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Sonoelasticity Imaging: Results in in Vitro Tissue Specimens[1]

The authors present a method for imaging tissue stiffness (sonoelasticity) that has been developed and tested in a laboratory setting by using in vitro canine and human prostate glands. A low-frequency acoustic source was used to induce vibration in tissue under examination, and a color Doppler ultrasound (US) instrument was modified to detect vibration amplitude. The resulting image is a color "map" of tissue vibration superimposed on conventional gray-scale US images. Stiffer tissues vibrated less in response to audible sound, regardless of echogenicity. Normal human and canine prostate glands demonstrated a uniform vibration pattern. Four of four human prostatic adenocarcinomas and two stiff inclusions injected into canine prostate glands demonstrated a lack of vibration in comparison with normal surrounding tissue. The authors conclude that while further study is necessary, sonoelasticity imaging may enhance the detection of neoplasms by enabling their identification solely on the basis of stiffness.

A method for imaging tissue stiffness (sonoelasticity) has been developed and tested in a laboratory setting, with emphasis on detection of prostatic cancer (1,2). The development was prompted by the insensitivity of palpation for the detection of lesions, both in clinical and laboratory settings (3–5). Sonoelasticity imaging is a method of "mechanical palpation" that we believe yields an objective and reproducible means of detecting stiff tumors, some of which may not have been detectable with palpation.

Prostatic cancer was used as an experimental model for several reasons. The first was that digital rectal examination, when used as the sole means of cancer detection, has a low sensitivity (5). This may be partially due to tumor location, though some accessible tumors simply cannot be differentiated from surrounding tissue with the examining finger (6). Use of transrectal ultrasound (US) can increase positive predictive value in a screening population (4), but its success is operator dependent. While most cancers are hypoechoic and located in the peripheral zone, the echo pattern of many tumors is subtle, and as many as 30% are located in the transition and central zones, regions that are often inaccessible to the examining finger and difficult to evaluate with transrectal US (7,8).

Conventional US imaging is based on variations in backscattered MHz-frequency soundwaves from a collection of small scatterers with acoustic impedance mismatches. The ultrasound wave propagation in tissues is usually modeled as longitudinal wave propagation in a fluid medium (9). In contrast, we believe findings at palpation relate to low-frequency mechanical properties. Solid elastic and shear properties are relevant for palpation, since compression and shear waves can propagate at low frequencies. Coupling of one region of tissue to an adjacent region is influenced largely by shear forces.

Sonoelasticity imaging is a new imaging modality that uses US technology to produce an image of vibration patterns in tissue excited with audible sound. The resulting image is a map of stiffness that ideally corresponds to palpation. The method employs a low-frequency (1–1,000 Hz) acoustic source to induce vibrations in the tissue under examination. A color Doppler US instrument that is adjusted to detect vibration amplitude generates maps of tissue vibration amplitude superimposed on conventional gray-scale US images. To a first approximation, the "stiffer" tissues vibrate less in response to the external stimulus, regardless of echogenicity (Fig 1). The "softer," more compliant tissues respond with greater amplitude vibrations and are displayed in color (1).

Sonoelasticity images from canine and human prostate glands obtained at surgery and/or autopsy are the subject of this report.

MATERIALS AND METHODS

Prostate gland specimens obtained from canines and humans were constrained in a specially constructed sample holder consisting of a ring of acoustic standoff or coupling pads within a Lucite cylinder with a bottom of thin plastic film for support. The inner diameter of the acoustic pad was 4 cm (chosen to hold canine and human whole prostate gland specimens), and the outer diameter was 10 cm.

Vibrations were coupled to the specimens by using an acoustic horn capable of output in the 20–1,000-Hz audio band. A hard plastic cone (tapered to a 4-mm-diameter opening) was coupled, by using light pressure, to the base of the sample holder (Fig 2). At these low frequencies, the acoustic wave lengths were on the order of many centimeters, and therefore the applied vibration could be modeled as a point source. Less than 10 watts of electric power were input to the acoustic source at all times, and the resulting vibration amplitude at the point of contact was

estimated, by observing the vibration spectra, to be less than 0.1-mm peak displacement at 200 Hz (1,10,11).

Images were obtained by using a color Doppler instrument (QAD 1; Quantum Medical Systems, Issaquah, Wash) at 7.5 MHz, with the transducer placed on top of the specimen (Fig 2). This instrument was adjusted to display vibration in a threshold mode (1,11). Saturated red or white indicated regions in which the vibration amplitude exceeded some threshold dictated by the gain (signal level) and Doppler threshold controls. The presence or absence of color was not dependent on B-scan reflectivity over a wide (greater than 30 dB) range (1). In the displayed images, red or white color represents the detection of at least one harmonic of 200 Hz vibration that was at least 10 dB above noise threshold. When vibration below threshold was present, the instrument displayed only conventional gray-scale information.

The study group of animal specimens included six fresh canine prostate glands that were obtained and imaged in vitro immediately after the animal was killed for unrelated experiments. Imaging was performed as described above. One canine prostate gland was injected with vinyl acetate, which created a stiff hyperechoic inclusion that was confirmed subjectively with palpation and objectively with compression measurements (2). A second canine prostate gland was injected with vinyl acetate in one lobe and a hypoechoic barium agar mixture in the contralateral lobe, thus creating stiff inclusions of differing echogenicity (11).

Two human prostate glands were obtained at autopsy. Both were presumed to be normal since they were obtained from patients aged 11 and 23 (12). The first patient died of brain stem hemorrhage, and the second was a victim of thoracic trauma. Four human prostate glands were studied immediately after radical prostatectomy for known prostatic carcinoma. Vibration source frequency and amplitude were tuned to display the normal portion of the peripheral zone as uniform red or white color overlay. This generally required use of 150–300-Hz vibration frequency. All cancers were palpable in vivo and in vitro. Imaging findings were correlated with findings at histopathologic examination.

RESULTS

Initially, all canine prostate glands demonstrated a uniform vibration pattern in all areas except periurethral tissue. After injection of stiff inclusions, less vibration was noted in the area of the injections, regardless of echogenicity. This was manifested during sonoelasticity imaging by absence of color in areas of increased stiffness (11).

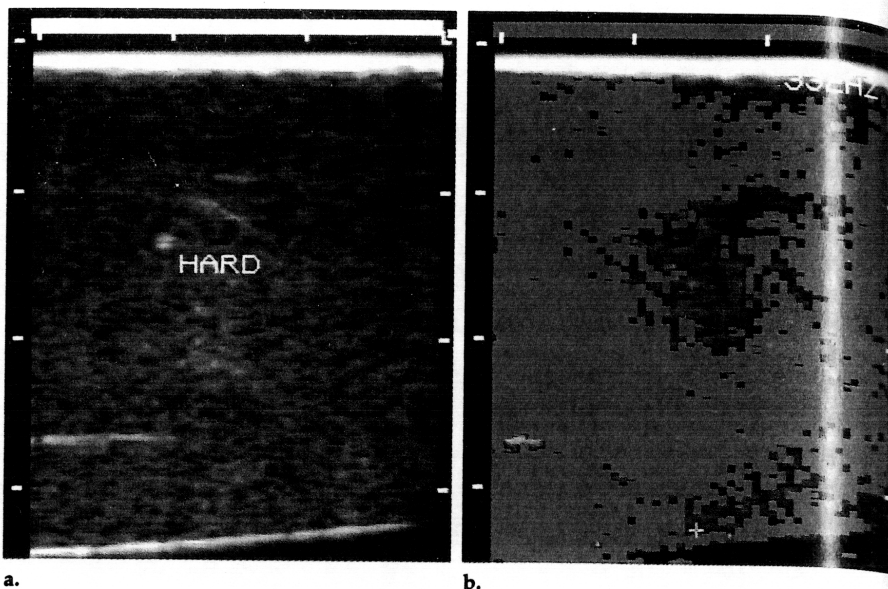The two normal human specimens showed uniform vibration patterns,

a.   b.

Figure 1. Images of a nearly isoechoic, hard, 5-mm-diameter "lesion" placed in a background of soft agar gel. **(a)** In the conventional US image, the lesion (HARD) is difficult to differentiate from background. **(b)** In the sonoelasticity image, the region of increased stiffness shows absence of color encoding. The vibration pattern defect extends beyond the margin of the hard inclusion.

with the exception of the periurethral tissues, which required use of higher amplitudes of applied sound to achieve the vibration threshold for color encoding (Fig 3).

In all human radical prostatectomy specimens, sonoelasticity images demonstrated absence of color in the tissue that corresponded to the cancer at gross histologic examination. The surrounding prostatic peripheral zone tissue that was not involved with cancer showed presence of color in all cases (Fig 4).

Color encoding in Figure 4, as in all freeze-frame sonoelasticity images, normally contained some flickering. This was due to the vibration source not being synchronized with the repetition frequency of the scanning pulse. In real-time imaging, the subjective fill-in of peripheral zone tissue was more uniform and consistent than is shown on any single freeze frame.

DISCUSSION

Previous work has demonstrated the ability of sonoelasticity imaging to enable discrimination of areas of differing stiffness regardless of echogenicity (1,13) (Fig 1). Extension of the experiment to canine prostate glands, some of which had stiff inclusions, further corroborated the validity of in vitro use of the imaging modality.

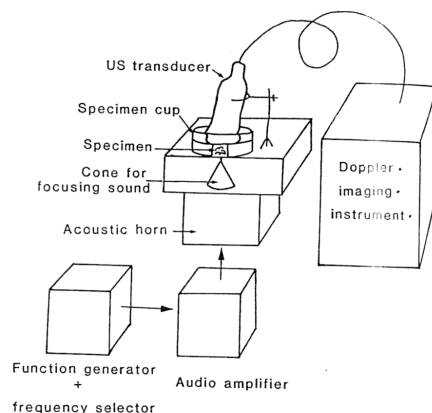We chose prostatic cancer as the first human model because of our clinical experience with transrectal US

Figure 2. Schematic of sonoelasticity imaging instrument. Sound is introduced into the specimen through a tapered, hard plastic cone. The 7.5-MHz ultrasound transducer is placed on top of the specimen and held in place by a clamp.

and the known low sensitivity of the digital rectal examination (5). The normal prostate glands imaged in this investigation demonstrated a uniform color pattern, with the exception of periurethral tissues (Fig 3). We speculate that this is due to a tethering effect of the urethra on adjacent tissues that alters vibration patterns. Since most cancers arise in the peripheral zone, recognition of a uniform vibration pattern in this area is important for tumor detection.

In the four prostate glands with known carcinoma, sonoelasticity imaging enabled correct identification of areas involved with cancer in all cases as demonstrated by absence of color
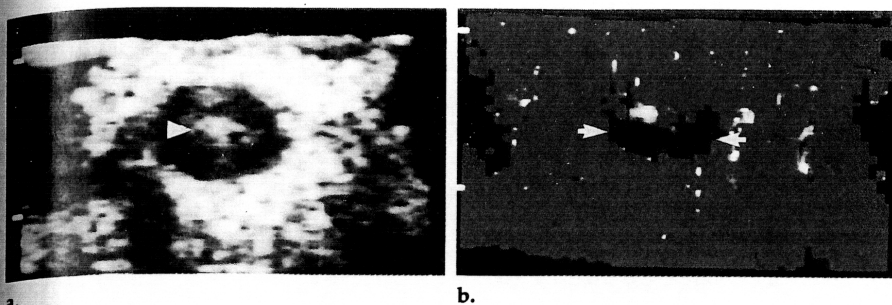
Figure 3. Images of a normal human prostate gland from an 11-year-old patient. **(a)** Transverse conventional US image was obtained through the middle of the gland. Arrowhead indicates urethra. **(b)** In the sonoelasticity image, the gland has uniform color encoding, with the exception of the periurethral area (arrows).
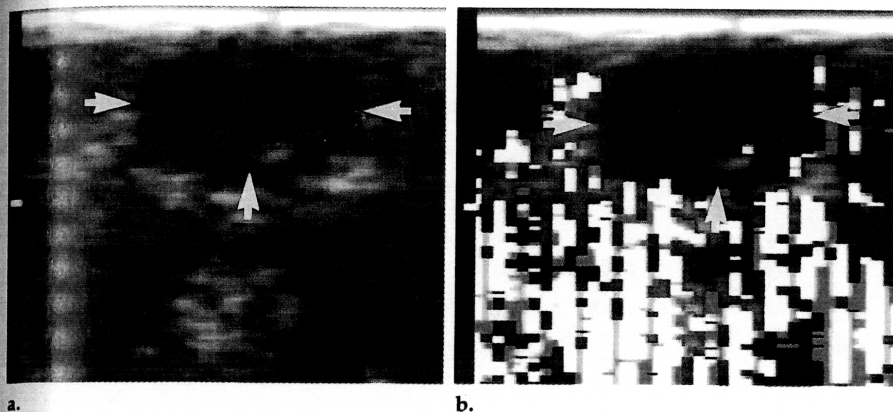

Figure 4. Images of prostatic cancer. A transverse image (zoom) is shown at midline, with the posterior peripheral zone at the top. **(a)** Conventional US image of the peripheral zone shows hypoechoic tumor (arrows). **(b)** In the sonoelasticity image, tumor (arrows) shows absence of color encoding.

encoding (Fig 4). Admittedly, all tumors were readily palpable with digital rectal examination, and all were hypoechoic on conventional US images. However, use of this method allowed detection of tumors with accurate mapping of the extent of involvement in in vitro human specimens, which suggests the potential of this new imaging technique.

We anticipate that sonoelasticity imaging will facilitate detection of neoplasms by enabling their detection solely on the basis of stiffness. While all tumors are not necessarily stiff, we believe that most have altered tissue stiffness due to differences in histopathologic composition when compared with normal tissue. This may ultimately aid in tumor detection, particularly in otherwise uniform organs. Soft areas, such as areas of tumor necrosis and liquefaction in rabbit liver VX2 tumors, have also been detected with sonoelasticity imaging (1,11).

There are several advantages of sonoelasticity imaging over conventional palpation. Palpation is subjective and sensitive mainly to superficial pathologic tissue, whereas sonoelasticity imaging provides an objective "palpation" map and is sensitive to deeply placed lesions. The only requirements for image production are controlled tissue vibration and the ability to image tissues of interest with Doppler US equipment.

Clearly, sonoelasticity imaging is in its infancy. Further work is necessary to prove its usefulness in a clinical setting. Large scale in vitro experiments in other organs with pathologic correlation are necessary. In vivo use awaits optimization of the imaging system, including vibration of the tissue being imaged and patient positioning, and optimization of signal detection, analysis, and display. In addition, we currently have little information regarding spatial and stiffness resolution. We note that the sonoelasticity images displayed herein are crude since they are bistable. Tissue vibration amplitudes are either above the threshold for color encoding, or they are not, which results in a bistable (binary) display. Further refinement of this system may improve the presentation by allowing for gray-scale or color-scale display of vibration amplitudes.

We believe that sonoelasticity imaging can potentially enable physicians to mechanically palpate previously inaccessible tissues in a quantitative and reproducible manner. ∎

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