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DETECTING REGIONAL STIFFNESS CHANGES IN AORTIC ANEURYSMAL GEOMETRIES USING PRESSURE-NORMALIZED STRAIN

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Abstract

Transabdominal ultrasound elasticity imaging could improve the assessment of rupture risk for abdominal aortic aneurysms by providing information on the mechanical properties and stress or strain states of vessel walls. We implemented a non-rigid image registration method to visualize the pressure-normalized strain within vascular tissues and adapted it to measure total strain over an entire cardiac cycle. We validated the algorithm's performance with both simulated ultrasound images with known principal strains and anatomically accurate heterogeneous polyvinyl alcohol cryogel vessel phantoms. Patient images of abdominal aortic aneurysm were also used to illustrate the clinical feasibility of our imaging algorithm and the potential value of pressure-normalized strain as a clinical metric. Our results indicated that pressure-normalized strain could be used to identify spatial variations in vessel tissue stiffness. The results of this investigation were sufficiently encouraging to warrant a clinical study measuring abdominal aortic pressure-normalized strain in a patient population with aneurysmal disease.

Keywords

Elastography; Elasticity imaging; Strain; Aneurysm; Ultrasound; Registration; Tissue-mimicking phantoms; 3-D printing

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.ultrasmedbio.2017.06.002>.

INTRODUCTION

An abdominal aortic aneurysm (AAA) is a dilation of the primary artery within the abdominal cavity (Vorp 2007). The majority of AAAs are focal and found within the infra-renal segment of the abdominal aorta (Taylor 1994). Since the development of the original reporting standard for arterial aneurysms, an AAA has been defined as a vessel diameter 50% greater than the expected normal vessel diameter (Johnston et al. 1991). Previous computer tomography studies defined the normal abdominal aortic diameter as 1.71 ± 0.06 cm in young women and 2.85 ± 0.04 cm in older men (Ouriel et al. 1992). Many clinical studies and government screening programs have accepted an abdominal aortic diameter >3.0 cm as diagnostic of an AAA (Ashton et al. 2002; Lederle 2000; LeFevre 2014). Although the diagnosis of an abdominal aortic aneurysm is straightforward and can be made using non-invasive imaging techniques, the natural history of a patient's specific AAA is not as precise. The feared sequel of AAA is the free rupture of the vessel wall, with some studies estimating an associated 80% 30-d mortality rate (Powell 2014; Robinson et al. 2016; Starnes et al. 2010).

Currently, surgical repair is the only known means of preventing rupture of an AAA (Schermerhorn et al. 2008). Surgical aneurysm repair itself is a significant source of mortality and morbidity; thus, an accurate quantification of a patient's rupture risk is required to determine the benefit of elective surgery. Attempts have been made to assign a given patient's risk of AAA rupture using a "maximum size criterion" (Darling et al. 1977; Szilagyi et al. 1966). Although a large body of both clinical trials (De Bruin et al. 2010; Lederle et al. 2002b; Parkinson et al. 2015; Powell et al. 2007; Schermerhorn et al. 2008; UK Small Aneurysm Trial Participants 1998) and epidemiologic data (Darling et al. 1977; Pleumeekers et al. 1995; Singh 2001) exist to quantify population-based risk of rupture at a given size, each of these studies accepted some degree of rupture mortality within the population (Thompson et al. 2012). A recent single-center report (Skibba et al. 2015) and meta-analysis (Parkinson et al. 2015) suggest that not only do patients rupture below clinically acceptable thresholds for repair, typically 5.0 cm in women and 5.5 cm in men (Grant et al. 2015), but most patients rupture at sizes substantially greater than the accepted diameters for surgical repair. These data would suggest that prior reports of rupture risk are likely overestimations and that many patients are exposed to surgical risk with possible limited personal benefit (Lederle et al. 2002a). Thus, an improved method for individualized patient rupture risk assessment is needed.

Extensive work has used computer models, such as finite elements (FE), to illustrate that calculations of stress within the aortic wall can provide improved AAA rupture risk prediction (Doyle et al. 2009; Fillinger et al. 2003; Helderma et al. 2008; Maier et al. 2010; Vande Geest et al. 2006). From a biomechanics perspective, the difficulty of any such model is the need for an accurate determination of the material properties of the aortic wall *in vivo*. Additionally, it is known that the aortic wall is a highly heterogeneous structure because of aortic vessel composition (collagen and elastin content and fiber orientation), atherosclerosis and spatial orientation of the aorta (Di Martino et al. 2006; Gasser et al. 2006; Raut et al. 2013; Ruddy et al. 2008; Tavares Monteiro et al. 2014; Vallabhaneni et al. 2004; Zou and Zhang 2012).

Various elastographic imaging methods such as magnetic resonance imaging (MRI) and electrocardiogram-gated computer tomographic angiography have been used to better define patient-specific aortic tissue mechanical properties non-invasively. The clinical utility of these methods has been limited largely by the high cost (Damughatla et al. 2015; Langham et al. 2011), significant ionizing radiation or nephrotoxicity of iodinated radiographic contrast dye (Auricchio et al. 2015; Budovec et al. 2010; Schlicht et al. 2013). As an alternative, ultrasound (US)-based elastographic methods are clinically convenient, as ultrasound is currently used as the standard of care to follow progression of AAA disease (Lee et al. 2009). Additionally, ultrasound-based methods come without the risks of ionizing radiation and can provide high-temporal-resolution data without the need for time-consuming and error-prone spatial reconstruction techniques.

Ultrasound-based elastographic methods can be broadly divided into the two methods for inducing a deformation in tissue: direct (surface induced or physiologic) and radiation force induced (Parker et al. 2012; Wells and Liang 2011). The large amount of tissue between the surface of the abdomen and the retroperitoneum makes freehand displacements of the abdominal aorta impractical and likely painful for patients. Although several studies have looked at the feasibility of performing acoustic radiation force impulse imaging on aneurysm-like geometries, clinical data from such techniques for the abdominal aorta have been limited by the acoustic depths of the aorta (Fahey et al. 2006; Tierney et al. 2011; Trahey et al. 2004).

The pulsatile nature of blood flow provides a physiologic deformation of the aorta that can be used for passive elastographic strain measurements. The Diamove (Teletec, Stockholm, Sweden) was one of the first commercially available cross-correlation-based tracking systems to provide strain measurements from B-mode ultrasound images (Benthin et al. 1991). This system has been used clinically to compare the strain and various calculated measures of stiffness in aneurysms that progress to rupture (Sonesson et al. 1999; Wilson et al. 1998, 2003). Although Sonesson et al. (1999) found no difference in calculated stiffness of aneurysms that progress to rupture in the longitudinal orientation, Wilson et al. (1998, 2003) reported a higher rupture risk in AAAs with lower calculated elastic modules in the axial orientation. Wilson et al. also suggested that aneurysm size was correlated, although poorly ($r^2 = 0.22$), to increases in elastic modulus, suggesting that larger AAAs are stiffer and that rupture risk is more closely associated with aortic material properties than size. Perhaps the greatest limitation of the Diamove system is the use of only two tracked points within the images measured at the posterior wall and anterior wall of the vessel, assuming a simplistic circular model of AAA geometry.

Numerous techniques and methodologies have been published to spatially resolve strain fields in deforming vessels with the end goal of improving knowledge of the tissue mechanics and disease state (Fromageau et al. 2005; Lopata et al. 2009, 2014; Mascarenhas et al. 2016; Vonk et al. 2014). In a novel method of AAA vessel wall tracking from clinical B-mode images, Brekken et al. (2006) used points along one-half the lateral edge of the circumferentially oriented aortic wall, imposing a cubic spline smoothing constraint to the curve to suppress noise. In a similar study, Vonk et al. (2014) tracked the manually segmented walls of a longitudinally oriented AAA and suppressed accumulated noise by

using an “adaptive region of interest (ROI) scheme,” in which the tracked elements within the ROI were updated based on the displacements. Vonk et al. reported that rapidly growing aneurysms were stiffer with lower values of pressure-normalized strain. A limitation of both these studies is the assumption of an axisymmetric geometric model with homogeneous material properties (Vonk et al. 2014). In addition, their use of cross-correlation-based measurements in their adaptive ROI may introduce large errors in their measurement.

Use of physiologic displacement to determine circumferential modulus is also limited by the accurate quantification of the imposing force or blood pressure. Although some authors have used invasive blood pressure measurements and simultaneous strain measurements to calculate stiffness, these techniques are clinically limited given the risks associated with placement of transducers within targeted blood vessels (Kim et al. 2005). To avoid the need for blood pressure measurement, some authors have advocated the use of pulse wave imaging (PWI) to directly measure tissue modulus from the Moens–Korteweg equation (Cloonan et al. 2014; Luo et al. 2009; Vappou et al. 2010). PWI has been validated in a series of FE modeling, vessel phantom and animal and human clinical feasibility studies (Apostolakis et al. 2016; Cloonan et al. 2014; Li et al. 2013; Luo et al. 2009; Shahmirzadi and Konofagou 2012). Although PWI can provide accurate measures of *in vivo* tissue stiffness, one of the greatest limitations of PWI is the degradation of the measurement second to pulse wave reflections at inclusion bodies and branch points, as well as variations in wall thickness, luminal radius and assumptions of tissue density (Apostolakis et al. 2016; McGarry et al. 2016; Shahmirzadi and Konofagou 2012). As with previous techniques, PWI is also limited in its assumption of simplistic axisymmetric homogenous geometries, which negatively bias results in complicated aneurysm geometries and locations of wave reflections. In addition, a PWI technique alone can resolve mechanical properties within the cross section of a vessel wall.

Although marked progress has been made in the field of ultrasound-derived mechanics of abdominal aortic aneurysms, several limitations remain. Patient-specific stress, for instance, requires not only the spatial variation and magnitude of material properties, but the geometry of the aorta and the deformation field as well. In this article, we present our ultrasound-based elastographic imaging technique for measurement of the accumulated 2-D displacement vector field for an arbitrary imaged geometry resolved over the entire cardiac cycle. This is accomplished by sequentially measuring frame-to-frame displacement fields at incrementally updated measurement locations such that all displacement fields share a common reference frame at diastole. The measurement location of a given frame is an accumulation of all the prior displacement measurements. This is equivalent to measuring the Lagrangian specification of the displacement field, as opposed to measuring the Eulerian displacement field, which is more common in elastography techniques (Batchelor 1973). To avoid propagation of error in the accumulated displacements, each of the frame-to-frame measurements is regularized. The total strain, calculated from the displacements and accumulated over a cardiac cycle, can be combined with measures of pulse pressure (systolic–diastolic pressure) to normalize strain. By quantifying pressure-normalized strain over the cardiac cycle, we can qualitatively detect variations in spatially modulated stiffness for a given vessel geometry.

We validated our elastographic imaging technique using simulated ultrasound images created from FE models with known displacement fields and complex heterogeneous polyvinyl alcohol (PVA) cryogel vessel phantoms. The simulated ultrasound images were used to quantify the error in our measurement imparted by our regularization technique. The phantom experiments validated the relationship between globally modulated tissue stiffness and pressure-normalized principal strain. In a second set of phantom experiments, we spatially modulated material properties by increasing PVA concentration in the simulated aneurysmal region only, to illustrate that the ratio of regional strain values can detect material contrast within a given geometry. Clinical images of patients with abdominal aortic aneurysms are used to illustrate the clinical feasibility of pressure-normalized mean principal strain with our elastographic measurement. This article describes the relationship between strain, vessel geometry and variations in material properties.

METHODS

Simulated ultrasound images from finite-element modeling

Simulated US images were created to test the accuracy of our registration algorithm and quantify the error in our measurement. Simulated images were created by convolution of a 2-D point spread function (PSF) with point scatterers in an image plane. The PSF was defined to mimic the point response of the Ultrasonix C7-3/50 convex transducer. To that end, the analytical expression for the PSF was defined as

$$\text{PSF}_k(r, \theta) = a_k \cos(f_c * (r - c_k^r)) e^{\left(-\frac{(r - c_k^r)^2}{2\alpha_r^2}\right)} \times e^{\left(-\frac{(\theta - c_k^\theta)^2}{2\alpha_\theta^2}\right)} \quad (1)$$

where r and θ are the curvilinear transducer coordinates; a_k is the k th scatterer amplitude; c_k^r and c_k^θ are the r and θ positions of the k th scatterer, respectively; f_c is the center frequency of the transducer (measured from the US machine, $f_c = 28.6/\text{mm}$); and α_r and α_θ are axial and lateral pulse widths, respectively (measured from the US machine, $\alpha_r = 0.224 \text{ mm}$ and $\alpha_\theta = 0.0112 \text{ rads}$). The scatterer positions were randomly and uniformly distributed within the image plane at a scatterer density of 5.7 mm^{-2} . The scatterer amplitudes (a_k 's) were also uniformly distributed, and the average amplitude was scaled such that the resulting simulated US image had power comparable to that of the radiofrequency (RF) images collected from the Ultrasonix system (Fig. 1A). The initial, un-deformed imaged material geometry was that of a vessel in cross section, with an inner lumen 5 cm in diameter and vessel thickness of 1.0 cm, and a soft homogeneous background material. The scatterers within the vessel lumen were removed from the image formation, and the scatterers within the simulated vessel were given an average amplitude three times that of the background material.

To simulate images of a deforming vessel, a FE model of the vessel was created in FEBio (FEBio Version 2.5, available at: www.febio.org) (Maas et al. 2012). The vessel geometry was modeled as a linear elastic material undergoing a quasi-static 2-D plane strain deformation with the vessel dimensions as described above. The background material surrounding the vessel extended to a 50-cm diameter. The material properties used for the

background were a Poisson's ratio of 0.495 and a Young's modulus of 10 kPa. The vessel wall had an equivalent Poisson's ratio, and the Young's modulus of the posterior half of the vessel wall (imaged bottom) was set to 60 kPa. Four distinct values of the Young's modulus (60, 120, 180 and 240 kPa) of the anterior half of the vessel wall (imaged top) were used to create four sets of imaged vessels with varying degrees of stiffness contrast (ratio 1:1 to 1:4). The boundary conditions of the model were such that the inner lumen had a time-varying hydrostatic pressure, and the outer boundary of the background material was traction free. A Gaussian pressure waveform was simulated (0–3 kPa) on the inner lumen and discretized 50 values, resulting in 51 US images per image sequence. The displacement field resulting from the FE model was interpolated to the scatterer positions and used to define the new positions for the deformed image frames in the US sequence. All US images were discretized with the axial sampling rate and lateral spacing of the Ultrasonix transducer (0.39 μm axially and 0.0094 radian laterally). Gaussian distributed white noise was added to the images such that the signal-to-noise ratio was 12 dB.

Phantom fabrication methods

We designed three aortic phantom geometries to form the basis of the phantom molds. These included an axisymmetric tube (Fig. 2a), an idealized AAA geometry (Fig. 2b) and a patient-specific AAA geometry (Fig. 2c). Solidworks (Dassault System's, Vélizy-Villacoublay Cedex, France) was used to design the negative molds of the axisymmetric tube and idealized AAA vessel geometries. The tube phantom geometry was designed as a hollow cylinder with an inner radius of 2.75 cm, an outer radius of 4 cm and a length of 10 cm (Fig. 2a). The idealized AAA phantom was designed similarly to aortic aneurysm model geometries previously described (Cloonan et al. 2014; Corbett et al. 2010; O'Brien et al. 2005; Vorp et al. 1998). Briefly, the proximal end of the geometry is an axisymmetric tube, mimicking the infrarenal aorta, the midportion of this aortic segment was made to mimic an aneurysm by modifying the diameter and cross section and the distal end of the aorta was bifurcated to mimic the iliac arteries. The diameter of the aneurysmal section was increased, with a 40% eccentricity relative to the diameter, whereas the thickness of the vessel wall of the model was unchanged. The patient-specific aneurysm geometry was created from an AAA patient's contrast-enhanced computed tomography scan collected retrospectively with institutional review board approval at the University of Rochester Medical Center. Mimics Innovation Suite (Materialise, Leuven, Belgium) was used to segment the inner and outer lumens of the patient's abdominal aorta. Solidworks was used to create the mold designs from the vessel geometries (Fig. 2c). The molds were printed using a Rostock Max V2 3-D desktop printer (See MeCNC, Goshen, IN, USA). The distal ends of the inner lumen molds were printed in a water-soluble filament for ease of removal after phantom manufacture. Photographs of the 3-D printed mold sections of the idealized and patient-specific phantoms are provided in Figure 3 (a, b), respectively. The PVA solutions used for these phantoms were modulated between 10% and 25% PVA, by mass, depending on the desired final stiffness (King et al. 2011). A 0.2% calcium carbonate powder was added for improved ultrasound scatter.

In total, four sets of phantoms were created, with each set composed of either homogeneous or heterogeneous material properties. For the axisymmetric tube and idealized

AAA geometries, with homogenous material properties phantoms were created, with each phantom in the set being cast entirely out of either 10%, 15%, 20% or 25% by mass powdered PVA to water. The phantom was then polymerized with five 12-h freeze–thaw cycles (–20°C 20°C) cycles. The combination of PVA concentration and number of freeze–thaw cycles was specifically chosen to match stiffness (Supplementary Material, online only, available at <http://dx.doi.org/10.1016/j.ultrasmedbio.2017.06.002>) and strain for physiologic pressures within the range of previously reported healthy and aneurysmal aortic tissue (Humphrey and Holzapfel 2012; Luo et al. 2009; Wilson et al. 1998, 1999, 2003). In addition, the idealized AAA and patient-specific AAA were made with heterogeneous material properties, in which the anterior aneurysm was modulated to be stiffer (Fig. 2b, 2c, *area shaded blue*). For the heterogeneous phantoms, 20 mL of 15%, 20% or 25% PVA solution was first injected into the anterior aneurysmal section with that portion of the mold oriented on the bottom, and then one freeze cycle commenced. The mold was then injected with a 10% PVA solution and subsequently underwent an additional five freeze–thaw cycles to complete the phantom polymerization. Representative photographs of the final axisymmetric, idealized and patient-specific vessel phantoms are provided in Figure 4.

A background was manufactured with a softer hydrogel material, which was made to simulate tissues of the retroperitoneum (Farsad et al. 2015; Kim et al. 2013; Kwon et al. 2015; Wells and Liang 2011). Using such a methodology for the vessel phantoms, a homogeneous axisymmetric cylinder (4-cm inner lumen × 16.5-cm outer lumen × 16.5-cm length) made from a 5% PVA solution and subjected to a total of two freeze–thaw cycles was created. Additional PVA samples were created for each of the phantom and background solutions, with an equivalent number of freeze–thaw cycles, for tensile testing and independent shear modulus (μ) measurements, to estimate the expected stiffness contrast (Supplementary Material).

Phantom imaging methods

To induce deformation, phantoms were placed in the background material with the anterior side up (Fig. 5), submerged in a water bath and connected to a hemodynamic pump, which was designed to produce programmable physiologic cyclic blood flows (Lillie et al. 2015; Varble et al. 2014). The phantoms were connected *via* a large-diameter tube at the proximal end of the phantom and two smaller-diameter tube connections at the distal bifurcation of the phantoms. The hemodynamic pressure profiles were designed to mimic the physiologic, cyclic cardiac profiles measured *in vivo* (Fig. 6) (Varble et al. 2014). It should be noted that no pre-stress was applied in this setup (*i.e.*, diastolic pressure was zero). During imaging, the pressure profile was measured by a catheter-based pressure sensor just proximal to the ultrasound imaging plane (Millar Mikro-Cath, Auckland, New Zealand). Pressure data were captured *via* a National Instruments USB-6251 DAQ (National Instruments, Austin, TX, USA) and synchronized with the ultrasound frames using the frame output trigger of the US system.

Ultrasound images were collected using a Sonix-TOUCH US system (Analogic), which allowed for the collection of RF image data, in conjunction with an Ultrasonix C7–3/50 convex transducer, with a center frequency of 5 MHz. The ultrasound imaging settings were

adjusted to a 60° sector at a depth of 12 cm, which resulted in a frame rate of 72 Hz. A single focus was set at the posterior wall of the phantom under test. Scans were performed with the ultrasound transducer supported in a ring stand and aligned in cross section at the location of the aneurysm's largest diameter as determined by inspection of the live B-mode images. For each experiment, 10 s (720 frames) of imaging and pressure data were recorded, corresponding to 10 cardiac cycles.

Clinical imaging methods

With institutional review board approval and in accordance with the human subject research protection board at the University of Rochester, two patients consented to the study, and clinical images of their abdominal aortic aneurysms were obtained. These patients were selected as age- and comorbidity-matched controls with differences in aneurysmal growth rate as determined by chart review. The first patient's aneurysm had been stable in size for the past year; however, the second patient's growth rate was 0.4 cm/y over the previous 6 mo. Each patient had a 4.6-cm aneurysm measured at its maximum diameter at the time of the elastographic examination. These patients were then followed by clinical ultrasound examination every 3 mo for a total of 6 mo. The first patient had no growth over the 6-mo study period. The second patient experienced 0.6 cm of growth over 6 mo and subsequently underwent an aneurysm repair.

Radiofrequency images were collected on a Sonix-Tablet US system (Analogic) with the Ultrasonix C7–3/50 convex transducer. The scans were performed by accredited registered vascular technicians (RVTs). The RVTs acquired cross-section images at the location that they determined to be the AAA's maximal diameter. A center frequency of 5 MHz was used, and the sector and depth were optimized to obtain the maximal possible frame rate. A single US focus was placed at the posterior edge of the aneurysm. The patient then performed a breath hold to prevent physiologic longitudinal displacement of the aorta, and RF US data were obtained until the breath hold was terminated. A non-invasive blood pressure cuff measurement (Spot Vital Sign device; Welch Allyn, Skaneateles, NY, USA) was performed on the right arm before and after the ultrasound image was obtained. Pulse pressure was calculated as the difference between the patient's recorded average systolic and diastolic blood pressures.

US image registration algorithm

A non-rigid image registration-based displacement estimation algorithm was used to measure the total, accumulated displacement vector field for an entire cardiac cycle (Fig. 7). This algorithm was adapted from previous work by our group (Chimenti et al. 2016; Richards and Doyley 2013). In this work, we use sequential measurements of frame-to-frame displacement fields ($\delta \mathbf{u}_i(\mathbf{x})$) and cumulatively sum these measurements to determine the continuous displacement field for all frames throughout the cardiac cycle. A single frame-to-frame measurement is found by minimizing the optimization function

$$\begin{aligned} \pi[\delta \mathbf{u}_i(\mathbf{x})] = & \frac{1}{2} \int_{\Omega_T} W_i(\mathbf{x}) (I_{i+1}(\mathbf{x} + \mathbf{u}_i(\mathbf{x}) + \delta \mathbf{u}_i(\mathbf{x})) - I_i(\mathbf{x} + \mathbf{u}_i(\mathbf{x})))^2 d\Omega_T + \frac{\alpha 1}{2} \int_{\Omega_T} (\nabla \delta \mathbf{u}_i(\mathbf{x})^s : \nabla \delta \mathbf{u}_i(\mathbf{x})^s) d\Omega_T \\ & + \frac{\alpha 2}{2} \int_{\Omega_T} (\nabla \cdot \delta \mathbf{u}_i(\mathbf{x}))^2 d\Omega_T \end{aligned}$$

(2)

The RF ultrasound image sequence was defined such that $I_{\lambda}(\mathbf{x})$ is the λ th frame of the sequence containing a total of N frames from the beginning of systole to the end of diastole. The beginning of systole was found by a registered physician in vascular interpretation by visualizing the RF data as B-mode cine loops to determine the frame in which the luminal area was minimized just before vessel expansion. The end-diastolic frame in the cardiac cycle was chosen similarly to select all the frames for one cardiac cycle. Finally, the physician selected the frame in which the vessel diameter was maximized, defining peak systole (Fig. 6).

The first term in eqn (2) is a normalized least-squares difference term that minimizes the RF image intensity difference between the sequential US frames I_i and I_{i+1} , subject to a non-linear image transformation, or deformation, of the second image, I_{i+1} . A common reference frame for all frame-to-frame comparisons within an image sequence is maintained by deforming both images by the accumulated displacement field, $\mathbf{u}_{\lambda}(\mathbf{x})$, which maps all measurements to the reference coordinates defined by I_1 (*i.e.*, $\mathbf{u}_{\lambda}(\mathbf{x}) = 0$). The accumulated displacement field, $\mathbf{u}_{\lambda}(\mathbf{x})$, is defined as the sum of all the previous calculated frame-to-frame measurements through the equation

$$\mathbf{u}_i(\mathbf{x}) = \sum_{j=1}^{i-1} \delta \mathbf{u}_j(\mathbf{x}) \quad (3)$$

Note that the value of $\mathbf{u}_{\lambda}(\mathbf{x})$ does not change for a given frame-to-frame optimization. The sequential optimizations are performed for each set of two frames, from $i = 1$ to $N-1$, with respect to the relative frame-to-frame displacement fields, $\delta \mathbf{u}_{\lambda}(\mathbf{x})$. A four-node, quadrilateral FE discretization with bilinear shape functions, regularly spaced in r and θ with respect to the curvilinear transducers' coordinate system, is used over the total image area (Ω). RF US images are interpolated at subpixel locations using a 2-D linear interpolation of the discretized image pixels.

In eqn (2), we defined Ω_T as the image area for which all frame-to-frame displacement measurements were calculated and $\mathbf{x}$ as the position within the image domain over which the integration was performed. We limit our measurement region (eqn (2)) to those elements within the tissue area (Ω_T) (*i.e.*, excluding the luminal area of the vessel where only blood would be present) as determined by image segmentation. The tissue/lumen region was

manually segmented from the first frame of the image set to define a polygon separating the tissue/lumen boundary of the vessel phantom wall such that $\Omega_T \cup \Omega_L = \Omega$ (total imaged area). The tissue region (Ω_T) was further divided into a vessel wall region (Ω_V) (*i.e.*, that portion of the phantom tissue within the vessel) and a background region (Ω_B) by a second polygon such that $\Omega_V \cup \Omega_B = \Omega_T$. Segmentation of the vessel/background region is used only in the post-processing analysis of the strains and is not used in the displacement estimation algorithm. Algorithmically, an element is determined to be within a polygon if the centroid of the element area is within that polygon. Figure 8 shows the resulting nodes (dots) and element boundaries (lines) within the lumen Ω_L (*red*), vessel wall Ω_V (*yellow*) and background Ω_B (*blue*) regions defined using $I_f(\mathbf{x})$.

In eqn (2), $W_i(\mathbf{x})$ is a weighting factor that is employed to normalize the magnitude of the imaging matching and account for large spatial fluctuations in the image power of $I_f(\mathbf{x})$. This function is defined as piecewise constant for each element, and the value for a given element is

$$W_i(\mathbf{x}) = \left[\int_{\Omega_e} (I_i)(\mathbf{x} + \mathbf{u}_i(\mathbf{x}))^2 d\Omega_e + \varepsilon \right]^{-1} \quad \text{for } \mathbf{x} \in \Omega_e \quad (4)$$

where Ω_e is defined as the area within the e th element. The value of ε is a small number used to ensure the weighting function stays finite for hypo-echoic image regions and is chosen such that, on average, $W_i(\mathbf{x}) \ll \varepsilon^{-1}$ (here $\varepsilon = 1 \times 10^{-10}$ was used). Note that the value of $W_i(\mathbf{x})$ is different for each i th frame-to-frame measurement.

The second term in eqn (2) is a strain regularization term, which penalizes large frame-to-frame strain magnitudes (Chimenti et al. 2016). The function $\nabla \delta \mathbf{u}_f^s(\mathbf{x})$ is the frame-to-frame strain tensor field defined as the symmetric portion of the displacement gradient tensor. The third term in eqn (2) is an incompressibility constraint imposed *via* a penalty. That is, we impose that the divergence of the frame-frame displacement field remains approximately zero for all frame-to-frame measurements.

Strain calculations

The optimization algorithm described here requires an initial guess of the displacement field to initiate the minimization process. This was found as follows. First, each of the frame-to-frame displacement vector fields, $\mathbf{d}_f(\mathbf{x})$, was estimated using a 2-D block matching, cross-correlation-based tracking algorithm used in previously described work (Doyley et al. 2001; Richards and Doyley 2011). These displacement estimates were found using a measurement window size of 4.6 mm radially and 3.2° angularly, with respect to the curvilinear transducer's coordinate system. Each measurement overlapped 50% radially and 33% angularly. The measured radial and angular displacements were then smoothed, spatially, with a 3×3 grid running average filter in two dimensions and linearly interpolated onto the registration mesh.

For computational efficiency, the Ultrasonix RF US images downloaded from the system are scaled to maximize their dynamic range and avoid clipping and then digitized as signed 16-bit integers ($|I_f(\mathbf{x})| \leq 2^{15}$). For all measurements in this work, the regularization constant was set to $\alpha_1 = 5 \times 10^7$. The weighting for the penalty term was chosen to be an arbitrarily large number, $\alpha_2 = 1 \times 10^{14}$. The functional, eqn (2), was minimized for each frame-to-frame measurement using an iterative Gauss–Newton method as described by Richards and Doyley (2011). The iterative process was terminated after 100 iterations (per measurement), which was assumed to be enough to allow the algorithm to converge. Each frame-to-frame measurement took approximately 10 s to complete, for a total time of approximately 10–11 min for the entire image sequence.

Figure 8B illustrates a representative example of the nodal locations and deformed elements at systole. By use of the time-resolved displacement vector field $\mathbf{u}_f(\mathbf{x})$, the full 2-D strain tensor was calculated as the gradient of the displacement field at the center of each element, Ω_e , using the bilinear shape functions. For each element, the maximum principal strain was calculated as the maximum eigenvalue of the 2-D strain tensor within that element. The vessel's mean maximum principal strain, $\overline{\varepsilon_{p+}}$, was calculated as the area-weighted average of the maximum principal strains across all elements within the vessel region (Ω_V) for each frame-to-frame comparison. The temporal (or frame) maximum value of the mean principal strain within Ω_V was then determined by finding the frame visually associated with the maximum vessel expansion (Fig. 6) (*i.e.*, systole). The pressure-normalized maximum mean principal strain, or $\overline{\varepsilon_{p+}}/PP$, was then calculated as maximum mean principal strain at systole, normalized by the catheter measured pulse pressure. Pulse pressure is defined as the difference between the maximum and minimum pressures recorded, either non-invasively (clinical images) or with the pressure transducer (phantom images), for a corresponding vessel deformation.

Spatial variations of strain within the vessel wall were characterized by dividing the vessel region (Ω_V) into four subregions. Imaged vessel regions were defined using the anatomic terms *anterior*, *posterior*, *lateral* and *medial*, which correspond to the top, bottom, right and left relative to the image field. By convention, the probe orientation marker of the transducer was placed facing to the right of the theoretical patient or the actual patient for all experiments. A line within the image connecting the centroid of the inner lumen to the location of the center of the ultrasound transducer was defined as the reference of 0° . Then the anterior region was defined as the segmented vessel region Ω_V between $+45^\circ$ and -45° from the centroid to the transducer surface. It then followed that the posterior region was defined between $+135^\circ$ and -135° , the medial between -45° and -135° and lateral between $+45^\circ$ and $+135^\circ$, as illustrated in Figure 9. By design, the stiffened region of the phantoms (15%, 20% or 25% PVA) was always located in the anterior/aneurysmal portion of the vessel and, thus, imaged nearest to the transducer.

RESULTS

Strain measurements: Simulated ultrasound based on finite-element models

Figure 10 compares the true ϵ_{p+}/PP as determined by the finite-element model (top row) with the resulting measured ϵ_{p+}/PP from the simulated finite-element ultrasound images (bottom row) for the increasing anterior to posterior wall stiffness ratios (left to right). The *vertical black line* represents the frame location of maximum $\overline{\epsilon_{p+}}/PP$ or peak systolic pressure. The measured values of ϵ_{p+}/PP (Fig. 11, right) are consistently lower than the true values of ϵ_{p+}/PP (Fig. 11, left) for all the vessel wall regions, in the simulated homogenous vessel. These consistently lower values for $\overline{\epsilon_{p+}}/PP$ are expected as the results of spatial smoothing created by any regularization technique. In the homogeneous simulated image, our measurement technique produces a spatially average error of 26.6% for $\overline{\epsilon_{p+}}/PP$ at the maximum vessel deformation (systole). Importantly, our method is meant to be qualitative, that is, to use the ratio one point in the image to determine that point's relative stiffness to the stiffness of other points within the image. Figure 12 illustrates the regional pressure-normalized principal strain $\overline{\epsilon_{p+}}$ strain in the posterior (*blue*) and anterior (*purple*) vessel walls across one cardiac cycle for the finite-element model (*solid line*) and our resulting measurement technique (*dashed line*). The mean and regional values are reported in Table 1 for both the finite-element model and our measurement techniques for each of the increasing posterior-to-anterior vessel wall ratios. Although the finite-element model ratio of $\overline{\epsilon_{p+}}$ in the posterior-to-anterior wall underestimates the true ratio of material stiffness. 12.5%–15.5%, our measurement of $\overline{\epsilon_{p+}}$ overestimates the true ratio of material stiffness 10%–21.1% because of the underestimations of $\overline{\epsilon_{p+}}$ caused by the regularization.

Strain measurements: Homogeneous vessel phantoms

Figure 13 illustrates the measured ϵ_{p+}/PP within each element overlaid on the B-mode image of the phantom at maximum deformation, or peak systolic pressure, for the axisymmetric tube (top row) and the homogenous idealized AAA geometry (bottom row). As the overall concentration of PVA increases for each of the vessel phantoms, the measured ϵ_{p+}/PP decreases within the vessel (Ω_V) as seen in the transition of the vessel from red (high ϵ_{p+}/PP) to blue (low $\overline{\epsilon_{p+}}/PP$).

Figure 14 illustrates the average $\overline{\epsilon_{p+}}/PP$ for the total vessel (Ω_V) as well as the anatomic subregions of the vessel, across the cardiac cycle for the axisymmetric tube (top row) and the idealized AAA phantoms (bottom row). As expected for the homogenous phantoms, there is little deviation between the measured $\overline{\epsilon_{p+}}/PP$ for the total vessel and the $\overline{\epsilon_{p+}}/PP$ of the anatomic subregions, suggesting uniform material properties or low material contrast within a given geometry. The exception of the 10% homogenous axisymmetric tube is likely due to the large magnitude of the measured frame-to-frame strains, causing image decorrelation, with expected increased error in the ϵ_{p+} measurement.

Table 2 lists the values of maximum mean principal strain $\overline{\epsilon_{p+}}$ and pressure-normalized maximum mean principal strain $\overline{\epsilon_{p+}}/PP$ for the vessel region, Ω_V . As the homogenous PVA concentration was increased, there was a decreasing $\overline{\epsilon_{p+}}$ trend for the axisymmetric tube;

however, this trend was not maintained between the 15% and 20% phantom experimental test conditions because of the increased pulse pressure. When $\overline{\varepsilon_{p+}}$ is normalized by pulse pressure, there is an expected decrease in $\overline{\varepsilon_{p+}}/PP$ with increasing PVA phantom concentration. To assess the stiffness contrast, the $\overline{\varepsilon_{p+}}/PP$ for each phantom PVA concentration was compared with the $\overline{\varepsilon_{p+}}/PP$ of the 10% PVA phantom as a qualitatively assessed material contrast ratio. For example, the 10% PVA $\overline{\varepsilon_{p+}}/PP$ to 10% $\overline{\varepsilon_{p+}}/PP$ ratio is a reference that will always be equal to one. There was an exponential increase in the material contrast ratio similar to the exponential increase in the measured shear modulus with increasing % PVA concentration (Supplementary Material). A similar trend in decreasing $\overline{\varepsilon_{p+}}, \overline{\varepsilon_{p+}}/PP$ and contrast ratio was also seen for the idealized AAA geometry. Note that the magnitude of the contrast ratio was blunted in the idealized AAA likely because of the complex phantom geometry.

Strain measurements: Heterogeneous vessel phantoms

Figure 15 provides the overlay of ε_{p+}/PP at each of the elements Ω_V and provides a visual reference to the spatial location of the modulated stiffened regions shown as decreased ε_{p+}/PP in *blue* and softer 10% PVA regions shown as decreased ε_{p+}/PP in *red*. Figure 16 illustrates the complex interaction between $\overline{\varepsilon_{p+}}/PP$ for Ω_V and the anterior and posterior subregions across the cardiac cycle. The temporal location (frame) of the maximum $\overline{\varepsilon_{p+}}/PP$ (systole) is indicated with a *black vertical line*. Again, the clearest indicator of the contrast ratio between the stiffened anterior and posterior subregions at systole is $PA\overline{\varepsilon_{p+}}$.

Table 3 shows the pressure-normalized maximum mean principal strain $\overline{\varepsilon_{p+}}/PP$ for the vessel region, Ω_V , as well as the $\overline{\varepsilon_{p+}}/PP$ anterior and $\overline{\varepsilon_{p+}}/PP$ posterior vessel subregions for the heterogeneous idealized and patient-specific AAA phantoms. As only the anterior subregion, or aneurysmal portion, of the vessel phantom PVA concentration was modulated (increased in stiffness), material contrast is examined by comparing the anterior to posterior walls within a given image. This contrast ratio between the vessel locations is shown the ratio of the posterior–anterior $\overline{\varepsilon_{p+}}(PA\overline{\varepsilon_{p+}})$ at systole. It would be expected that if a portion of a given vessel became stiffer than the pressure-normalized mean principal strain $\overline{\varepsilon_{p+}}/PP$ for the total vessel area, Ω_V should also decrease; in general for both the idealized and patient-specific phantoms, a decrease in $\overline{\varepsilon_{p+}}/PP$ was noted. For both phantoms, the anterior belly of 20% PVA concentration had a higher than expected $\overline{\varepsilon_{p+}}/PP$; however, this discrepancy is correlated to an increase in the experimental pulse pressure. In the subregion analysis of $\overline{\varepsilon_{p+}}/PP$, the anterior wall $\overline{\varepsilon_{p+}}/PP$ tends to decrease as the region stiffness, but simultaneously affects the posterior $\overline{\varepsilon_{p+}}/PP$. For the idealized AAA phantom, an exponential increase in the anterior-to-posterior wall strain ratio follows the exponential increase in the known shear modulus independently measured with increasing PVA concentration. The patient-specific AAA geometry also has an increase in the $PA\overline{\varepsilon_{p+}}$, which is most significant for the 25% PVA concentration.

Phantom strain measurement reproducibility

To determine the repeatability of our measurements, eight separate cardiac cycles were collected independently and processed for four different phantoms; the 15% axisymmetric tube phantom, the 15% homogeneous ideal AAA phantom, the 15% heterogeneous ideal AAA phantom and the 15% heterogeneous patient-specific phantom. For the 15% axisymmetric tube phantom, the measured pulse pressure over the eight cycles was 8.21 ± 0.11 kPa. The average principal strain for the eight individually processed cardiac cycles was $\overline{\varepsilon_{p+}} = 7.67 \pm 0.19\%$. This resulted in a mean pressure-normalized principal strain of $\overline{\varepsilon_{p+}}/PP = 0.94 \pm 0.02\%/kPa$. For the 15% homogeneous ideal AAA phantom, the average pulse pressure was 6.9 ± 0.03 kPa with a mean $\overline{\varepsilon_{p+}}$ of $8.46 \pm 0.25\%$, resulting in an average pressure-normalized principal strain of $\overline{\varepsilon_{p+}}/PP = 1.22 \pm 0.03\%/kPa$. For the 15% heterogeneous ideal AAA phantom, the average pulse pressure was 6.76 ± 0.02 kPa with a resulting mean $\overline{\varepsilon_{p+}}/PP$ of $1.34 \pm 0.04\%/kPa$. This resulted in a mean posterior $\overline{\varepsilon_{p+}}/PP = 1.61 \pm 0.05\%/kPa$ and mean anterior $\overline{\varepsilon_{p+}}/PP$ of $0.88 \pm 0.03\%/kPa$. The variation in the average $\overline{\varepsilon_{p+}}$ posterior to $\overline{\varepsilon_{p+}}$ anterior ratio was 1.81 ± 0.09 . Finally, for the 15% patient-specific phantom, the average pulse pressure was 8.9 ± 0.02 kPa with a resulting mean $\overline{\varepsilon_{p+}}/PP$ of $0.62 \pm 0.01\%/kPa$. This resulted in a mean posterior $\overline{\varepsilon_{p+}}/PP$ of $1.25 \pm 0.05\%/kPa$ and mean anterior $\overline{\varepsilon_{p+}}/PP$ of $0.35 \pm 0.02\%/kPa$ deviation of the means. This yielded an $\overline{\varepsilon_{p+}}$ posterior to $\overline{\varepsilon_{p+}}$ anterior ratio of 3.51 ± 0.29 .

Strain measurements: Clinical images

Figure 17a is the ε_{p+}/PP overlay for the first patient whose aneurysm both prospectively and retrospectively experienced no growth over the 6-mo study period. At the time Figure 17a was obtained, the patient's non-invasive blood pressure (NIBP) was noted to be 148/92.5 mm Hg for a pulse pressure of 55.5 mm Hg or 7.3 kPa. The patient had a maximum systolic total $\overline{\varepsilon_{p+}} = 1.41\%$ for Ω_V , which corresponded to a total $\overline{\varepsilon_{p+}}/PP$ of $0.191\%/kPa$. The second patient, who had a historical growth rate of 0.4 cm/y, which increased 0.6 cm in the 6 mo after his scan was obtained (Fig. 14b), had an NIBP of 137.5/69 mm Hg for a PP of 68.5 mm Hg or 9.13 kPa. This patient had a maximum systolic total $\overline{\varepsilon_{p+}}$ of 2.77% for Ω_V , which corresponded to a total $\overline{\varepsilon_{p+}}/PP$ of $0.303\%/kPa$. On visual inspection, the overlay image the patient with low growth (Fig. 14a) had lower regional ε_{p+}/PP contrast than that of the patient who experienced high growth (Fig. 17b).

DISCUSSION

Since the work of Vorp and others, who found that mechanical properties and stress are important factors in AAA rupture, many researchers have worked toward a non-invasive, clinical method to determine patient-specific aortic mechanical metrics (Doyle et al. 2009, 2014; Fillinger et al. 2003; Helderma et al. 2008; Li et al. 2008; Raghavan et al. 2000; Speelman et al. 2010; Vorp et al. 1998; Wang et al. 2002). US elastography techniques offer a clinically accessible tool for potentially providing these metrics. Many of these techniques rely on simplifying assumptions of geometry or material properties to obtain measures of stiffness. Although the technique used here does not provide a direct measure of the material properties, it does provide a spatially resolved measurement of strain that, when normalized

by pressure, is directly related to stiffness. In this work, we have provided evidence that such a measure can detect stiffness changes in simulated ultrasound images, PVA vessel phantoms and clinical images. We believe that this measurement is a critical step toward using diagnostic US to assess spatially resolved mechanical properties and stress in a clinical setting.

To assess the accuracy of our measurement technique, we used simulated ultrasound images, created from finite-element models with known displacement fields, resulting in measurements with known ε_{p+}/PP . These simulated experiments indicated that the “true” ratio of ε_{p+} between vessel regions with differing stiffness within the image underestimates the stiffness (~15%) in an idealized geometry in the range of known vessel material stiffness (Table 1). Our “measured” ratio of ε_{p+} ratios systematically overestimated the modulus contrast (10%–21%). Likewise, these experiments indicate the detrimental effect of regularization on our measurement and 27% underestimation of $\overline{\varepsilon_{p+}}$ during large frame-to-frame deformations that occur during the systolic upstroke. Our regularization more heavily penalizes relatively large displacements, which would occur in softer regions of vessel geometry. This leads to an overall overestimation of the material stiffness contrast ratio in our measurement compared with the finite-element model contrast ratio (Table 1). The large differences realized in our measured strains versus the “true strain” values can be attributed to the regularization, particularly of the strains at the luminal interface. For radial deformations, these strains tend to be high (they increase as $1/r^2$) near the lumen and are affected the most by the regularization. The results from the simulated homogeneous vessel also indicate strain artifacts that occur near the corners of the vessel (close to our region boundaries). These strain artifacts are likely caused by the regularization and the alignment of the “true” principal strains at an angle between those of the axial and lateral directions of the US image. Although the regularization causes underestimations of the “true” strain, it provides for a relatively reproducible measure across complex experimental conditions, as highlighted in the 0.25% variation in our $\overline{\varepsilon_{p+}}$ measurement experimentally.

Our imaging technique provides the flexibility to obtain both strain and pressure-normalized strain at systole. The homogenous axisymmetric tube experiments (results in Table 2) illustrate the importance of normalizing principal strain by the pulse pressure. In each of these experiments, stiffness is globally increasing. If principal strain alone was used, one might erroneously conclude that the 15% phantom, $\overline{\varepsilon_{p+}}=8.2\%$, was stiffer than the 20% phantom, $\overline{\varepsilon_{p+}}=9.5\%$, given the lower strains measured in this phantom. Normalizing by pulse pressure, $\overline{\varepsilon_{p+}}/PP$ qualitatively decreases with increasing stiffness in the phantoms. This is also illustrated as the ratio of comparing $\overline{\varepsilon_{p+}}/PP$ of each of the experimental conditions to stiffness of the 10% PVA phantom (Table 2) or the decreases of the overlaid ε_{p+}/PP visually seen with the individual Ω_V elements (Fig. 13). Normalizing by pulse pressure would be clinically important when monitoring a given patient’s geometry, as illustrated in the homogeneous phantom experiments. If a given patient’s vessel was scanned in a short-interval follow-up, and his or her aortic material properties did not change but the pulse pressure progressively increased over that interval, then $\overline{\varepsilon_{p+}}/PP$ would adjust for the expected increase in ε_{p+} .

Previous experiments have indicated that material contrast can be seen in just a single frame-to-frame comparison (Richards and Doyley 2013). Our accumulation of principal strain continues to systole with the explicit purpose of creating a non-invasive clinical metric of $\overline{\varepsilon_{p+}}/PP$ over the cardiac cycle (Figs. 11, 12, 14 and 16). This accumulative measure provides both an assessment of the time-resolved deformation information and a measure of the total strain in a situation where the strain decorrelation is large enough to corrupt single-frame comparisons. The accumulation does require an initial guess of the frame-to-frame displacement field for each registration step. In this work, we used a cross-correlation-based, block matching algorithm to obtain this guess. We chose this type of algorithm for its ability to measure accurate displacement fields for displacements much larger than a wavelength. Figure 18 illustrates the pressure-normalized strain measured from our algorithm when a zero initial guess (Richards and Doyley 2013) is used for each step in the registration accumulation (*i.e.*, $\mathbf{d}_i(\mathbf{x}) = 0$), for the simulated homogeneous finite-element model (Fig. 11, left). It is clear from this plot that, although the results have aspects similar to those of our previous measurements (Fig. 11, right), erroneous large jumps in the average strains result. This is due to our optimization algorithm finding local minima, rather than global minima. When a measurement frame optimizes to a local minimum, as seen here, all subsequent measurements will also be affected. However, it should be noted that the initial guess need only to be accurate to within approximately a wavelength (axially) of the true displacement to find the proper minimum and avoid these types of errors. A more extensive study of various methods of initializing the optimization can be found in Richards et al. (2013).

Another important feature of our technique is the measurement of strain within arbitrary regions of complex geometries, qualitatively providing data on material contrast throughout a cardiac cycle. In the homogeneous phantoms, strains within subregions would be expected to be uniform. However, for the 10% axisymmetric tube phantom, there is a large deviation in posterior wall $\overline{\varepsilon_{p+}}/PP$ (Fig. 14, *blue line*) from the wall regions. The regularization weight (α_1) used in this work was chosen based on previously measured strains expected in the abdominal aorta and aortic aneurysms (Long et al. 2004a, 2004b, 2005; Vonk et al. 2014; Wilson et al. 2000, 2003). For the softer 10% homogeneous axisymmetric vessel, large principal strains, $12.43 \pm 5.51\%$, were observed that correlated to non-physiologic vessel wall displacements and velocities. As with any image matching technique, large frame-to-frame displacements risk image decorrelation and erroneous measurements. This phantom's experimental conditions likely illustrate the upper limits of our algorithm's ability to measure large frame-to-frame displacements.

Arbitrary regions of principal strain can also be compared within vessel geometries, qualitatively providing data on material contrast throughout a cardiac cycle, such as the anterior-to-posterior contrast ratio that is seen within our heterogeneously modulated phantoms (Table 3). The heterogeneous idealized AAA phantoms (Fig. 16, top row) illustrates the $\overline{\varepsilon_{p+}}/PP$ in the anterior (*purple*) to posterior wall (*blue*) and their complex interaction across the cardiac cycle even for this simplified geometry. This point illustrates that our measure of mean principal strain is a combined measure of both geometry and material properties. For example, as the anterior belly of the idealized AAA stiffens, there is an overall decrease in $\overline{\varepsilon_{p+}}/PP$, but there appears to be an increase in $\overline{\varepsilon_{p+}}/PP$ of the

posterior region. This relationship maintains the $PA\overline{\varepsilon}_{p+}$ (posterior–anterior mean principal strain) ratio showing the expected increase in material contrast, based on the material properties between the anterior and 10% PVA posterior wall. This contrast can be seen graphically in the top row of Figure 15, in the overlaid pressure-normalized strains at peak systole.

Interpretation of the $PA\overline{\varepsilon}_{p+}$ for the patient-specific model is complicated by the increased thickness of the aneurysmal belly. The contrast in $PA\overline{\varepsilon}_{p+}$ for the patient-specific, homogeneous model is clearly due to the difference in thickness of the anterior vessel region. The initial minimal increase in $PA\overline{\varepsilon}_{p+}$ for the heterogeneous patient-specific phantoms, with a marked increase for the 25% PVA concentration, is likely caused by the interplay between geometry and mechanical stiffness that exists in more complex geometries. Nevertheless, an increase in this contrast measure in the vessel phantom at systole is still present for all heterogeneous phantoms. This contrast can be visually appreciated in Figure 16 (bottom row) or in the strain overlays in Figure 15 (bottom row).

The clinical images (Fig. 17) presented here illustrate the feasibility of obtaining pressure-normalized strain measurements in patients with abdominal aortic aneurysms. In this study, the variability of growth was chosen, as Vonk et al. (2014) have reported large variation in mechanical properties during periods of growth. It should be noted that in our measurements, both thrombus and aortic wall are included in the measure of mean principal strain, which accounts for the large apparent difference in vessel diameters. Our measured strains of 2.7%–1.4% are consistent with previously reported values of strain in AAAs (Long et al. 2004b, 2005). Notably, the $\overline{\varepsilon}_{p+}/PP$ was nearly 50% greater in the rapidly growing AAA with large variations in regional strain contrast compared with the slow-growing AAA. From a clinical standpoint, it is also interesting that there is an increase in the values of ε_{p+}/PP at systole in the posterior lateral region of both AAAs, which corresponds to the side of the aneurysm away from the spinal column and is historically the location of most AAA ruptures (Johansson and Swedenborg 1986; Simão Da Silva et al. 2000). Although insufficient to draw any conclusions, the clinical data reported here indicate that our algorithm can provide measures of mean principal strain and strain contrast in the clinical setting.

The amount of deformation in a vessel over a cardiac cycle can vary depending on the individual's blood pressure at the time of the measurement. To account for this variation, some measurement of the deforming force (*i.e.*, pressure) is needed to account for these variations. Clinically, the most readily available, non-invasive metric of the deformation force is a measure of the pulse pressure (difference between systolic and diastolic blood pressures) measured on an extremity (NIBP). Normalizing $\overline{\varepsilon}_{p+}$ by the pulse pressure may provide a reproducible metric between a given patient with varying hemodynamic parameters and an unrelated patient. We acknowledge that oscillometric NIBP measurements are influenced by many clinical factors (cuff size, cuff location and predisposing atherosclerotic lesions), and multiple studies have found that non-invasive brachial artery pressures are significantly different from central aortic pressures. Typically, NIBP systolic pressures are underestimations of the true systolic pressure and overestimate

diastolic pressures, which would result in an artificially low pulse pressure, inflating the measured value of $\overline{\varepsilon_{p+}}/PP$ (Ribezzo et al. 2014; van't Veer et al. 2008). It should be noted that although use of the NIBP, clinically, would result in a quantitative underestimate of $\overline{\varepsilon_{p+}}/PP$, the pulse pressure is not required for measurement of the regional contrast ratio. It should also be noted that previous work has indicated that the difference between NIBP measures and central aortic pressure may not be significant enough to preclude their use in the determination of AAA material properties (van't Veer et al. 2008).

The limitations of our method include issues of reproducibility of the manual selection of diastolic frames and the segmentation of the inner and outer lumens. We attempted to minimize this error by having a registered physician in vascular interpretation, experienced with images of AAA, perform the frame selection and segmentations. Our strain accumulation measurement will iteratively sum error along with the measurement, meaning our measure will be limited in the number of cardiac cycles for which ε_{p+} can be measured before the error dominated. We acknowledge that measuring the complete 2-D strain field is computationally expensive; however, it provides data necessary for solving the elastic inverse problem. Although an advantage of our method is the ability to measure complex geometries, one of the major limitations is that the resulting $\overline{\varepsilon_{p+}}/PP$ is a combined geometric and material property measure, which would require an inverse modulus reconstruction to distinguish the two. It should also be noted that the diastolic pre-strain in the tissue is not accounted for in our technique, and, presumably, the greater the prestrain, the lower the stiffness contrast within the nonlinear aortic tissue will decrease.

Another limitation of our method is the assumption that the tissue is incompressible and deforming in plane strain. We acknowledge that aneurysmal anatomies are geometrically and mechanically complex. In this work, we have illustrated that 2-D measurements alone may be sufficient to infer the mechanical property changes within a cross-sectional image plane. Serial cross-sectional images, at varying locations longitudinally, could potentially be used for such an assessment throughout the aneurysm. However, the assumptions inherent to our measurement technique may be erroneous for more complicated geometries or planes other than in cross section. Although 3-D US elastography techniques have been developed by others (Fisher et al. 2010; Treece et al. 2008), they require the acquisition of 3-D images at volume rates significantly higher than the rate of deformation. The availability and acquisition speed of 3-D US imaging transducers and systems limit the practicality of these techniques for measuring cardiac-induced deformations of AAAs.

CONCLUSIONS

We have described our ultrasound-based elastographic imaging technique for the measurement of the accumulated 2-D displacement vector field, with adaptive measurement locations, in complex aortic aneurysmal geometries. This allows us to obtain measurements of strain and a known force that induced that strain (*i.e.*, pulse pressure) in simulated ultrasound images, vessel phantoms and clinical images of human AAAs. Using pressure-normalized strain is the first step toward creating a spatially and temporally resolved measurement of tissue stiffness. This allows us to compare measurements made at different time points for a given patient or between patients. Our diastolic/systolic strain and pulse

pressure measurements could ultimately result in a spatially resolved mechanical modulus image and diastolic/ systolic stress estimation. These latter two measurements are well understood metrics that relate directly to a tissue clinical pathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Representative B-mode images for (a) simulated ultrasound image compared with polyvinyl alcohol vessel geometries, (b) axisymmetric tube, (c) idealized abdominal aortic aneurysm and (d) patient-specific abdominal aortic aneurysm.

Fig. 2. Computer renderings of vessel geometries for the (a) axisymmetric tube, (b) idealized abdominal aortic aneurysm and (c) patient-specific phantoms with ultrasound plane indicated at location of maximum diameter. For the heterogeneous phantoms, *red areas* represent regions with 10% polyvinyl alcohol concentration. The *blue anterior belly* represents regions of modulated polyvinyl alcohol by concentration (10%, 15%, 20% and 25%).

Fig. 3. Idealized abdominal aortic aneurysm (a) and patient-specific (b) mold assembly with outer mold and proximal inner mold printed in PLA filament (*white*). The distal inner segment (*beige*, top middle) is printed out of dissolvable polyvinyl alcohol filament to allow for removal from the phantom after polyvinyl alcohol polymerization.

Fig. 4. Completed polyvinyl alcohol (a) axisymmetric tube, (b) idealized abdominal aortic aneurysm and (c) patient-specific abdominal aortic aneurysm geometries after five 12-h (-20°C to 20°C) freeze-thaw cycles.

Fig. 5.
Complete experimental setup with idealized axisymmetric tube constrained within soft idealized polyvinyl alcohol background and submerged within water bath.

Fig. 6.

Pressure profiles of the patient-specific phantoms measured using a pressure transducer (Millar Mikro-Cath) placed just proximal to the imaging plane. The component of the wave pressure wave highlighted in *blue* represents the one cardiac cycle selected based on pressure foot and verified to be where luminal area was minimized (*dashed line* on pressure profile). The peak pressure, or systole, was visually determined to be at the location where the vessel lumen was maximized (*dash-dot line*).

Fig. 7. Flow diagram depicting the manual pre-processing to define one cardiac cycle and the algorithm for measuring the accumulated 2-D displacement field from radiofrequency (RF) ultrasound images. AAA = abdominal aortic aneurysm

Fig. 8. Finite-element meshes at both (a) beginning of systole and (b) peak systolic pressure for the homogeneous, idealized abdominal aortic aneurysm phantom. Nodes are represented by *dots*, and element boundaries, by *lines*. Those elements within the lumen Ω_L (*red*) are excluded from the measurement. Elements within the vessel wall (*yellow*) (Ω_v) and in the background polyvinyl alcohol (*blue*) (Ω_B) define the displacement measurement region (Ω_T).

Fig. 9. B-Mode images of (a) clinical patient with abdominal aortic aneurysm with labeled inferior vena cava (IVC) and vertebra and (b) idealized abdominal aortic aneurysm phantom, with anatomic definitions of regional vessel wall locations related to centroid of the inner lumen and the center of the imaging transducer. Anterior (image top), posterior (image bottom), lateral (image right) and medial (image left).

Fig. 10. Overlay of actual pressure-normalized strain ϵ_{p+}/PP , at maximum expansion, for the simulated images (top row) and resulting measure pressure-normalized strain ϵ_{p+}/PP as determined by the regularization algorithm (bottom row). FE = finite-element.

Fig. 11.

Time-resolved vessel mean (Ω_v) pressure-normalized strain $\overline{\epsilon_{p+}}/PP$, indicated by *black crosses*, over the cardiac cycle for the homogenous finite-element model (left image) and measured by the regularization algorithm (right image). Regional $\overline{\epsilon_{p+}}/PP$ reported for posterior (*blue*), lateral (*red*), medial (*gold*) and anterior (*purple*) vessel subregions. Frame number of maximum $\overline{\epsilon_{p+}}/PP$ indicated by *vertical black line*. Maximum $\overline{\epsilon_{p+}}$ and measured $\overline{\epsilon_{p+}}$ reported in annotation box.

Fig. 12.

Time-resolved regional $\bar{\epsilon}_{p+}/PP$ for posterior (*blue*) and anterior (*purple*) vessel subregions of the finite-element model (*solid line*) and measured by our regularization algorithm (*dashed line*), for increasing anterior to posterior stiffness ratios (1:1 to 1:4). Frame number of maximum $\bar{\epsilon}_{p+}/PP$ indicated by vertical black line. Maximum $\bar{\epsilon}_{p+}$ and measured $\bar{\epsilon}_{p+}$ reported in annotation box. FEA = finite-element analysis.

Fig. 13. Overlay of pressure-normalized strain $\bar{\epsilon}_{p+}/PP$, at maximum expansion, for the homogeneous axisymmetric tube (top row) and homogeneous idealized abdominal aortic aneurysm (AAA) phantoms (bottom row), in the idealized background. Note the decrease in $\bar{\epsilon}_{p+}/PP$ with the increase in polyvinyl alcohol (PVA) concentration.

Fig. 14.

Time-resolved vessel mean (Ω_v) pressure-normalized strain $\bar{\varepsilon}_{p+}/PP$, indicated by *black crosses*, over the cardiac cycle for the homogenous axisymmetric tube (top row) and homogeneous idealized abdominal aortic aneurysm (AAA) phantoms (bottom row).

Regional $\bar{\varepsilon}_{p+}/PP$ reported for posterior (*blue*), lateral (*red*), medial (*gold*) and anterior (*purple*) vessel subregions. Frame number of maximum $\bar{\varepsilon}_{p+}/PP$ indicated by *vertical black line*.

Fig. 15.

Overlay of normalized strain $\overline{\varepsilon_{p+}}/PP$ (at systole) for the idealized (top row) and patient-specific abdominal aortic aneurysm (AAA) phantoms (bottom row). PVA = polyvinyl alcohol.

Fig. 16.

Time-resolved vessel mean (Ω_v) pressure-normalized strain $\overline{\epsilon_{p+}}/PP$, indicated by *black crosses*, over the cardiac cycle for each of the idealized AAA phantoms in the idealized (top row) and anatomic (bottom row) backgrounds. Regional $\overline{\epsilon_{p+}}/PP$ reported for posterior (*blue*) and anterior (*purple*) vessel subregions. Frame number of maximum $\overline{\epsilon_{p+}}/PP$ indicated by the *vertical black line*.

Fig. 17.

Overlay of normalized strain $\overline{\varepsilon_{p+}}/PP$ (at systole) for two 4.6-cm abdominal aortic aneurysms. (a) Aneurysm had a growth rate notable for 0.0 cm/y without notable growth on 6-mo follow-up. (b) Aneurysm had a growth rate of 0.4 cm/y, which increased to 0.6 cm on 6-mo follow-up (growth rate = 1.2 cm/y).

Fig. 18.

Normalized mean principal strain measured using a modified registration algorithm, with a zero initial guess for each frame-to-frame displacement measurement (*i.e.*, $\mathbf{d}(\mathbf{x}) = 0$). Jumps seen in the estimate of strains indicate point where the optimization did not find the global minimum.

Table 1

True and measured mean (Ω_v) principal strain $\overline{\varepsilon_{p+}}$ and strain ratios for the posterior to anterior regions of simulated vessel images

FEA model ratio of posterior to anterior stiffness	True $\overline{\varepsilon_{p+}}$ (%/kPa)	Measured $\overline{\varepsilon_{p+}}$ (%/kPa)	$\frac{\overline{\varepsilon_{p+}}^{\text{Posterior}}}{\overline{\varepsilon_{p+}}^{\text{Anterior}}}$	
			True PA $\overline{\varepsilon_{p+}}$ ratio	Measured PA $\overline{\varepsilon_{p+}}$ ratio
1:1 (60:60 kPa)	7.14	5.24	1.00	1.15
1:2 (60:120 kPa)	5.90	4.17	1.75	2.20
1:3 (60:180 kPa)	5.27	3.88	2.54	3.64
1:4 (60:240 kPa)	4.96	3.62	3.62	4.67

FEA = finite-element analysis.

Table 2

Mean (Ω_v) principal strain $\overline{\varepsilon_{p+}}$ and pressure-normalized mean principal strain $\overline{\varepsilon_{p+}}/PP$ for all homogeneous axisymmetric tube phantoms and homogeneous idealized AAA phantoms in the idealized background

Homogenous phantoms (% PVA by weight)	Pulse pressure (kPa)	$\overline{\varepsilon_{p+}}$ (%)	$\frac{\overline{\varepsilon_{p+}}}{PP}$ (%/kPa)	$\frac{\frac{\overline{\varepsilon_{p+}}}{PP} \text{ 10\% PVA}}{\frac{\overline{\varepsilon_{p+}}}{PP} \text{ \% PVA}}$
Axisymmetric tube				
10%	8.10	12.43 ± 5.51	1.53	1.00
15%	8.19	7.67 ± 2.35	0.93	1.64
20%	13.61	9.51 ± 3.86	0.70	2.20
25%	10.86	2.64 ± 1.13	0.24	6.34
Ideal AAA geometry				
10%	6.50	12.70 ± 4.89	1.95	1.00
15%	6.90	8.41 ± 3.43	1.21	1.60
20%	7.87	7.79 ± 2.94	0.99	1.97
25%	8.40	6.78 ± 2.96	0.80	2.42

AAA = abdominal aortic aneurysm; PVA = polyvinyl alcohol.

Pulse pressure, pressure-normalized mean (Ω_v) principal strain $\overline{\varepsilon_{p+}}$ /PP and pressure-normalized mean strain for the anterior and posterior subregions of the vessel and the strain ratio of the posterior to anterior regions^{*}

Heterogeneous phantoms (% PVA by weight, anterior wall only)	Pulse pressure (kPa)		$\overline{\varepsilon_{p+}}$ PP (%kPa)	$\overline{\varepsilon_{p+}}$ PP Posterior (%kPa)	$\overline{\varepsilon_{p+}}$ PP Anterior(%kPa)	PA $\overline{\varepsilon_{p+}}$ ratio	$\overline{\varepsilon_{p+}}$ Posterior $\overline{\varepsilon_{p+}}$ Anterior
Ideal AAA phantom							
10%	6.50	1.95	1.75	1.91			0.92
15%	6.79	1.36	1.56	0.83			1.87
20%	7.35	1.13	1.51	0.36			4.23
25%	6.77	1.49	2.22	0.30			7.37
Patient-specific AAA phantom							
10%	5.30	0.94	1.76	0.58			3.01
15%	6.95	0.60	1.28	0.38			3.39
20%	7.47	1.12	2.03	0.58			3.49
25%	6.72	0.44	1.08	0.10			10.71

AAA = abdominal aortic aneurysm; PVA = polyvinyl alcohol.
^{*} Values are reported as measured at systole for the idealized AAA and patient-specific phantoms.