White Paper

ShearWave™ Elastography Prostate

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Introduction

Palpation was, at the start of medicine, the only technique used to assess tissue stiffness reflecting the underlying pathological disease, such as a solid tumor, a tissue abscess etc. However, palpation efficacy for the detection and characterization of parenchymal disorders is limited in non-superficial tissue and is highly dependent on physician training. Recently, a new diagnostic imaging modality has emerged, called elastography, which uses ultrasound (US) or Magnetic Resonance Imaging (MRI) to assess tissue differences in stiffness (or elasticity). It provides an imaging representation of what has been historically assessed qualitatively by palpation. US elastography has been developed for a longer period compared to MRI elastography. It can be included in the routine workflow of US examinations and benefits from the advantages of US imaging (absence of contra-indication, lack of exposure to radiation and magnetic field, large availability, real-time imaging technique etc). US elastography should be able to increase the diagnostic performance of US imaging.

SuperSonic Imagine’s ShearWave™ Elastography is a new ultrasound imaging concept designed to achieve these objectives. Based on automatic generation and analysis of transient shear waves, the method has the major advantage of assessing true tissue elasticity in real-time with reproducible and user-skill independent results.

Shear wave based elastography is the only approach able to measure local tissue elasticity information, in kilopascals, in real time [1]. However, its implementation as an imaging mode requires major technological breakthroughs in the ultrasound medical imaging field.

ShearWave™ Elastography

Presentation

ShearWave Elastography (SWE™) provides quantitative elasticity maps in real-time as illustrated in Figure 1.

The true tissue elasticity is assessed based on shear wave propagation speed in the tissue. If shear wave propagation speed can be measured, then local tissue elasticity can be deducted quantitatively and shown on a color coded map.

The color coded image is superimposed on a B-mode image. The color scale is quantitative with values expressed in kPA. Stiffer tissues are coded in red and softer tissues in blue. The elasticity image is refreshed in real-time.

The image resolution remains around 1mm. The imaging frame rate is optimized to meet acoustic output limitations defined by international standards [2].

ShearWave technology enables an unbiased elastography image where each pixel has a true local evaluation independent of surrounding tissue. This is achieved by scanning with a conventional ultrasound probe without requiring any external compression by the user.

The SuperSonic Imagine Aixplorer® is the first ultrasound system to leverage this technology and implement a true shear wave based elastography imaging concept.
Shear Wave Generation

Shear waves can be generated in the body in different ways. The beating heart is a natural source of shear waves but its vibrations remain localized in its vicinity. The use of external vibrators, such as those used in dynamic MR elastography, are not ideal in the ultrasound environment as they require the manipulation of two devices simultaneously [3]. ShearWave Elastography uses the acoustic radiation force induced by ultrasound beams to modify underlying tissue properties. This pressure or "acoustic wind" pushes the tissue in the direction of propagation. An elastic medium such as human tissue will react to this push by a restoring force. This force induces mechanical waves and, more importantly, shear waves which propagate transversely in the tissue. This is illustrated in Figures 2 and 3.

Conventional ultrasound imaging generates shear waves that are very weak, amounting to only a few microns of displacement. Therefore, they cannot be used for real-time elastography imaging. The challenge was to find a way to increase the amplitude of the shear wave while limiting the acoustic power to safe levels. SuperSonic Imagine's patented SonicTouch™ technology generates a supersonic shear wave source within tissue [4, 5]. Using SonicTouch™, ultrasound beams are successively focused at different depths in tissue (Figure 4). The source is moved at a speed that is higher than the speed of the shear waves that are generated. In this supersonic regime, shear waves are coherently summed in a "Mach cone" shape, which increases their amplitude and improves their propagation distance. For a fixed acoustic power at a given location, SonicTouch increases shear wave generation efficiency by a factor of 4 to 6 compared to a non supersonic source.

Figure 2: Radiation force induced by a traditional focused ultrasound beam.

Figure 3: A shear wave induced by an ultrasound beam focused in the center of the image.

Figure 4: Radiation force induced by SonicTouch™. Shear waves are amplified in a Mach cone shape (in yellow), which increases the propagation distance of shear waves while minimizing acoustic power.
UltraFast™ Imaging

The shear waves generated using the SonicTouch™ excitation need to be captured by the ultrasound system. Shear waves typically propagate in tissue at speeds between 1 and 10 m/s (corresponding to tissue elasticity from 1 to 300 kPa). Consequently, they cross an ultrasound image plane of 3 to 6 cm width in 10 - 20 milliseconds (less than 1/50 of a second). Conventional ultrasound (US) systems generate only 50 - 60 images per second. This is too slow to image a propagating shear wave since the shear wave will have disappeared in the time needed to make a single frame. In order to capture shear waves in sufficient detail, frame rates of a few thousands of images per second are needed. That is 100 times faster than the frame rates offered by current state-of-the-art US technology. Axplorer is the first ultrasound system able to reach ultrafast frame rates of thousands of Hz. UltraFast imaging is performed by sending US plane waves into the tissues to insonify the full imaging plane in one shot, as illustrated in Figure 5. The maximum frame rate achievable is determined by the time it takes the US wave to travel from the transducer to the tissue and back. For a typical breast image of 4 cm depth, the maximum frame rate achievable is 20,000 Hz.

The technological challenge is the ability to process the ultrasound images acquired at these ultrafast frame rates. In conventional systems, this capability is limited by the number of lines of an image the system is able to compute in parallel. This number is usually between 4 and 16 on radiology systems. Thanks to its full software architecture (SonicSoftware™), Axplorer computes all the lines of each image in parallel, therefore managing to achieve ultrafast frame rates of thousands of Hz.

UltraFast imaging allows detailed monitoring of the shear waves traveling through the imaging plane. Propagation of the shear wave induces small tissue displacements which are recorded by the UltraFast imaging system, and quantified using tissue Doppler techniques. In this manner, a movie of the particle velocity induced by the shear wave is formed. This provides a faithful representation of the propagation of the shear wave-front as illustrated in Figure 6.

The shear wave propagation speed is estimated at each pixel from the shear wave particle velocity movie (Figure 6) using cross correlation algorithms. The resulting speed map is shown in Figure 7.

Figure 5: UltraFast™ imaging. A flat wave insonifies the whole medium in one shot.

Figure 6: Plane shear wave induced by SonicTouch™ technology in a medium containing a harder inclusion (red circle). The plane shear wave-front is deformed because the shear wave travels faster in the harder inclusion.

Figure 7: Map of the shear wave propagation speed in m/s deduced from the velocity movie.
**Elasticity Estimation**

To compute a full elasticity image as displayed on the system screen (Figure 1), several supersonic lines are generated using SonicTouch technology, as illustrated on Figure 8. For each line, several ultrastart images are acquired and the shear wave propagation velocity movie is computed. Shear wave speed maps from all the pushing lines are calculated and then combined into a final image. The elasticity map in kPa is directly derived from the final speed map, using the following equation: \( E = 3pc^2 \)

SonicTouch technology reduces the number of pushing beams necessary to compute a full elasticity map in a region of tissue. SonicTouch technology is the key to real-time ShearWave Elastography. Its efficiency enables continuous refreshing of the elasticity image while remaining in the classic acoustic power limitations of ultrasound systems.

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The Prostate: A Clinical Work Flow

Prostate cancer is the second leading cause of cancer-related deaths in men, with lung cancer being the most common. In addition, prostate cancer is the most commonly diagnosed malignancy in men with an estimated 790,000 cases in the USA in 2010 and 217,730 new cases diagnosed every year in the USA [8]. These numbers are very slightly higher than breast cancer incidence for the same year. Despite diagnostic improvements related to imaging techniques and more efficient therapies, prostate cancer specific mortality remains stable.

Prostate cancer is often referred to as an elusive disease. For over 30 years and still today, the screening standard for prostate cancer has been the combination of digital rectal examination (DRE) and the prostate specific antigen (PSA) dosage. Despite the larger use of biological tests such as prostate specific antigen (PSA) dosage and imaging modalities (transrectal ultrasonography (TRUS) and Magnetic Resonance Imaging), there is a slight increase in the annual death rate. The detection and characterization of prostate nodules with US and MRI remains difficult.

Prostate Screening

For most men at average risk, screening starts at age 50. Men at higher risk of prostate cancer, African-American men or men with a family history start screening earlier, often at age 40.

Prostate cancer screening is based on the digital rectal examination (DRE) and PSA dosage. The PSA is a normal enzyme secreted by the epithelial cells of prostate ducts and seminal vesicles. PSA elevation is not specific of prostate cancer and can be found in benign prostatic hyperplasia, acute and chronic prostatitis, prostate trauma (such as cystoscopy, resection, biopsies). DRE is done at distance of PSA dosage to avoid a false increase in PSA levels. The DRE exam may be done as part of a regular examination or to check on symptoms, such as a change in urination.

Prostate Cancer Diagnosis

Prostate cancer may be suggested by an abnormal or rising serum PSA level, or by an abnormal DRE, which triggers further evaluation, typically transrectal ultrasound (TRUS)-guided sextant biopsies. Prostate biopsy findings are also widely used to estimate the tumor volume (number and spatial dispersion of positive cores, length of tumor in each positive core) and aggressiveness (Gleason score of the tumor detected at biopsy, capsule and neuro-vascular pedicles invasion).

However, this approach has some limitations. First, using PSA as a screening tool leads to a substantial number of unnecessary biopsies in patients with no cancer or with indolent cancer that do not need immediate treatment. Currently, overdiagnosis rates are estimated to be between 27% and 58% [7]. Second, a negative set of biopsies does not rule out the presence of cancer. Among the patients with negative 10 to 12 core biopsy schemes, 17-21.2% have cancer at the repeated biopsy [8, 9]. Hence, a dilemma faces many urologists with patients with persistent abnormal PSA level and negative biopsies: when to repeat biopsy and when to stop biopsying [10]. Third, although PSA level and biopsy findings correlate positively with clinical stage, tumor volume and histologic grade, they are of limited value in predicting tumor burden and aggressiveness in individual patients [7].

To overcome these difficulties, some authors propose to further increase the number of biopsy samples in order to improve volume registration of the core location (so-called saturation biopsies). This approach can rule out prostate cancer and offers a better estimation of the tumor volume and Gleason score [11]. However, it is associated with increased cost and morbidity and increased risk of over diagnosing microscopic tumor foci that do not need treatment [13, 14].

Another option would be to develop an imaging method that could accurately distinguish prostate cancer.

MRI has recently yielded interesting results in tumor detection/localization [14-18]. Functional prostate MRI combines several MR sequences such as diffusion-weighted MRI (DWI), MR spectroscopy (MRS) and dynamic contrast-enhanced MRI (DCE-MRI) to improve tumor diagnosis. Thus, the so-called multi-modality MRI, combining T2-weighted imaging (T2WI) and functional MRI, recently gave promising results in tumor detection in candidates to radical prostatectomy, with areas under the ROC curve > 0.9 [19, 20].

Interesting results have also been published in more challenging populations such as patients with negative biopsy and elevated PSA levels [21]. However, MRI
still needs improvements. First, there is a lack of standardization, both in imaging protocols and in the interpretation of MRI findings. As a consequence, good results obtained in specialized groups are not always reproduced by others. Second, even if high-grade tumors seem better detected, little has been published yet about the distinction between aggressive and indolent tumors. Quantitative approaches, especially for DWI and DCE-MRI, could probably help in standardizing the interpretation of images and defining thresholds to distinguish aggressive tumors. Finally, little is known about the best way of combining the results of the different functional MR techniques, especially when they are discordant [22]. This further aggravates the inter-observer variability in interpreting multi-modality MRI.

The ability of TRUS to delineate cancer foci is limited, even with the adjunct of Color/Power Doppler, with sensitivity and specificity varying around 40-50% [23]. Some functional techniques such as contrast-enhanced Ultrasound (CEUS) has also recently given interesting results, preliminary studies suggesting it was able to sensitize prostate biopsy [24, 25].

It is well known that prostate cancer is stiffer than normal prostate tissue, at least in the peripheral zone, and therefore any imaging technique mapping tissue elasticity might be of interest for detecting/localizing cancer foci in the prostate. This white paper describes a feasibility study of transrectal quantitative* ShearWave Elastography for prostate cancer evaluation.
Methods and Materials

This preliminary study presented 21 patients with increased PSA values (4-10 ng/mL) who were prospectively enrolled after signing an informed consent form. The prostate was studied using transrectal ultrasound with spatial compound B-mode, color Doppler US (CDUS) and ShearWave Elastography (SWE) on the Aixplorer MultiWave Ultrasound System using an endocavitary transducer, SE12-3. The elasticity measurements and ratios between nodules and adjacent perenchyma were calculated.

Contrast-enhanced US (CEUS) was performed using low MI pulse subtraction after injection of 4.8-9.6 ml of SonoVue® (Bracco, Milan, Italy) using an Aplio XG system. Imaging findings were correlated to sextant prostate biopsies (n=12) and targeted biopsies on suspicious areas (n=2-6) detected with SWE and CEUS. MRI with axial and coronal T2w acquisition, axial T1w acquisition, diffusion and dynamic contrast-enhanced MRI, with Signia 1.5T and Discovery MR450 was also evaluated.

The blinded analysis of the SWE acquisition was performed retrospectively from cine loops and frames. Normal and abnormal patterns were matched with pathology results.

Results

In three patients, it was not possible to localize normal and abnormal patterns using SWE due to a technical problem during the export of the data. The analysis was performed from the remaining 18 patients (mean age 65 ± 6 years, min 54 - max 79). The PSA values were 6.9 ± 2.2 ng/mL.

Eight patients were presenting significant prostate adenocarcinomas. Among the 26 nodules detected either with US or at pathology, 10 were adenocarcinomas with Gleason scores above 6. Sixteen of the nodules were adenomatous hyperplasia or focal prostatitis. The correlation between B-mode plus pathology and CDUS, CEUS or MRI could not be obtained for 3 / 3 / 4 nodules, respectively.

ShearWave Elastography imaging was feasible in all patients, tissue elasticity signals were obtained in both the peripheral and the transition zones with good correlation to anatomical areas. Because of higher attenuation, the deepest transition zone could not be correctly assessed at 4-5 cm. In addition, macro-calcifications exhibited very high stiffness values on the SWE elasticity map. The transition zones appeared heterogeneous with stiffness values above 40 kilopascals. SWE signals were adequate for all peripheral nodules. However, there were imaging limitations due to intestinal gas, interposition and higher pressure of the end-fire transducer on the rectal wall and the adjacent posterior gland.

The prostate cancer nodules exhibited a high stiffness (mean 55±45 kPa, min 23/ max 180 kPa) than the adjacent peripheral gland (mean 18 ± 9 kPa) on the ShearWave Elastography map, while peripheral adenomatous hyperplasia and focal prostatitis exhibited a significantly lower stiffness (mean 19 ± 5 kPa, min 12/ max 28 kPa; p<0.01). The stiffness ratio between nodule and adjacent parenchyma was significantly higher for cancer (3.0 ± 1.0) compared to benign nodules (1.0 ± 0.20; p<0.01). The cut-off value of 1.5 allowed the best discrimination of the two populations.

The sensitivity (Se), specificity (Sp), Positive predictive value (PPV) and Negative predictive value (NPV) were calculated for each modality: CDUS, CEUS, SWE and MRI.

The results were as follows:

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Clinical images

Figure 9: ShearWave™ Elastography study of a normal prostate. There is a homogeneous coding of the SWE™ signals in the peripheral zone and a clear match between the SWE pattern and anatomical morphology.
Figure 10: Patient presenting a soft benign nodule in mid peripheral prostate zone (left picture, straight arrow). Close to the apex, a stiff area was detected and biopsy revealed a Gleason 7 adenocarcinoma (right picture).

Figure 11: Patient with no detected nodule on B-mode imaging. However, SWE™ revealed a diffuse increase in stiffness values over 180 kPa within the entire prostate. All biopsies showed the presence of adenocarcinoma with a Gleason score of 9.
Figure 12: The hypoechoic nodule in the peripheral zone at mid prostate exhibited a strong increase in stiffness values with a ratio of 2.8 compared to the surrounding peripheral parenchyma. This is the typical pattern of an adenocarcinoma.
Figure 13: A poorly visible nodule in B-mode imaging was reported on the left peripheral zone (straight arrow). Pathology showed this nodule to be benign. However, a stiff area was detected incidentally on the right peripheral zone. Pathology revealed a Gleason 7 adenocarcinoma.

Study Conclusion

Transrectal quantitative ShearWave Elastography is a feasible technique for prostate cancer evaluation. It provides additional information about stiffness of nodules localized in the peripheral zone, complementary to that of CEUS. These preliminary results are encouraging but a larger multicentric evaluation remains necessary.
Conclusion

SuperSonic Imagine’s ShearWave Elastography is a new ultrasound imaging concept used to determine tissue elasticity.

ShearWave Elastography is the result of the exploration of a new type of wave – the shear wave - by a revolutionary new architecture which enables assessment of tissue elasticity in real time.

SonicTouch technology creates a supersonic vibration source within tissue, allowing efficient and automatic generation of shear waves without increasing the acoustic power delivered by the ultrasound system.

The SonicSoftware platform allows acquisition of ultrasound images at ultrafast frame rates (100 to 200 times faster than conventional systems) in order to capture shear wave propagation and measure tissue elasticity in kPa.

Combined, these powerful technologies deliver new capabilities to the clinical arena:

- Quantitative information on human tissue properties through the measurement of elasticity in kPa;
- The ability to visualize the elasticity of small lesions with millimetric resolution;
- Fully automatic generation of shear waves from the ultrasound transducer, allowing user-skill independent and reproducible imaging;
- Real-time scanning, which reduces the complexity and duration of the elastography exam as compared to other elastography ultrasound systems.
References


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