A Novel Noninvasive Ultrasound Vibro-elastography Technique for Assessing Patients With Erectile Dysfunction and Peyronie Disease

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OBJECTIVE	To translate a novel ultrasound vibro-elastography (UVE) technique for noninvasively measuring viscoelasticity of the penis.
METHODS	A pilot study of UVE was performed in men with erectile dysfunction or Peyronie disease. Assessments were performed in triplicate on the lateral aspect of the penis (bilaterally) at 100, 150, and 200 Hz before and after erectogenic injection administration. Viscoelasticity of the corpora was also calculated and compared before and after injection and against measures of erectile function, including the International Index of Erectile Function-Erectile Function Domain, and the total erectogenic medication volume required for achieving a firm erection.
RESULTS	Significant increases in viscoelasticity were found after erectogenic injection, validating the ability of UVE to measure dynamic changes with erections. Baseline measures also significantly correlated with the volume of erectogenic medication required to achieve an erection (100 Hz, parameter estimate [PE] 2.21, P <.001; 150 Hz, PE 0.53, P = .03; 200 Hz, PE 0.34, P = .07) but not with age and International Index of Erectile Function-Erectile Function Domain. As erectogenic medications likely represent the most accurate measure of erectile function, these findings suggest a potential role for UVE as a viable diagnostic modality for erectile dysfunction.
CONCLUSION	This first report of the use of elastography with erectile function in humans demonstrates significant associations with responsiveness to erectogenic injection medications. These data have significant potential implications for broader clinical practice and merit further study and validation. UROLOGY 116: 99–105, 2018. © 2018 Elsevier Inc.

Erectile dysfunction (ED) is a common condition that increases with age and is estimated to occur in 52% of men aged 40-70 years.[1] ED is increasingly recognized as an important marker of overall health, as it is commonly associated with medical comorbidities, including hypertension, hyperlipidemia, cardiovascular disease, and diabetes mellitus, among others.[2] The process of erection involves chemical and mechanical interactions in the penile tissues. Nitric oxide, a neurotransmitter released by the parasympathetic nervous system, chemically relaxes the smooth muscles in the corpora. This results in several effects including increased blood flow, expansion of corpora, and closure of venous sinuses, which subsequently leads to penile engorgement and tumescence.[3] Although the pathogenesis of ED is often multifactorial, it commonly results from changes in penile corporal smooth muscle and endothelial cells. Specifically, the ratio of collagen to smooth muscle often increases in men with ED, resulting in corporal fibrosis and eventual veno-occlusive dysfunction.[4]

In additon to ED, Peyronie disease (PD) represents another condition associated with penile fibrosis that occurs in 0.4%-13% of men.[5,6] However, in contrast to ED, where the fibrosis predominantly affects the corporal smooth muscle, PD is associated with fibrotic plaque formation in the tunica albuginea of the penis (and preservation of corporal smooth muscle). Fibrosis in this location often results in penile morphologic changes, including curvature, indentation, hourglass deformities, or other similar findings.[7-9]

The clinical evaluation of ED includes a comprehensive sexual, medical, and psychosocial history, validated sexual function questionnaires, and a thorough physical examination. In addition, routine laboratory tests of fasting glucose, lipid profile, and serum testosterone are often performed to evaluate the common comorbid conditions of diabetes, hyperlipidemia, and hypogonadism, respectively.[10,11]

Penile ultrasonography is an additional test that is often performed in select cases of ED or PD. The test provides

objective, minimally invasive, and relatively inexpensive assessments of penile characteristics, including vascular parameters and structural abnormalities.[12] During the procedure, an artificial erection is typically induced using a vasoactive medication, such as prostaglandin. Penile ultrasonography is then used to identify areas of arterial obstruction or venous leak.[13] In men with PD, penile ultrasonography also offers several potential benefits, including the ability to evaluate the extent and quality of penile plaques. This information is often helpful from a clinical standpoint, as it provides prognostic information and assists the clinician in further determining appropriate treatment options.

Despite these benefits, penile ultrasonography is limited in its ability to differentiate the functional status of the penis, including minor or diffuse changes in corporal smooth muscle fibrosis. This is relevant, as erectile function depends largely on the function and ratio of smooth muscle to collagen cell within the penis.[14,15] Penile ultrasounds, therefore, are unable to provide information on the current erectile state, beyond broad assessments of vascular status.

In contrast to traditional penile ultrasonography, UVE has the potential to provide more detailed information as to the current state of the corporal smooth muscle. To date, only 2 studies have evaluated the use of shear wave elastography in humans to measure the stiffness of CCP. Both of these studies confirmed an association between results and age; however, no attempts were made to correlate outcomes with erectile function, and no assessments were performed on the penis in the erectile state.[16,17] Given the lack of available data, we sought to evaluate the efficacy of a novel ultrasound UVE technique on assessing men with ED or PD.

METHODS

Human Study Protocol

After approval by the Mayo Clinic Institutional Review Board, 10 men were recruited from a sexual medicine clinic in the department of urology. All patients had previously been selected to undergo a penile ultrasound based on clinical assessment for suspected end-stage ED or PD. Once informed consent was obtained, the participant was placed on an examination bed in the supine position. At this point, UVE was performed on each side of the penis, with 3 assessments each obtained on the right and left corpora cavernosa. Assessments were specifically obtained of the corporal tissue and not of the tunica albuginea. After baseline assessments, men underwent intracavernosal injections with a vasoactive compound (alprostadil 10 µg/mL, papaverine 30 mg/mL, phentolamine 1 mg/mL). The initial starting dose for injection was selected at the discretion of the ultrasound team and was based on patient baseline erectile function status and age. The erection was reassessed after 15 minutes, with additional medication administered until either a fully rigid erection was achieved or a maximum of 1 mL of medication was instilled. At that point, repeat UVE assessments were performed in a similar manner to the baseline testing, and then a traditional penile ultrasound was conducted.

Clinical Parameters

A retrospective chart review was performed in participants to evaluate clinicopathologic characteristics relevant to erectile function. Specifically, factors abstracted included age, partner status, subjectively reported erectile function (scale 0-10, where 10 is maximum, 6 is sufficient to penetrate, 0 is no erectile function), the presence of PD (yes or no), subjective ED (yes or no), and results from the Erectile Function Domain of the International Index of Erectile Function (IIEF-EFD) standardized questionnaire.

Penile Ultrasonographic Elastography Technique

A 0.1-second vibration was generated on the penis using an indenter of the handheld shaker (Model FG-142, Labworks Inc., Costa Mesa, CA).[18] The probe was located at a region away from any penile plaques (if present) on the lateral aspect of the penis and aiming to the contralateral side. The excitation force from the indenter of the shaker was much less than 1 N, and the subject only felt a small vibration on his penis. An ultrasound probe was positioned about 5 mm away from the indenter to measure the resulting wave propagation in the penis. A Verasonics ultrasound system (Verasonics V1, Verasonics, Inc., Kirkland, WA) with an ultrasound probe of L11-4 with a central frequency of 6.4 MHz was used. The measurement of shear wave speed in the penis was independent of the location and amplitude of excitation. A small tissue motion in tens of µm was enough for sensitive ultrasound detection of the generated tissue motion.
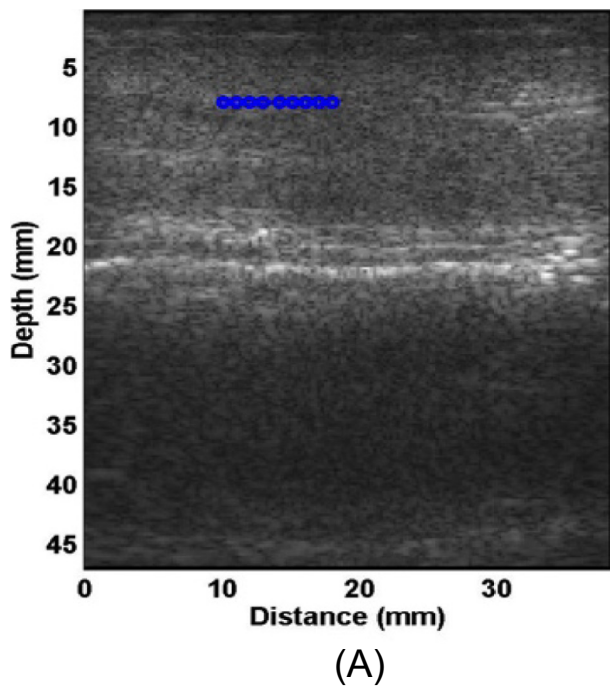
The tissue motions at 9 locations inside the penis at a depth of about 8 mm and across a distance of 8 mm were measured (Fig. 1A). The tissue motion velocities at these locations were measured in the normal direction using the ultrasound tracking beams through those locations.[19-21] Motion velocity occurred in response to the external vibration excitation induced by the handheld vibrator. A high pulse repetition rate of 2000 frames/s was used to detect tissue motion in response to the vibration excitation at 100, 150, and 200 Hz. A Verasonics ultrasound system was used to collect up to a few thousand imaging frames per second using a plane-wave pulse transmission method.

Data Processing

Let $s_1(t)$ and $s_2(t)$ represent the displacement responses at 2 locations in the penis, the phase change of wave propagation over the 2 location can be calculated with a cross-spectrum method. The cross-spectrum $S(f)$ of 2 signals $s_1(t)$ and $s_2(t)$ is defined as[19]

$$S(f) = S_1^*(f) \cdot S_2(f) = |S_1(f) \cdot S_2(f)| \cdot e^{-j\Delta\varphi(f)}, \qquad (1)$$

where $S_1(f)$ and $S_2(f)$ are the Fourier transforms of $s_1(t)$ and $s_2(t)$, respectively, * denotes the complex conjugate, and
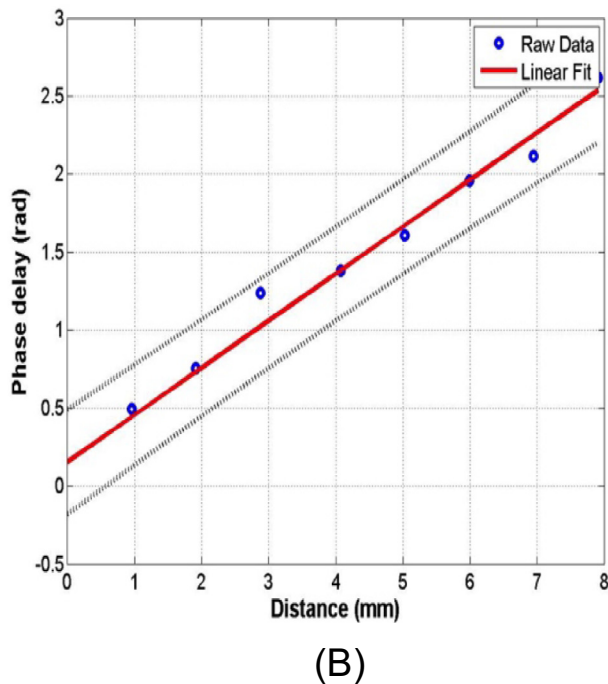
(A)

Wave speed = 2.08 +/- 0.12 (m/s)

(B)

Figure 1. (A) The tissue motions at 9 locations inside the penis at a depth of about 8 mm were measured. The tissue motion velocities at these locations were measured in the normal direction using the ultrasound tracking beams through those locations. **(B)** The wave phase delay of the remaining locations, relative to the first location, is used to measure the surface wave speed. Representative wave speed at 100 Hz is for a patient before injection. (Color version available online.)

$\Delta\phi$ (f) is the phase change between $s_1(t)$ and $s_2(t)$ over distance at frequency f.

The phase change of shear wave with distance is used to measure the shear wave speed,

$$c = 2\pi f \left| \Delta r / \Delta\phi \right|, \qquad (2)$$

where Δr is the distance of 2 measuring locations, $\Delta\phi$ is the wave phase change over distance, and f is the frequency.[22] The estimation of wave speed can be improved by using multiple phase change measurements over distance.[23] The regression of the phase change $\Delta\phi$ with distance Δr can be obtained by "best fitting" a linear relationship between them, and the regression model is $\widehat{\Delta\phi} = \alpha\Delta r + \beta$, where $\Delta\hat{\phi}$ denotes the regression value of multiple $\Delta\phi$ measurements, α and β are regression parameters, and $c = 2\pi f \left| \Delta r / \widehat{\Delta\phi} \right| = \omega/\alpha$.

Using the tissue motion at the first location as a reference, the wave phase delay of the tissue motions at the remaining locations, relative to the first location, is used to measure the wave speed.

The shear wave speed can be related to the elastic modulus of tissue as[24,25]

$$c = \sqrt{\frac{\mu}{\rho}}, \qquad (3)$$

where μ is the shear elasticity in pascal and ρ is the mass density of the tissue in kg/m^3.

For soft tissue under low frequency harmonic excitation, the Voigt model, which consists of a spring of elasticity μ_1 and a damper of viscosity μ_2 connected in parallel, has been proved to be effective in modeling the linear viscoelastic materials.[26,27] The wave dispersion curve of wave speed c with respect to the excitation frequency ω can be formulated by

$$c = \sqrt{\frac{2\left(\mu_1^2 + \omega^2\mu_2^2\right)}{\rho\left(\mu_1 + \sqrt{\mu_1^2 + \omega^2\mu_2^2}\right)}}. \qquad (4)$$

The wave speed was measured at 3 excitation frequencies of 100, 150, and 200 Hz. The 100-Hz excitation signal is stronger than those of higher frequency excitations. The higher frequency waves have smaller wave length but decay more rapidly over distance than the lower frequency waves. The frequency ranges chosen in this study consider the wave motion amplitude, spatial resolution, and wave attenuation. By measuring the wave speeds at the 3 frequencies, the elasticity μ_1 and viscosity μ_2 are estimated from Eq. (4) with a nonlinear least-squares fitting technique.[28,29] Estimation of tissue viscoelasticity is dependent on the mass density of tissue. As most soft tissues have mass density close to 1.0 g/cm^3, the assumed density of the penis was set at 1.0 g/cm^3 for purposes of evaluation.

Table 1. Clinicopathologic and demographic variables for cohort

Number	Age	PD	ED	Dose Required	Subjective EF	IIEF-EFD
1	66	Y	N	0.15	8	30
2	60	Y	Y	1.0	1	1
3	23	Y	Y	0.1	6	6
4	22	Y	N	0.1	10	4
5	70	N	Y	1.0		24
6	57	Y	Y	0.1	6	
7	50	Y	N	0.1	8	9
8	47	N	Y	0.1	6	2
9	70	Y	Y	0.2	6	29
10	74	Y	Y	0.06	3	6
Mean (SD)	53.9 (18.7)	80%	70%	0.29 (0.38)	6.0 (2.69)	12.3 (11.8)

ED, erectile dysfunction; EF, erectile function; IIEF-EFD, International Index of Erectile Function-Erectile Function Domain; PD, Peyronie disease; SD, standard deviation.
Subjective erectile function based on scale of 0-10, where 0 = no function, 10 = perfect function, and 6 = sufficient rigidity to penetrate.

Study Objectives and Statistical Analysis

Primary objectives of the current study were changes in the elasticity and viscosity before and after erectogenic medication administration at 100, 150, and 200 Hz. Secondary objectives included evaluating associations between measures of erectile function and viscoelasticity at baseline, postinjection, and the difference between pre- and postinjection. Statistical analyses included matched pairs analysis, linear regression, and logistic regression where appropriate. Statistical significance was set at .05, and tests were two-sided where appropriate.

RESULTS

A total of 10 men (mean age 53.9; standard deviation [SD] 18.7) underwent penile UVE from June through August 2017. See Table 1 for demographic and clinicopathologic variables. Seventy percent of men had sexual partners at the time of assessment, 30% of men had isolated PD, 20% isolated ED, and 50% with combined ED/PD. Overall, men required a mean 0.3 mL (SD 0.38) of erectogenic medication, although 60% of men required 0.1 mL or less to achieve a satisfactory erection. Two men required a full 1.0 mL with unsatisfactory response (veno-occlusive dysfunction). Self-assessments of erectile function were rated at a mean and median 6 (SD 2.7), whereas the mean IIEF-EFD score was 12.3 (SD 11.8)

Figure 1(B) shows representative wave speeds at 100 Hz for a patient before injection. The wave speed in the penis is determined by analyzing ultrasound data directly from the penile tissue. The wave speed represents a local measure, independent of the location and amplitude of excitation. A comparison of wave speeds for 10 patients with ED or PD before and after the injection is shown in Figure 2(A)-(C) for both sides of the penis at 100, 150, and 200 Hz. Data were only available on 9 patients before injection, as 1 patient was tested only after the injection. The P values for analyses were <.05 for both sides of the penis and at each of the 3 frequencies, respectively.

Figure 2(D) and (E) shows the comparison of elasticity and viscosity for 10 patients before and after the injec-tions. The P values for the analyses were <.05 for both sides of the penis. Results demonstrate that the magnitudes of both elasticity and viscosity were statistically higher after the injection than those of the baseline.

In evaluating correlations between viscoelasticity and clinical measures of erectile function, several notable findings emerged (Table 2). Statistically significant associations were identified between the erectogenic medication dose required at the time of assessment and baseline assessments for 100 and 150 Hz, but not for 200 Hz (P = .07). This is notable because the dose required to achieve an erection is likely the best measure of true erectile function. No statistically significant findings were identified after administration of erectogenic medications or when evaluating the change in viscoelasticity (post minus pre), with the exception of 1 value.

DISCUSSION

The current study demonstrates a proof of concept for utilizing elastography during the assessment of men with ED and validates the use of a novel UVE technique. Findings demonstrated significant changes in viscoelasticity after erectogenic medication administration, suggesting that the instrument is able to accurately detect relevant changes in penile physiology with tumescence. Perhaps, more importantly, UVE was able to accurately correlate with baseline ED (as measured by the amount of erectogenic medication required to achieve an erection). This is a notable finding and, to our knowledge, represents the first data of its kind.

One of the most significant ramifications of these results is that penile UVE has the potential to represent the first true objective measure of physiological erectile function. As UVE is essentially an indirect measure of the extent of penile fibrosis, it provides a more discriminating look into the current state of erectile tissue functionality. Other historically utilized tests (nocturnal penile tumescence testing, dynamic infusion cavernosometry and cavernosography), advanced imaging modalities (penile ultrasound, magnetic resonance imaging, and computed to-
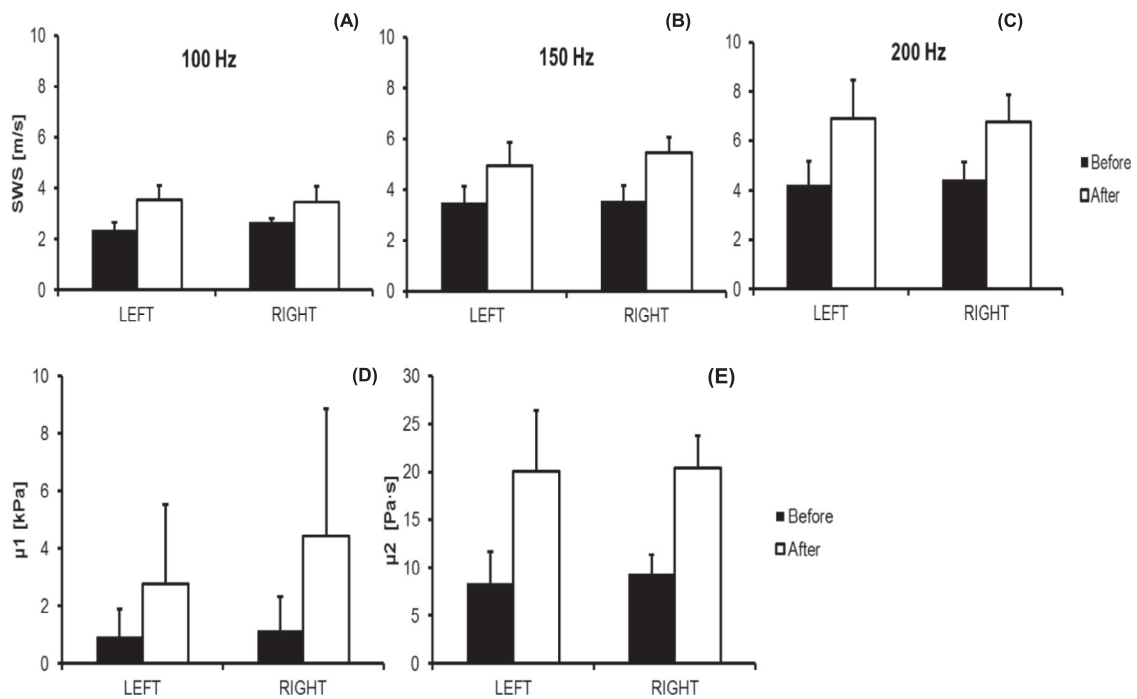
Figure 2. (A) Comparison of wave speeds for patients before and after injections at both sides of the penis. Wave speeds at **(A)** 100 Hz, **(B)** 150 Hz, **(C)** 200 Hz (n = 10). Comparison of elasticity $\mu1$ **(D)** and viscosity $\mu2$ **(E)** before and after injections at both sides of the penis (n = 10).

Table 2. Association between viscoelastography measures and erectile dysfunction clinicopathologic paramaters

Assessment	Age PE (P Value)	PD OR (P Value)	ED OR (P Value)	Dose Required PE (P Value)	Subjective EF PE (P Value)	IIEF-EFD PE (P Value)
Preinjection assessment						
100 Hz	52.23 (.15)	3.41 (.58)	0.01 (.12)	2.21 (<.001)	**−16.68 (.02)**	10.46 (.74)
150 Hz	6.85 (.56)	0.42 (.76)	0.12 (.43)	**0.53 (.03)**	−3.47 (.07)	−7.36 (.42)
200 Hz	7.10 (.41)	0.30 (.63)	1.08 (.97)	0.34 (.07)	−1.59 (.31)	1.13 (.87)
Avg of 3	12.34 (.39)	0.41 (.75)	0.32 (.64)	**0.68 (.02)**	−3.79 (.13)	−2.23 (.85)
Postinjection assessment						
100 Hz	5.53 (.69)	139.30 (.08)	0.15 (.44)	0.16 (.57)	−0.54 (.79)	−0.41 (.96)
150 Hz	−8.18 (.50)	0.46 (.79)	0.15 (.46)	0.14 (.58)	−0.48 (.79)	3.13 (.70)
200 Hz	−7.58 (.41)	0.02 (.15)	30.15 (.21)	0.00 (.99)	1.06 (.44)	4.62 (.44)
Avg of 3	−11.14 (.51)	0.46 (.78)	1.18 (.95)	0.17 (.62)	0.58 (.82)	6.92 (.53)
Difference (postinjection minus preinjection)						
100 Hz	−8.21 (.52)	41.05 (.18)	0.22 (.58)	−0.12 (.70)	0.52 (.83)	−3.64 (.72)
150 Hz	−1.88 (.86)	2.09 (.76)	2.09 (.73)	−0.21 (.41)	2.20 (.22)	11.90 (.12)
200 Hz	−10.04 (.28)	0.10 (.37)	134.35 (.08)	−0.36 (.10)	**3.70 (.01)**	7.15 (.33)

ED, erectile dysfunction; EF, erectile function; IIEF-EFD, International Index of Erectile Function-Erectile Function Domain; OR, odds ratio; PD, Peyronie disease; PE, parameter estimate.
All represent P values of association. Subjective erectile function based on scale of 0-10, where 0 = no function, 10 = perfect function, and 6 = sufficient rigidity to penetrate.
Bold text indicate statistical difference.

mography), and blood tests have never been able to accurately assess the current state of the erectile tissue. Indeed, the only true way to assess similar findings would be to obtain a penile biopsy, which is invasive and not ideal.[30] Additionally, inadequate population-based data would ever be available to correlate outcomes with penile biopsies, making it an impractical tool.

If validated with further studies, penile UVE may have several notable roles in evaluating men with ED. It could potentially provide information as to an age-equivalency of erectile function, prognostic information on responsiveness to select agents such as phosphodiesterase-5 inhibitors or intracavernosal injections, or even serve as a surrogate for assessing overall physical health. This latter point is particularly relevant given that ED is correlated with future cardiovascular events and may be a stronger predictor than hyperlipidemia, body mass index, family history, or even hypertension.[31] Additionally, ED often

precedes more severe cardiovascular events such as myocardial infarction and stroke. As such, future studies are warranted to investigate the role of elastography in identifying early changes to penile corporal tissue and its subsequent ability to predict impending cardiovascular disease. This may further increase the lead-time available to perform necessary lifestyle and medical changes to reduce cardiovascular risk. Elastography also represents a widely available, minimally invasive, rapid assessment tool that could serve as a viable adjunctive test to penile ultrasonography and become an indispensible instrument for assessing erectile function.

In reviewing the data presented, there are several interesting observations and important comments. First, the results were only observed using data on dosing of erectogenic agents to achieve an erection. As noted previously, this likely represents the best assessment of a man's true erectile function. Several important issues including a need for a current sexual partner, lack of efficacy in men with PD or other findings that preclude penetration, and validation only in heterosexual males limit subjective assessments such as rating erectile function on a scale of 0-10 or utilization of the IIEF-EFD. These limitations become apparent when reviewing the data on the 10 men included in the current study (Table 1). Among these 10 men, the highest IIEF-EFD scores were found in men aged 66, 70, and 70, whereas the 2 men in their 20s had IIEF-EFD scores of 4-6. Clearly, the underlying erectile capacity for the 20-year-old men likely was far higher than those in their 60s-70s; however, given the presence of PD, this assessment was invalid. Similarly, self-assessments on a scale of 0-10 were unhelpful. Age also failed to be an adequate predictor alone, a finding that mirrors what is seen clinically, where wide disparities in erectile function are noted among men of similar ages.

Another interesting finding from the current data is that the strongest correlation was noted at the 100-Hz frequency, whereas the 200-Hz frequency was nonsignificant (0.07). This could possibly relate to the ability of the 100-Hz frequency to penetrate the penile tissue further, to obtain a more accurate "whole penis" assessment, whereas the 200-Hz frequency may be more impacted by the fibrous tunica (note that in men with PD, probes were placed in locations away from plaques). Similarly, no significant differences were identified after erectogenic medication administration. This is likely due to the fact that with erections, the tissue becomes more rigid and less elastic, thus rendering any test of elasticity less sensitive. From a clinical standpoint, however, this is beneficial, as it potentially would allow for assessments without need for erectogenic medication administration.

The current study also validates the potential role for a novel UVE method. Compared with most shear wave elastography techniques that use ultrasound radiation force (URF) to generate shear waves inside the tissue, UVE safely generates larger tissue motion than URF because the ultrasound energy of URF is limited by the Food and Drug Administration safety requirements. Moreover, long duration of high-intensity ultrasound radiation may break the ultrasound system or probe element. UVE in this study, however, was performed by safely generating a local mechanical vibration on the penile tissue, whereas diagnostic ultrasound was only used to detect wave propagation of the penile tissue. Hence, UVE represents a potentially safer option for screening erectile function.

The current study has several notable limitations. The sample size is small and represents pilot data only. As such, all findings require further study and validation before acceptance and routine implementation. The population assessed is also very heterogeneous, as penile ultrasounds are only recommended in our practice in certain clinical scenarios (ie, PD, severe ED, or if the patient specifically requests). As PD and ED represent very distinct conditions, these differences in our study cohort may have impacted outcomes. There are also challenges in obtaining an accurate measure of true baseline penile rigidity. Although the IIEF-EFD provides some historical information on current erectile function, the combined use of the erectile hardness score may provide additional relevant information with future studies.

Despite these limitations, the current study demonstrates several potential strengths. This is the first study to specifically evaluate the role of elastography in assessing erectile function. Additionally, it is the first to compare elastography against any measure of erectile function, including arguably the gold standard measure of erectile responsiveness, erectogenic injections. The current data also support and expand on other recently published findings that have identified an association between cavernosal elastography and age.[16,17] As the data only involve 10 patients, the associations identified suggest a strong ability to identify differences between disease states (very limited power). This may suggest that with additional patients, further associations may be identified. Finally, although not randomized with a true control, assessments were performed in men with varying degrees of ED (ranging from no ED to complete ED), which provides important, contrasting data.

CONCLUSION

The current study provides the first proof of concept for utilizing elastography as a valid measure of erectile function and validates the utility of a novel UVE technique. The findings demonstrated significant associations between baseline viscoelasticity (100 and 150 Hz) and the volume of erectogenic injection medication required to achieve a firm erection. The data also demonstrated significant changes in the viscoelasticity between the pre- and the postinjection assessments, which further validates the use of elastography for this clinical condition. As the clinical implications of this new application of technology may be large and far-reaching, these preliminary data mandate a need for additional study and validation.

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