|E^*|$ magnitude values versus the percent pre-compression in kPa at 2%, 3%, and 4% strain amplitudes for dynamically tested samples.

Figure 7.

Young's modulus $|E^*|$ magnitude variations versus the percent pre-compression at dynamic mechanical testing frequencies of 1, 10, 20, and 30 Hz and 2% strain amplitude for: a) normal uterine tissue, b) Leiomyoma, c) Cancer.

Figure 8. Modulus contrast $|C^*|$ with respect to background (normal uterine tissue) for fibroids and carcinoma, versus the percent pre-compression. These results are for dynamically tested samples.

Figure 9.

Stress-strain curve for human uterine tissue samples: a) normal, b) leiomyoma, c) cancer. Strain rate was set to 0.1% for testing in the range from 0–15%.

Figure 10.

(a) Young's modulus estimates in kPa versus the percent pre-compression under constant strain rate of 0.1% or quasi-statically tested human uterine tissue samples. (b) Modulus contrast $|C^*|$ with respect to background (normal uterine tissue) for fibroids and carcinoma, versus the percent pre-compression. These results are for quasi-statically tested samples.