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Acoustic Radiation Force Induced Creep-Recovery (ARFICR): A non-invasive method to characterize tissue viscoelasticity

Carolina Amador,

Department of Ultrasound Imaging and Interventions, Philips Research North America, Cambridge, MA, 02141, USA

Shigao Chen,

Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN 55902, USA

Matthew W. Urban [Senior Member IEEE], and

Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN 55902, USA

James F. Greenleaf [Life Fellow IEEE]

Department of Physiology and Biomedical Engineering, Mayo Clinic College of Medicine, Rochester, MN 55902, USA

Abstract

Ultrasound shear wave elastography is a promising noninvasive, low cost, and clinically viable tool for liver fibrosis staging. Current shear wave imaging technologies on clinical ultrasound scanners ignore shear wave dispersion and use a single group velocity measured over the shear wave bandwidth to estimate tissue elasticity. The center frequency and bandwidth of shear waves induced by acoustic radiation force depend on the ultrasound push beam (push duration, F -number, etc.) and the viscoelasticity of the medium, and therefore are different across scanners from different vendors. As a result, scanners from different vendors may give different tissue elasticity measurements within the same patient. Various methods have been proposed to evaluate shear wave dispersion to better estimate tissue viscoelasticity. A rheological model such as the Kelvin-Voigt model is typically fitted to the shear wave dispersion to solve for the elasticity and viscosity of tissue. However, these rheological models impose strong assumptions about frequency dependency of elasticity and viscosity. Here we propose a new method called Acoustic Radiation Force Induced Creep-Recovery (ARFICR) capable of quantifying rheological model-independent measurements of elasticity and viscosity for more robust tissue health assessment. In ARFICR, the creep-recovery time signal at the focus of the push beam is used to calculate the relative elasticity and viscosity (scaled by an unknown constant) over a wide frequency range. Shear waves generated during the ARFICR measurement are also detected and used to calculate the shear wave velocity at its center frequency, which is then used to calibrate the relative elasticity and viscosity to absolute elasticity and viscosity. In this study, finite element method (FEM) simulations and experiments in tissue mimicking phantoms are used to validate and characterize the extent of viscoelastic quantification of ARFICR. The results suggest that ARFICR can measure tissue viscoelasticity reliably. Moreover, the results showed the strong frequency-dependency of viscoelastic parameters in tissue mimicking phantoms and healthy liver.

Index Terms

elastography; viscoelasticity; liver

I. Introduction

Ultrasound-Based elasticity imaging has proven to be a useful medical imaging modality providing inherent imaging contrast that exist among different types of tissues and within the same tissue when disease is present [1]. In ultrasound-based shear wave elasticity imaging an external mechanical vibration or acoustic radiation force (ARF) from a focused ultrasound beam are commonly used to generate shear waves. Multiple techniques have been developed to measure shear wave propagation such as shear wave elasticity imaging (SWEI), transient elastography (TE), supersonic shear wave imaging (SSI), shear wave dispersion ultrasound vibrometry (SDUV) and comb-push ultrasound shear elastography (CUSE) [2-7]. The use of ARF has become the most common approach to generate shear waves for several reasons: 1) an ultrasound system can create a focused beam to apply ARF to push tissue where an acoustic window exists, 2) shear waves from ARF excitation propagate a few millimeters from the source because of shear wave attenuation, which overcomes boundary conditions problems encountered by externally generated shear waves and 3) the ARF excitation is impulsive thus the generated shear wave is broadband, allowing viscoelasticity analysis.

It is well established in the elasticity imaging community that tissue exhibits time-dependent mechanical properties, also referred to as viscoelastic behavior [8]. Tissue viscoelastic properties can be estimated in a model-dependent manner from fitting rheological models to the shear wave phase velocity measured at various frequencies [6, 9] and a model-independent manner if shear wave speed and attenuation are known [10-13]. In addition to shear wave propagation, tissue viscoelastic properties can also be measured by studying creep and relaxation responses [8]. As with shear wave propagation methods, the tissue creep response from a step-stress excitation has been proposed from external mechanical and internal ARF excitation [14-19]. These creep and relaxation based methods to study tissue viscoelasticity are capable of estimating tissue viscoelastic parameters from fitting a rheological model to the creep and/or recovery response. Hybrid methods that combine creep or recovery response and shear wave propagation have also been proposed to solve for tissue viscoelasticity in a model-independent manner [20-22].

Although considerable efforts are being made to extend the ultrasound-based elasticity imaging methods to study tissue viscoelasticity, current shear wave imaging technologies on clinical ultrasound scanners ignore shear wave velocity (SWV) dispersion from tissue viscosity and use a single shear wave group velocity measured over the shear wave bandwidth (usually between 100 Hz to 500 Hz) to estimate tissue elasticity. In a homogeneous, isotropic, incompressible, elastic material, the shear elastic modulus, G , is estimated by $G = c^2 \rho$, where c is the shear wave velocity (SWV) and ρ is the tissue density (assumed to be 1,000 kg/m³) [2]. With the pure elastic material assumption, SWEI have been found to be useful for evaluation of various diseases in different organs such as breast,

thyroid, prostate, kidney, arteries and heart [23]. However, the shear wave center frequency and bandwidth of shear waves induced by acoustic radiation force depend on the ultrasound push beam (push duration, F -number, etc.) [24] and the viscoelasticity of the medium, and therefore are different across scanners from different vendors. As a result, scanners from different vendors may give different tissue elasticity measurements within the same patient [25-27]. This can be very problematic for clinical practice, which is a challenge well recognized by experts in the Quantitative Imaging Biomarkers Alliance Ultrasound Shear Wave Speed Biomarker Committee [28]. The charge of this Committee is to develop protocols that allow consistent measurements of liver stiffness across different scanners. Although various methods have been proposed to evaluate SWV dispersion and estimate tissue viscoelasticity, they still rely on rheological models that typically impose strong assumptions about frequency dependency of material parameters, which are hard to validate in biological tissues *in vivo*. One alternative to using a rheological model is to report the SWV at a fixed frequency or use the slope of the SWV versus frequency over a limited bandwidth [29]. These two parameters, however, still cannot cleanly separate the effects of viscosity from elasticity. The current challenges of measuring SWV at a fixed frequency *in vivo* include the ability to measure SWV with high signal-to-noise ratio (SNR) when shear wave motion is typically very weak and noisy and establishing a fixed frequency in a clinical practice where shear-wave frequency content varies across scanner and patients. In summary, there is a pressing need for a model-free measurement of viscoelasticity with high SNR to facilitate more accurate and consistent tissue elasticity measurements.

We have previously proposed a method capable of quantifying tissue viscoelasticity in a model-independent manner called Acoustic Radiation Force Induced Creep (ARFIC) method [20]. A limitation of the ARFIC method, is that to study viscoelastic parameters over a wide range of frequencies, the creep period needs to be maintained for long times, usually up to 30 ms, which means the total exposure time to acoustic radiation force in some cases may be too large. In this paper we present the Acoustic Radiation Force Induced Creep-Recovery (ARFICR) method [21, 22], a method capable of quantifying viscoelastic properties without relying on rheological models by estimating the complex shear modulus from time-dependent creep-recovery response induced by acoustic radiation force. The overall capabilities of ARFICR method are presented, including its use of short ARF excitation capable of exciting tissue viscoelastic response over a wide range of frequencies (up to 1 kHz) and measuring complex shear modulus in a localized region of interest with high SNR. Finally, we report on the ARFICR method validation with Finite Element Method (FEM) simulations and phantoms. Preliminary results in *in vivo* liver are also presented.

II. Materials and Methods

A. Principles of acoustic radiation force induced creep-recovery (ARFICR)

Amador *et al.* originally reported using focused ultrasound beams interspersed with focused detection beams to excite and measure creep response simultaneously to compute the model independent complex shear modulus of viscoelastic tissue [20]. The method was advanced to make measurements of the creep-recovery response as a result of short acoustic radiation

force excitation [21, 22]. A summary of the Acoustic Radiation Force Induced Creep (ARFICR) method theoretical principles is described below.

In viscoelastic theory, creep is a slow, progressive deformation of a material under constant stress. The removal of the step-stress elicits a response similar to that caused by the imposition of the step-stress; this response is called creep-recovery. In a homogeneous, isotropic, linear, viscoelastic material, the shear strain response to an arbitrary stress is described by the Boltzmann constitutive integral [30]:

$$\gamma(t) = \int_0^t J(t-\xi) \frac{\partial \tau(\xi)}{\partial \xi} d\xi \quad (1)$$

where $\gamma(t)$ is the shear strain response, $\tau(t)$ is the applied shear stress, $J(t)$ is creep compliance (ratio of shear strain and $[\cdot]/\xi$ represents the first derivative with respect to an independent variable ξ). Evans et al. [31] have reported the analytic solution of (1) by using the Fourier transform and its properties. Briefly, the time-dependent creep strain response, $\gamma(t)$, is converted to the frequency-dependent complex shear modulus, $G^*(\omega)$:

$$G^*(\omega) = \frac{FT[\tau(t)]}{FT[\gamma(t)]} \quad (2)$$

where $FT[\cdot]$ represents the Fourier transform and ω is angular frequency.

The creep-recovery strain response, $\gamma_{\text{creep-recovery}}(t)$, is the strain response to the removal of the applied step-stress, and it is expressed as the application at $t = t'$ of another step-stress of equal magnitude but opposite sign to the applied step-stress at $t = 0$. This stress excitation can be expressed in terms of the unit step function as:

$$\tau(t) = \beta \cdot H(t) - \beta \cdot H(t - t') \quad (3)$$

The first term in (3) represents the imposition of a step-stress of magnitude β (N m⁻²) at $t = 0$, while the second term represents the removal of the applied stress at $t = 0$, expressed as the imposition of a step-stress of equal magnitude but opposite direction delayed by t' . Using numerical simulations of a viscoelastic material model, Amador *et al.* demonstrated the creep-recovery strain in (4) contains the same time-dependent viscoelastic information as the creep strain $\gamma(t)$ [22].

$$\gamma_{\text{creep-recovery}}(t) = \gamma(t) - \gamma(t'), t > t' \quad (4)$$

As previously described by Amador et al. [21], the magnitude of the applied step-stress from acoustic radiation force is unknown, thus (2) can be written as:

$$G^*(\omega) = \beta \cdot \mu^*(\omega) \quad (5)$$

where $\mu^*(\omega)$ is a unitless relative complex shear modulus and β (N m⁻²) is the magnitude of the applied step-stress. Because the applied acoustic radiation force, $F = 2aI/c$ [32], is a function of speed of sound of the media, c , the absorption coefficient of the media, a , and the temporal average intensity of the acoustic beam at given spatial location, I , the relative complex shear modulus $\mu^*(\omega)$ would vary as a function of c , a and I . To overcome this problem, a widely used property of viscoelastic material called loss tangent, $\tan(\delta)$, is used. The loss tangent of a viscoelastic material is defined as the ratio of the imaginary part of the complex shear modulus, $\text{Im}[G^*(\omega)]$, to the real part of the complex shear modulus, $\text{Re}[G^*(\omega)]$ [30]:

$$\tan(\delta) = \frac{\text{Im}[G^*(\omega)]}{\text{Re}[G^*(\omega)]} = \frac{\text{Im}[\beta \cdot \mu^*(\omega)]}{\text{Re}[\beta \cdot \mu^*(\omega)]} = \frac{\text{Im}[\mu^*(\omega)]}{\text{Re}[\mu^*(\omega)]} \quad (6)$$

To fully characterize viscoelastic material properties, the magnitude of the applied stress from ARF impulse β is required. A method to estimate the unknown ARF magnitude β from shear wave propagation was previously proposed by Amador *et al.* [20]. In summary, in a viscoelastic material the complex shear modulus, $G^*(\omega)$ is related to the complex wavenumber, $k^*(\omega)$, and material density, ρ (kg m³), by [33]:

$$G^*(\omega) = \rho \frac{\omega^2}{(k^*(\omega))^2} \quad (7)$$

The real part of the complex wavenumber is defined as $k_r(\omega) = \omega/c_s(\omega)$, where $c_s(\omega)$ is the shear wave phase velocity. On other hand, the imaginary part of the complex wavenumber is defined as $k_i(\omega) = \alpha_s(\omega)$, where $\alpha_s(\omega)$ is the shear wave attenuation. Rewriting (5) and (7) and solving for β yields:

$$\beta = \rho \frac{\omega^2}{(k^*(\omega))^2 \cdot \mu^*(\omega)} \quad (8)$$

Several methods have been proposed to estimate shear wave phase velocity that results from ARF excitation [6, 34]. On the other hand, few methods exist to compute shear wave attenuation [12, 13]. Because the shear wave frequency bandwidth varies with shear wave excitation parameters [24], to standardize the ARFICR method we propose to use (9) with

the shear wave phase velocity at the shear wave center frequency, ω_c , the frequency at which the shear wave energy is highest. See Appendix A for a more detailed development. It should be noted that the development in Appendix A assumes that at ω_c , it is assumed that the loss modulus is much smaller than the storage modulus.

$$\beta = \rho \frac{c_s^2(\omega_c)}{\text{Re}[\mu^*(\omega_c)]} \quad (9)$$

Finally, (2), (5), and (9) are used to solve for the complex shear modulus $G^*(\omega)$ at multiple frequencies. The complex shear modulus $G^*(\omega)$ is defined as $G^*(\omega) = G_s(\omega) + iG_l(\omega)$, where $G_s(\omega)$ is the storage modulus or shear elastic modulus and $G_l(\omega)$ is loss modulus. A direct measure of material viscosity can be computed from the complex shear modulus, this is known as the complex viscosity, $\eta^*(\omega) = \eta'(\omega) + i\eta''(\omega)$, where $\eta'(\omega) = G_l(\omega)/\omega$ is the dynamic viscosity and $\eta''(\omega) = G_s(\omega)/\omega$ is the out-of-phase viscosity [35].

A diagram of the ARFICR method is described in Fig 1. In summary, ARFICR uses focused acoustic radiation force (ARF) along the z -axis (Fig. 1-A) to excite the dynamic response of viscoelastic material. This impulsive ARF (with duration typically below 1 ms) perturbs the tissue in two ways: 1) at the push beam focus x_0 , the ARF impulse acts as a step-stress, $\gamma(t)$ in (3), inducing creep-recovery strain response $\gamma_{\text{creep-recovery}}(t)$ in (4); 2) the ARF impulse creates shear waves that propagate radially outward from the focal location along the x -axis. Following the ARF impulse, the transducer is switched to an ultrafast (or high frame rate) imaging mode to detect $\gamma_{\text{creep-recovery}}(t)$ at the focus x_0 (Fig. 1-B) and shear waves propagating outwards, (Fig. 1-C). The time to frequency conversion described in (2) yields the relative complex shear modulus $\mu^*(\omega)$ shown in Fig. 1-D. The shear wave propagation that occurs outside the focal area allows the computation of the shear wave phase velocity at the shear wave center frequency, $c_s(\omega_c)$, where the shear wave energy is highest (Fig. 1E). Finally, once the relative complex shear modulus $c_s(\omega)$ in (5) and β in (9) are known, the model-independent complex shear modulus $G^*(\omega)$ is computed according to (5) refer to Fig. 1-F.

B. Simulations and experiments

A numerical simulation study with Finite Element Method (FEM) is used to demonstrate the extent of ARFICR method characterization of viscoelastic properties. Moreover, ARFICR viscoelastic measurements are validated with an independent method called hyper frequency viscoelastic spectroscopy (HFVS) in tissue mimicking phantoms. Finally, an *in vivo* preliminary study in healthy human subjects is used to demonstrate the feasibility of ARFICR method characterization of liver viscoelastic properties.

1) Simulations—A finite element method (FEM) model was used to simulate the dynamic response of a viscoelastic material from an acoustic radiation force excitation [36]. The acoustic intensity fields associated with a focused push and $f/2.0$ configuration excitation of a linear array transducer were simulated using Field II [37, 38]. The intensity field, I , was calculated in a domain with 50 mm lateral, 15 mm elevation and 100 mm axial (represented

by x , y , and z , respectively) with a spatial resolution of 0.25 mm in elevation and axial, and 0.25 mm in lateral direction. A three-dimensional FEM was constructed in Abaqus/CAE 6.01-EF1 (Dassault Systèmes S.A., Vélizy-Villacoublay, France). The geometry was the same as described in Field II simulation. The body force was then converted to nodal point loads applied in the beam direction z [36]. A homogeneous Kelvin-Voigt material was approximated from a one-branch generalized Maxwell model as proposed by Qiang *et al.* [39]. The Kelvin-Voigt model shear elastic modulus, G , was set to 9 kPa and three levels of dynamic viscosity, η , were defined, 0.1 (Material 1), 2.0 (Material 2) and 5.0 Pa-s (Material 3). The mass density and Poisson's ratio were 1000 kg/m³ and 0.4999, respectively. At $t = 0$ s, a body force in z direction and duration of 500 μ s (step function) was introduced. The total simulation time was 10 ms with a sampling frequency of 10 kHz.

2) Experiments

a) Phantom Study: Three viscoelastic tissue mimicking phantoms were made as described by Amador et al. [40], consisting of 8% gelatin (Sigma-Aldrich, St. Louis, MO), 1% potassium sorbate (Sigma-Aldrich), 1% cellulose (Sigma-Aldrich), 6% propylene glycol and 0.5% xanthan gum were made by volume concentration. To vary the viscoelastic properties, two phantoms were made with 5% (Phantom 2) and 10% (Phantom 3) of Vanicream Lite (Pharmaceutical Specialties, Inc., Rochester, MN), made by volume concentration. The control phantom (Phantom 1) did not have Vanicream and xanthan gum. The acoustic velocity of the designed phantoms was close to soft tissue values, 1540 m/s. From a given batch each phantom mixture was poured into 3 cylinders (9.4 mm diameter and 44 mm height) for hyper frequency viscoelastic spectroscopy (HFVS) [41] measurements and in a cube with 40 mm x 60 mm x 38 mm (width x length x height) dimensions for ARFICR measurements. Experiments were completed one week after phantom preparation. A RheoSpectris C500+ (Rheolution, Inc., Montreal, QC, Canada) with the cylinder fixture was used to measure the complex shear modulus, $G^*(\omega)$, with frequencies between 10 Hz and 1000 Hz for the HFVS experiments.

A Verasonics V-1 ultrasound system (Verasonics, Inc., Kirkland, WA) equipped with a linear array transducer (L11-4v, Verasonics, Inc., Kirkland, WA) was used. Acoustic radiation force was used to induce dynamic responses by using 500 μ s push length with a focused $f/2.0$ push beam of 6.43 MHz center frequency. Plane wave imaging was used for detection at a 10 kHz frame rate for 20 ms. Received signals from 3 steering angles (-1° , 0° , $+1^\circ$) were compounded [42], giving an effective pulse repetition frequency (PRF) of 3.33 kHz.

b) Phantom Study: Healthy individuals with no history of liver disease were included in the study. The experiment protocol was approved by the Mayo Clinic Institutional Review Board and written informed consent was obtained prior to scanning. Seven subjects (3 female, 4 male, mean Body Mass Index (BMI): 26 ± 3 kg/m²) were recruited for the study. Imaging and measurements were performed by an experienced sonographer with the ultrasound probe positioned at the 8th intercostal space during breath holds. Under the guidance of B-mode imaging, the sonographer located the tissue of interest and a region of interest 1.5 cm below the liver capsule. Five sequential acquisitions were performed. The shear wave generation and detection was completed following the procedure described by

Amador et al. [43]. A Vantage ultrasound system (Verasonics, Inc., Kirkland, WA) equipped with a curved array transducer (C5-2v, Verasonics, Inc., Kirkland, WA) was used. The detection beams were wide beams with an $f/9.9$ focal configuration transmitted with a frequency of 2 MHz. During receive, the radiofrequency (RF) signals from two steering angles (-1° , $+1^\circ$) were coherently compounded [42], giving an effective pulse repetition frequency (PRF) of 2.77 kHz. The Verasonics system converts the RF signals to in-phase/quadrature (IQ) signals, which were saved for later analysis.

c) ARFICR analysis: A 2D autocorrelation method was used to estimate particle velocity and displacement [44]. The creep-recovery shear strain was computed from the partial derivative of axial displacement respect to lateral distance as described in Amador *et al.* [21]. The shear wave center frequency and shear wave phase velocity at the center frequency were computed using the two-dimensional Fourier transform method as described in [24].

d) Viscoelastic parameters analysis: The viscoelastic parameters that are reported are the shear elastic modulus, G_s , and dynamic viscosity, η' . Hereinafter the shear elastic modulus G_s will be denoted as G and the dynamic viscosity η' will be denoted as η . In all simulations and phantom studies, the measured viscoelastic parameters (shear elastic modulus, $G(\omega)$, and dynamic viscosity, $\eta(\omega)$ with ARFICR are compared to a control measurement (theoretical value in FEM simulations and HFVS in experiments) with a percent error (PE):

$$PE(\omega) = 100\% \left(\left| \frac{X_{\text{measured}}(\omega) - X_{\text{control}}(\omega)}{X_{\text{control}}(\omega)} \right| \right) \quad (10)$$

where X_{measured} is the viscoelastic parameter computed with ARFICR or Kelvin-Voigt model fit, X_{control} is the viscoelastic parameter from FEM or measured with HFVS and ω is the angular frequency.

III. Results

1) Simulations

For simplicity, the computed creep-recovery strains are normalized. The computed normalized creep-recovery strain and relative complex shear modulus, μ^* , in all simulated materials is illustrated in Fig. 2. The normalized creep-recovery strains of simulated materials with higher dynamic viscosity were in good agreement with the theoretical Kelvin-Voigt model normalized creep strain that was computed from (12) [30].

$$\gamma_{\text{control}}(t) = 1 - e^{-\frac{G}{\eta}t} \quad (12)$$

Fig. 3 shows the two-dimensional Fourier transform (k-space) of spatiotemporal shear wave motion at the nominal focal depth in all simulated materials. The measured shear wave

center frequencies, $\omega_c/2\pi$, were 306 Hz, 201 Hz and 155 Hz in simulated materials 1, 2 and 3 respectively.

Shear wave phase velocity, $\alpha(\omega_c)$, and the real part of the relative complex shear modulus, $\text{Re}[\mu^*(\omega_c)]$, are used to calculate the calibration factor, β , to compute the model independent shear elastic modulus, G , and dynamic viscosity, η . Fig. 4 illustrates the computed shear elastic modulus and dynamic viscosity in all simulated materials.

The slight difference in shear elastic modulus and dynamic viscosity computed with ARFICR and the control that is observed in Fig. 4 was quantified by computing the percent error from (10) as a function of frequency. A summary of the medians of percent error (PE) with respect to frequency of shear elastic modulus and dynamic viscosity are shown in Fig. 5.

By inspection of (12), when $t \rightarrow \infty$, the creep-strain $\gamma(t)$ determines the shear elastic modulus G , as a consequence, the estimates of shear elastic modulus G from creep methods are robust as long as the creep-strain reaches steady-state. As expected, the median percent error of shear elastic modulus G was similar in all simulated materials. On the other hand, the time-dependency of (12) is mostly due to the dynamic viscosity η thus the estimates of dynamic viscosity η from creep methods are highly affected by measured the creep-strain. For instance, because Material 1 was highly elastic, the measure creep-strain shown in Fig. 2 elucidated the transient response; therefore the median percent error of dynamic viscosity was considerably high in Fig. 5. In the case of simulated materials with higher dynamic viscosity, the ARFICR method was able to estimate the dynamic viscosity with median percent error less than 23%.

2) Experiments

a) Phantoms study—The computed normalized creep-recovery strain and relative complex shear modulus, μ^* , in the studied phantoms are illustrated in Figs. 6 and 7. A difference in the time to reach steady-state strain is observed in the phantoms, suggesting viscoelastic behavior in Fig. 6. Phantom 1 was expected to be highly elastic, as a consequence of low viscosity the transient response is revealed on top of the creep response, refer to Fig. 6, as it is carried out to the computed relative complex shear modulus in Fig. 7(a). On the other hand, the viscoelastic behavior of Phantoms 2 and 3 can be appreciated in the frequency-dependent behavior of the computed relative complex shear modulus in Figs. 7(b)(c).

Fig. 8 shows the two-dimensional Fourier transform (k-space) of shear wave motion and shear wave phase velocity dispersion in all the studied phantoms. The measured wave center frequencies, $\omega_c/2\pi$, were 222 Hz, 152 Hz and 125 Hz in phantoms 1, 2 and 3 respectively. As with the FEM study, the shear wave center frequency is inversely related to dynamic viscosity.

The most common approach to measure tissue viscoelasticity is fitting a Kelvin-Voigt model to the shear wave phase velocity dispersion to solve for shear elastic modulus and dynamic viscosity [6]. Shear wave phase velocities computed from the Fourier transform (k-space) of

shear wave motion and $c_s(\omega) = \omega/k_f(\omega)$ are illustrated in Fig. 9. By replacing the Kelvin-Voigt model complex shear modulus $G_{KV}^*(\omega) = G_{KV} + i\eta_{KV}\omega$, in (7) and solving for shear wave speed, (13) is commonly used to solve for Kelvin-Voigt model shear elastic modulus G_{KV} and dynamic viscosity η_{KV} [6].

$$c_s(\omega) = \sqrt{\frac{2(G_{KV}^2 + \eta_{KV}^2 \omega^2)}{\rho(G_{KV} + \sqrt{G_{KV}^2 + \eta_{KV}^2 \omega^2})}} \quad (13)$$

Fig. 9 illustrates the Kelvin-Voigt model fits to shear wave phase velocity derived from k-space.

Fig. 10 illustrates the ARFICR computed shear elastic modulus, G , and dynamic viscosity, η , the Kelvin-Voigt model fit result of shear elastic modulus, G_{KV} , and dynamic viscosity, η_{KV} , as well as the control measurements (from HFVS) in all phantoms.

Interestingly, the shear elastic modulus G and dynamic viscosity η of the viscoelastic Phantoms 2 and 3 is strongly dependent on frequency. A summary of the percent error (PE) of shear elastic modulus, G , and dynamic viscosity, η , measured with ARFICR and Kelvin-Voigt model with respect to control measurements (HFVS) in all phantoms are shown in Table I

b) Liver study—Acoustic Radiation Force Induced Creep-Recovery (ARFICR) method was used to measure the model-free shear modulus, G , and dynamic viscosity, η , in 7 healthy livers. The ARFICR results are compared to the Kelvin-Voigt model fits to shear wave phase velocity (Fig. 11). The frequency-dependent nature of shear elastic modulus and dynamic viscosity of liver tissue is observed in the ARFICR estimates.

IV. Discussion

Ultrasound-based shear wave elasticity imaging has shown to be a useful clinical tool to the noninvasive assessment of tissue pathological state. Very few methods have been proposed to quantify soft tissue viscoelasticity without relying on rheological models. The ARFICR method presented here is a novel approach that overcomes the challenges associated with assumption of pure elasticity behavior, selecting rheological models to describe soft tissue viscoelasticity and fitting approaches.

In this study the FEM simulations and phantom study served to illustrate the ARFICR method viscoelastic quantification limits in materials with dominant elastic behavior with respect to viscous behavior. The field of solid mechanics establishes the pure elastic materials strain response from a stress stimulus with the Hooke's law, where the strain response is proportional to the stress with respect to the modulus of elasticity [8]. In two and three dimensional settings, in addition to the modulus of elasticity, the strain response is affected by factors such as inertia. Because in viscoelastic material the strain response is time-dependent according to the viscous component, in two and three dimensional settings

the time-dependent strain can be greatly affected by material transient response (inertia) if the elastic component is dominant. For instance, in Fig. 2(a) the time-dependent creep-recovery strain was highly affected from the dominant elastic behavior in Material 1. On the other hand, as the dynamic viscosity was increased in Materials 2 and 3, the time-dependent creep-recovery strain response was dominated by the viscous component (Figs. 2(b) and 2(c)). Similarly, the measured creep-recovery strain in the viscoelastic phantoms also illustrates the material transient response in a material with dominant elasticity, refer to Fig. 6.

In all simulated materials and phantoms the ARFICR method was able to estimate the relative complex shear modulus $\mu^*(\omega)$. Because the estimated relative complex shear modulus is derived directly from the creep-recovery strain, the transient response effects on the creep-recovery strain easily propagate to the relative complex shear modulus computation. However, the analytic solution of the constitutive equation in viscoelastic materials used in ARFICR estimates the relative complex shear modulus in a frequency range set by the temporal resolution and range of the creep-recovery strain [31]. For instance, the time of the first temporal creep-recovery strain sets the highest frequency and the last temporal creep-recovery strain sets the lowest frequency point recovered by the analytic solution [31]. The inertia response on the simulated Material 1 occurs on a time window between 0.1 ms to 1 ms (refer to Fig. 2(a)), the relative complex shear modulus computation will be sensitive to the transient response between 1 kHz to 10 kHz (refer to Fig. 2(d)). Similar results were encountered in the phantom study. The transient response of Phantom 1 is observed in the creep-recovery strain up to approximately 10 ms which will be reflected in the frequency response at 100 Hz refer to Figs. 6 and 7(a). As expected, the computed relative complex shear modulus, μ^* , of Phantom 1 carried out the transient response observed in the creep-recovery strain, refer to Fig. 7(a). On the other hand both the creep-recovery strain and computed relative complex shear modulus of Phantoms 2 and 3 were not highly affected by their transient response, as a result of their higher viscous composition. To limit the inertia effects on materials with a dominant elastic response, we evaluated the ARFICR viscoelastic measurements between 100 to 1 kHz.

One of the advantages of the ARFICR method is the use of the ARF to excite a viscoelastic transient response in a fast and localized way. In addition, ARFICR method uses the creep-recovery strain response at the focal ARF excitation, the ARFICR measured creep-recovery strain is less subjected to speckle decorrelation noise thus are high signal-to-noise measurements. From Eqs. (2)–(5) the applied step-stress and measured creep-recovery strain, the complex shear modulus G^* can be fully recovered without assuming rheological models. Nonetheless, in ARF based methods the applied force is unknown hence the magnitude of the applied stress, τ , is also unknown. In previous studies, we proposed to use the widely used viscoelastic parameter called loss tangent or $\tan(\delta)$ because it is independent of the unknown step-stress magnitude β [20]. It is important to note that because the loss tangent is the ratio of the loss modulus and the storage modulus (refer to (6)), a potential limitation of using loss tangent to differentiate tissue pathological state occurs when both storage modulus and loss modulus increase or decrease with the same proportion.

To fully recover the complex shear modulus G^* , ARFICR method takes advantage of the shear wave that is generated from the focused ARF excitation (refer to Fig. 1(A)). From the same ultrasound ARF excitation, both creep-recovery at the focus and shear wave propagation outside the focal area excited and acquired. Fig. 3 and Fig. 8 illustrate the shear wave propagation two-dimensional Fourier transform or k-space of the simulated viscoelastic materials and studied viscoelastic phantoms. The k-space is used to derive the shear wave phase velocity, c_s , at the most dominant frequency also known as the center frequency, ω_c . By inspection of Fig. 3 and Fig. 8, as the dynamic viscosity was increased, the energy distribution of k-space was shifted to the lower frequencies. Influences in shear wave center frequency from material properties and excitation characteristics have been previously reported by Palmeri *et al.* [24], for instance the shear wave center frequency is directly proportional to material shear elastic modulus and inversely proportional to push/excitation duration. In this study, for fixed shear elastic modulus and push duration we found an inverse proportional relation between shear wave center frequency and dynamic viscosity in simulated viscoelastic materials and viscoelastic phantoms; supporting the importance of fully viscoelasticity characterization as a function of frequency.

The ARFICR measured shear elastic modulus and dynamic viscosity were in good agreement with the simulation theoretical values, refer to Fig. 4. It can be observed ARFICR is capable of recovering shear elastic modulus and dynamic viscosity over a wide range of frequencies (200 Hz to 1000 Hz). To quantify the level of agreement between ARFICR and theoretical values of shear elastic modulus and dynamic viscosity, a percent error was computed and the median of percent error over the frequency range is reported in Fig. 5. As expected, the percent error was larger for the material with dominant elasticity (Material 1) and decreased as the material viscosity was increased. Surprisingly, the frequency behavior of ARFICR measured shear elastic modulus and dynamic viscosity of the Phantoms was rather different from the FEM simulation. For instance, in the FEM simulations a Kelvin-Voigt material was used, where both shear elastic modulus and dynamic viscosity are not function of frequencies. By inspection of Fig. 10, the studied viscoelastic phantoms, especially Phantoms 2 and 3, exhibited a frequency-dependent shear elastic modulus and dynamic viscosity suggesting a simple rheological model such as the Kelvin-Voigt model may be too simple to described viscoelastic properties of the studied phantoms. The latter statement is reinforced by comparing the Kelvin-Voigt model shear elastic modulus and dynamic viscosity from fitting it to shear wave phase velocity dispersion to the ARFICR measurements that are shown in Fig. 10. By inspection of Fig. 10, measures of shear elastic modulus and dynamic viscosity from ARFICR were in excellent agreement with the control method in the studied phantoms. On the other hand, the shear elastic modulus and dynamic viscosity from Kelvin-Voigt model fit were rather different than the control method. The computed median percent error (Fig. 5 and Table I) of ARFICR shear elastic modulus and dynamic viscosity were no greater than 23% in materials with less dominant elasticity (Materials 2 and 3, Phantoms 2 and 3). On the other hand, the computed median percent error of Kelvin-Voigt model fit shear elastic modulus was less than 14% and dynamic viscosity less than 100 % in viscoelastic phantoms (Phantoms 2 and 3). An important aspect observed in Figures 9 and 10 is that the shear wave phase speed does not completely characterize the viscoelastic properties. Fitting a rheological model to shear wave speed

assumes specific behavior of the complex modulus, therefore fully validating the complex modulus of rheological models is essential to achieve the accuracy needed in tissue diagnostic purposes.

One of the most important clinical applications of elasticity imaging is liver fibrosis staging. Recently, Nightingale *et al.* reported significant fibrosis staging shear wave speed threshold variability as a function of shear wave frequency [29]. In spite of significant efforts to study diagnostic capabilities of shear wave elasticity imaging; there is still the need of methods than can provide consistent measurements of liver elasticity. We conducted a pilot study in 7 healthy volunteers where ARFICR measurements in liver were obtained. Fig. 11 shows the results of shear elastic modulus and dynamic viscosity obtained with ARFICR and the Kelvin-Voigt model fitting to shear wave velocity dispersion. The shear elastic modulus and dynamic viscosity estimates of ARFICR and Kelvin-Voigt model fitting are within the same range, thus providing credibility to ARFICR measurements *in vivo*. Interestingly, the variation of dynamic measured by ARFICR is much lower than the Kelvin-Voigt model fitting. Thus ARFICR measurements may be more robust than Kelvin-Voigt fitting to shear wave speed dispersion. Among the limitations that exist when fitting rheological models to shear wave dispersion, the most common ones are eluded to limited frequency bandwidth due to shear wave attenuation and poor signal quality in *in vivo* measurements. One of the uniquely beneficial features of ARFICR is illustrated in Fig. 12; the creep-recovery time signal is inherently wideband as opposed to the narrowband shear wave signal, thus providing high SNR measurements over a large bandwidth.

We have described and validated a method to fully quantify regional viscoelastic properties in a manner independent of models. Previous work in this area involved the use of rheological models; nonetheless the need for such models affects the viscoelastic parameter estimation as well as the fitting process. There are few limitations of this study. First, to completely evaluate the robustness of ARFICR measurements, the effects of acoustic radiation force excitation (e.g. geometry, force duration) in the creep-recovery strain signal need to be evaluated in a more controlled manner. Second, shear wave reflections and overall motion during the acquisition time that can affect the measured creep-recovery strain could have implications in the shear elastic modulus and dynamic viscosity estimates. Although the limitations of the study could affect the consistency of ARFICR shear elastic modulus and dynamic viscosity measurements, the ARFICR method has the potential to be a clinical viable alternatively invasive procedures.

V. Conclusion

We have described and validated a method to fully quantify regional tissue viscoelastic properties. The Acoustic Radiation Force Induced Creep-Recovery (ARFICR) method is a novel approach to overcome difficulties encounter with imposition of rheological models and fitting approaches. The results suggest ARFICR is capable of measuring viscoelasticity over a wider range of frequencies in a robust and reliable manner, thus a method than can facilitate clean and consistent comparison of elastographic results at any selected frequency across scanner and patients.

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Appendix A

Expanding μ^* and k^* in (8) yields:

$$\begin{aligned} & k_r^2(\omega) \cdot \mu_s(\omega) \\ & - 2 \cdot k_r(\omega) \cdot k_i(\omega) \cdot \mu_l(\omega) \\ & - k_i^2(\omega) \cdot \mu_s(\omega) \\ & - i \cdot \left[2 \cdot k_r(\omega) \cdot k_i(\omega) \cdot \mu_s(\omega) + k_r^2(\omega) \cdot \mu_l(\omega) - k_i^2(\omega) \cdot \mu_l(\omega) \right] = \rho \frac{\omega^2}{\beta} \end{aligned} \quad (A1)$$

Separating the real and imaginary parts of (A1):

$$k_r(\omega)^2 \cdot \mu_s(\omega) - 2 \cdot k_r(\omega) \cdot k_i(\omega) \cdot \mu_l(\omega) - k_i(\omega)^2 \cdot \mu_s(\omega) = \rho \frac{\omega^2}{\beta} \quad (A2)$$

$$2 \cdot k_r(\omega) \cdot k_i(\omega) \cdot \mu_s(\omega) + k_r(\omega)^2 \cdot \mu_l(\omega) - k_i(\omega)^2 \cdot \mu_l(\omega) = 0 \quad (A3)$$

Assuming that at the center frequency (ω_c) the relative loss modulus is significantly smaller than the relative storage modulus ($\mu_l(\omega_c) \ll \mu_s(\omega_c)$), (A3) can be approximated to:

$$2 \cdot k_r(\omega_c) \cdot k_i(\omega_c) \cdot \mu_s(\omega_c) = 0 \quad (A4)$$

The solutions of equation (A2) could be found depending on equation (A4):

Case 1: $k_i(\omega_c) = 0$, equation (A4) becomes

$$-k_i(\omega_c)^2 \cdot \mu_s(\omega_c) = \rho \frac{\omega_c^2}{\beta} \quad (A5)$$

Case 2: $k_l(\omega_c) = 0$, equation (A4) becomes

$$k_r(\omega_c)^2 \cdot \mu_s(\omega_c) = \rho \frac{\omega_c^2}{\beta} \quad (\text{A6})$$

Case 3: $\mu_\sigma(\omega_c) = 0$, equation (A4) becomes

$$-2 \cdot k_r(\omega) \cdot k_i(\omega_c) \cdot \mu_l(\omega_c) = \rho \frac{\omega_c^2}{\beta} \quad (\text{A7})$$

Case 1 and Case 3 are not realistic because of the negative sign; the only realistic solution is Case 2. This implies that β in this case is determined by the shear wave speed

$C_s(\omega_c)^2 = \frac{\omega_c^2}{k_r(\omega_c)^2}$ and the storage modulus or the real part of the complex modulus at the center frequency, $\mu_s(\omega_c)$.

$$\beta = \rho \frac{\omega_c^2}{k_r(\omega)^2 \cdot \mu_s(\omega_c)} = \rho \frac{c_s^2(\omega_c)}{\mu_s(\omega_c)} \quad (\text{A8})$$

To explore the implications of our assumptions, Table II shows the relative storage and loss modulus at the shear wave center frequencies for each phantom from the ARFICR method. The relative storage modulus is 5 to 8 times larger than the relative loss modulus, which generally meets the assumption that the loss modulus is much smaller than the storage modulus.

Table III shows the ratio of loss modulus to storage modulus (loss tangent) at the shear wave center frequencies for each phantom from the ARFICR method and the hyper frequency viscoelastic spectroscopy (HFVS) method as well as the Percent Errors (Eq. 10 in the manuscript). It can be observed that in the viscoelastic phantoms (Phantoms 1 and 2) the error is less than 13%.

Likewise, two sample paired t-tests with one side tail show that loss modulus measured with HFVS (gold standard) at shear wave center frequency is significantly smaller than storage modulus measured with HFVS (gold standard) at the shear wave center frequency ($p < 0.001$). The sample size was 4 repeated measurements. Statistical significance for all results was accepted at $p < 0.05$.

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Fig. 1.

Principles of ARFICR. (A) Acoustic radiation force from an ultrasound transducer is used to excite dynamic response of viscoelastic material. Ultrasound imaging is used to measure (B) $\gamma_{\text{creep-recovery}}(t)$ at x_0 and (C) shear wave propagation. ARFICR converts creep-recovery strain in (B) to a relative complex shear modulus $\mu^*(\omega)$ in (D). Shear wave propagation in (C) is used to estimate the shear wave velocity at the center frequency (E). Finally, the model-independent complex shear modulus $G^*(\omega)$ in (F) is computed from calibrating the relative complex shear modulus $\mu^*(\omega)$ in (D) and β . Panels B through F illustrate experimental data from a viscoelastic tissue mimicking phantom.

Fig. 2.

Top row: Normalized creep-recovery strain in (a) Material 1, (b) Material 2 and (c) Material 3; ARFICR measurements are represented with dots and the continuous line represents the control value (theoretical). Bottom row: Relative complex shear modulus, μ^* , in (a) Material 1, (b) Material 2 and (c) Material 3; the real part of the relative complex shear modulus, $\text{Re}[\mu^*]$, is represented with (o) symbol and the imaginary part of the relative complex shear modulus, $\text{Im}[\mu^*]$, is represented with (*) symbol.

Fig. 3.

Two-dimensional Fourier transform (k-space) of shear wave propagation in (a) Material 1, (b) Material 2 and (c) Material 3. The shear wave center frequencies, ω_c , are shown with (*) symbol.

Fig. 4.

FEM simulations (Top row) Shear elastic modulus G and (Bottom row) dynamic viscosity η of (a, d) Material 1, (b, e) Material 2 and (c, f) Material 3. ARFICR measurements are represented with (.) symbols and the continuous line represents the control value (theoretical).

Fig. 5. Median of percent errors (%) over 200 to 1000 Hz each 100 Hz of (a) shear elastic modulus and (b) dynamic viscosity from FEM simulations.

Fig. 6.
Normalized creep-recovery strain in Phantom 1, Phantom 2 and Phantom 3.

Fig. 7.

Relative complex shear modulus, μ^* in (a) Phantom 1, (b) Phantom 2 and (c) Phantom 3; the real part of the relative complex shear modulus, $\text{Re}[\mu^*]$, is represented with (o) symbol and the imaginary part of the relative complex shear modulus, $\text{Im}[\mu^*]$, is represented with (*) symbol.

Fig. 8.

Two-dimensional Fourier transform (k-space) of shear wave propagation in (a) Phantom 1, (b) Phantom 2 and (c) Phantom 3. The shear wave center frequency, ω_s , is shown with (*) symbol.

Fig. 9. Shear wave phase velocity dispersion in (a) Phantom 1, (b) Phantom 2 and (c) Phantom 3. The continuous lines represent the Kelvin-Voigt model fits to shear wave phase velocity dispersion.

Fig. 10.

(Top row) Shear elastic modulus G and (Bottom row) dynamic viscosity η of (a,d) Phantom 1, (b,e) Phantom 2 and (c,f) Phantom 3. ARFICR measurements are represented with (*) symbols, Kelvin-Voigt measurements are represented with (o) symbols and the continuous line represents the control value (HFVS).

Fig. 11.

Box-and-whisker plots of shear elastic modulus G (Top row) and dynamic viscosity η (Bottom row) of 7 healthy livers from ARFICR (b, d) and fitting the Kelvin-Voigt model (a, c) to shear wave velocity dispersion. The box represents the interquartile range (IQR), the red continuous line represents the median and the cross symbols (+) represent outliers (n = 7).

Fig. 12.

Frequency spectrum: creep-recovery strain at x_0 of Fig. 1-B and shear wave motion at x_1 , x_2 , x_3 of Fig. 1-C.

Table I

Median of percent errors (%) over 200 to 1000 Hz each 100 Hz of storage modulus and dynamic viscosity from phantoms.

Phantom	Shear elastic modulus, G		Dynamic viscosity, η	
	ARFICR	Kelvin-Voigt	ARFICR	Kelvin-Voigt
1	6.58	5.27	94.49	100
2	1.26	9.59	13.62	99.95
3	1.14	14.64	6.49	99.95

Table II

Relative storage and loss modulus of phantoms measured by ARFICR.

Relative modulus	Phantom		
	1	2	3
Storage	0.98	1.01	1.05
Loss	0.17	0.13	0.23

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Table III

Loss tangent of phantoms measured by ARFICR and HFVS. Percent Errors (PE, %) of loss tangent from by ARFICR and HFVS.

Method	Loss tangent		
	Phantom		
	1	2	3
ARFICR	0.17	0.13	0.22
HFVS	0.08	0.14	0.25
PE, %	112.50	7.76	12.67