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In vitro comparative study of vibro-acoustography versus pulse-echo ultrasound in imaging permanent prostate brachytherapy seeds

F.G. Mitri^{a,*}, B.J. Davis^b, J.F. Greenleaf^a, and M. Fatemi^a

^a Department of Physiology and Biomedical Engineering, Ultrasound Research Laboratory, Mayo Clinic 200 First Street SW, Rochester, MN 55905, United States

^b Department of Radiation Oncology, Mayo Clinic 200 First Street SW, Rochester, MN 55905, United States

Abstract

Background—Permanent prostate brachytherapy (PPB) is a common treatment for early stage prostate cancer. While the modern approach using trans-rectal ultrasound guidance has demonstrated excellent outcome, the efficacy of PPB depends on achieving complete radiation dose coverage of the prostate by obtaining a proper radiation source (seed) distribution. Currently, brachytherapy seed placement is guided by trans-rectal ultrasound imaging and fluoroscopy. A significant percentage of seeds are not detected by trans-rectal ultrasound because certain seed orientations are invisible making accurate intra-operative feedback of radiation dosimetry very difficult, if not impossible. Therefore, intra-operative correction of suboptimal seed distributions cannot easily be done with current methods. Vibro-acoustography (VA) is an imaging modality that is capable of imaging solids at any orientation, and the resulting images are speckle free.

Objective and methods—The purpose of this study is to compare the capabilities of VA and pulse-echo ultrasound in imaging PPB seeds at various angles and show the sensitivity of detection to seed orientation. In the VA experiment, two intersecting ultrasound beams driven at $f_1 = 3.00$ MHz and $f_2 = 3.020$ MHz respectively were focused on the seeds attached to a latex membrane while the amplitude of the acoustic emission produced at the difference frequency 20 kHz was detected by a low frequency hydrophone.

Results—Finite element simulations and results of experiments conducted under well-controlled conditions in a water tank on a series of seeds indicate that the seeds can be detected at any orientation with VA, whereas pulse-echo ultrasound is very sensitive to the seed orientation.

Conclusion—It is concluded that vibro-acoustography is superior to pulse-echo ultrasound for detection of PPB seeds.

Keywords

Acoustic emission; Brachytherapy; Finite element; Pulse-echo; Ultrasound imaging; Vibro-acoustography

*Corresponding author. mitri@ieee.org, mitri.farid@mayo.edu (F.G. Mitri).

1. Introduction

Transperineal interstitial permanent prostate brachytherapy (TIPPB) provides an improved alternative for minimally invasive treatment of early stage prostate cancer [1]. Prostate cancer alone accounts for about 29% of incident cancer cases in men in the US [2], while it is estimated that 16% of these patients underwent treatment with this modality. Published guidelines by the American Brachytherapy Society (ABS) [3] elucidate the need for methods of real-time determination of seed location that would permit real-time intra-operative radiation dosimetry. Although progress is being made in this area [4], no means are widely available at present which allow accurate intra-operative radiation dosimetry, but clinicians often use a combination of intra-operative trans-rectal ultrasound (TRUS) [5] and fluoroscopy [6] to aid in imaging seed placement and for qualitative assessment of the seed distribution. In current prostate brachytherapy, seed location is typically verified using computed tomography (CT) which enables determination of the three-dimensional distribution of seed locations with respect to the prostate and adjacent structures. However, post-implant CT scanning leads to potential inaccuracies because the prostate is not necessarily in the identical position as during the seed implantation process. In addition, the prostate boundary is poorly shown in CT and dosimetric evaluation is not uniformly reproducible [7–9].

Over 100 seeds containing radiation sources (I-125 or Pa-103) are implanted by needles through the perineum in and around the prostate. The brachytherapy capsules are hollow titanium cylindrical shells with a diameter of 0.8 mm, a length of 4.5 mm, and a wall thickness of 0.05 mm. The end of the cylindrical shells are usually hemispherical. Seeds based on I-125 most often contain a loose silver wire impregnated with iodine. During implantation, a metallic frame is used for precise parallel alignment and positioning of the ultrasound transducer and the implantation needles with respect to each other. The seeds are implanted with their axis oriented along the patient's body axis. However, accurate seed location is hampered by deformation and swelling of the prostate caused by inserting the needles. As a result, the seeds frequently become oriented in a non-parallel manner with respect to one another and the trans-rectal ultrasound (TRUS) probe. It is therefore difficult to visualize the seeds once released from the needle because ultrasound beams are reflected specularly and backscattered wave motion cannot reach the ultrasound probe unless the incidence happens to be normal [10].

An improvement in the seeds ability to scatter ultrasound back towards the imaging transducer at a wider angular range is obtained by using the EchoSeed™ (Amersham Health, Inc., Arlington Heights, IL) which have a corrugated surface. However, reduction in the backscatter signal from these seeds still occurs as the incident angles increases away from normal incidence [10]. In addition to that, speckles caused by the multiple interference of ultrasound energy from randomly distributed scatterers within tissue degrade the contrast resolution in ultrasound images and thereby makes it hard to detect small targets such as seeds when implanted in the prostate. Limitations with TRUS justify the development of a new imaging modality suitable for seed detection. Ideally, such a method would be (a) insensitive to seed orientation, (b) speckle free and (c) applicable to the intra-operative setting.

The purpose of the present study is to examine seed imaging as a function of seed orientation using an innovative ultrasound-based imaging method known as vibro-acoustography (VA) [11–13], which is based on the dynamic radiation force of ultrasound [14]. In this method, two intersecting ultrasound beams driven at slightly different frequencies are focused on or inside the object to be imaged, producing a localized tapping radiation force oscillating at the difference frequency of the incident ultrasound beams. Radiation force causes vibration at the arbitrary low-frequency and produces an acoustic emission field which is detected by a hydrophone. The image is formed by displaying the amplitude of the acoustic field at a position corresponding to the excitation point on the object. Unlike the conventional ultrasound pulse-

echo imaging method, VA does not rely on the reflection of ultrasound; hence, it is not critically sensitive to object orientation. VA is particularly sensitive to tissue stiffness which makes it reliable in detecting solid inclusions such as seeds. Because VA images are based on the low-frequency sound emitted from the object, the resulting images have high contrast resolution. Finally, VA can be conducted intra-operatively, in a manner similar to conventional ultrasound imaging systems. It is notable that VA satisfies all the required criteria of an ideal imaging tool for detection of brachytherapy seeds.

In the medical field, VA has been successfully used for imaging small particles such as calcium deposits on heart valve leaflets [15], microcalcifications in breast tissue [16–19], calcifications in arteries [11,20], excised human cancerous liver tissue [21], and standard brachytherapy seeds in gel phantoms [22].

The goal of this paper is to compare the capabilities of VA and Pulse-echo ultrasound in imaging PPB seeds. For this purpose, we image a set of PPB seeds at various orientations by two methods: pulse-echo ultrasound (PE-U) and VA. Three seed types, namely OncoSeed™ (standard), EchoSeed™ (echogenic), and RAPID Strand™ (RS) are used. Particularly, it is shown here how the angle of incidence affects the VA technique's sensitivity in detecting the seeds. These experiments are conducted in a water tank under well-controlled conditions. Then a comparison between VA and PE-U (in a C-scan format) results is performed in order to assess the advantages and disadvantages of each method. These results may be useful for evaluation of VA-based real-time intraoperative dosimetry strategies and for the design of VA probes specifically for brachy-therapy applications.

2. Method and materials

2.1. Vibro-acoustography (VA)

In previous publications, VA was presented as a technique based on the modulated radiation pressure (MRP) of ultrasound waves [11,12]. Two intersecting ultrasound beams slightly shifted in frequency and focused at the same point in space produce a dynamic radiation force (or stress in 3D) on or inside an object. Subsequent acoustic emission field is produced in the surrounding medium due to object harmonic vibrations at the difference frequency of the ultrasound beams. However the equations describing the acoustic emission based on the MRP approach do not include the “parametric” interaction [23,24] of the primary incident beams. In a nonlinear medium, the simultaneous propagation and mixing of two primary waves give rise to nonlinearly induced waves at sum and difference frequencies. These secondary waves are generated by the “parametric interaction” since they depend on the nonlinearity parameter $\beta = (1 + \frac{B}{A})$, where B/A determines the nonlinear property of an acoustically driven medium. The objective of this paper is not to discuss the contribution of the “parametric” interaction with the MRP phenomenon, a topic that will be discussed in a forthcoming article [25]. In this work, we assume the generation of low-frequency waves (acoustic emission) is dominated by the MRP mechanism, which is consistent with the results presented herein.

2.2. Sensitivity to seed orientation of B-mode ultrasound versus VA

2.2.1. Sensitivity study on a single seed—To verify experimentally the sensitivity to seed orientation of the PE-U, an initial test was performed in which a dummy standard seed (OncoSeed, Amersham model 6711) was glued on a stretched latex rubber membrane of 50 μm thickness. The seed attached to the membrane were suspended in a water tank and filled with degassed water in an anechoic room used for making precise ultrasound measurements. The seed attached to the membrane were placed at the focus of an ultrasound transducer driven by a Panametrics 5050PR ultrasonic pulser/receiver (Panametrics, Waltham, MA) at 3 MHz. The transducer has a diameter dimension of 45 mm and focal length of 70 mm. The backscatter

signal was full-wave rectified and low-pass filtered at 3 MHz before digitization with 12 bits of resolution at 10 MHz. The seed attached to the membrane were rotated with a precision optical rotation stage. At 3 MHz, the angle of incidence was varied from 90° down to 30° in 1° increments and the amplitude of the reflected signal was recorded versus angle. Measurements at angles less than 30° angle of incidence were not performed because of geometrical constraints posed by the rotation stage, transducer, and water bath. At 90°, the long axis of the seed was oriented perpendicular to the incident ultrasound beam and thus produced the highest backscatter signal.

Pulse-echo ultrasound (PE-U) imaging (B-mode) operates on the reflection of ultrasound from a target. Fig. 1 illustrates a two-dimensional model for a pulse-echo system at normal and oblique incidence angles with respect to the target. Sensitivity to object orientation is measured in terms of the ratio of received to incident ultrasound pressure over the active surface of the transducer. In other words, the amplitude of the received signal is proportional to the size of region x where the reflected signal is projected back on the transducer over the size of region D . The normalized received signal versus the angle $\beta = (\pi/2 - \alpha)$ (where α is the angle measured from the normal to the target) can be written as

$$\begin{aligned} R_b(\beta) &= x/D \\ &\approx \frac{2z_0 \sin(\theta - \alpha)}{2z_0 \sin(\theta)} \\ &\approx \sin(\theta - \pi/2 + \beta) / \sin(\theta) \end{aligned} \quad (1)$$

where θ is the beam half-angle. For a 45 mm diameter transducer and focal length of 70 mm, we have $\theta = 18.7^\circ$.

To verify experimentally the sensitivity to seed orientation of VA, the experiment described above was repeated with a VA system setup using the same transducer. In VA, two ultrasound beams were driven at frequencies of 3 MHz and 3 MHz + 50 kHz, respectively. The driving radio frequency (RF) signals were obtained from two stable synthesizers (HP 33120 A). The two beams interacted at the joint focal region producing an oscillatory radiation stress field on the object. Spatial resolutions are determined by the focal depth of the transducer and the diameter of the central lobe. For this system, the longitudinal and transverse resolutions, defined as the focal spot size at full-width at half-maximum, were about 10 mm and 0.7 mm, respectively. The acoustic emission was detected by a submerged audio hydrophone (Model ITC – 6050 C) with sensitivity –157 dB re 1 V/ μ Pa, and frequency response between 1 Hz and 60 kHz, placed in the water tank at a 10 cm behind the seed. The signal received was bandpass filtered and amplified (Stanford Research Systems, SR650) to eliminate noise, then digitized by a 12-bits/sample digitizer (National Instruments VXI-1000) at a rate sufficiently higher than the Nyquist rate. The angle of incidence was varied from 90° down to 30° in 1° increments and the amplitude of the VA signal was recorded versus angle (Fig. 2).

To verify the VA experimental results, a coupled harmonic acoustic analysis is performed using finite element software (Ansys, Inc.) in which the seed is excited by an oscillatory force and the resulting pressure is calculated at a particular point in the fluid. The coupled acoustic harmonic analysis involves modelling the fluid medium and the surrounding structure taking the fluid interaction into account. The oscillatory force beating at $\Delta f = 50$ kHz was applied at the center of the seed, over a nodal line corresponding to the lateral dimension of the focal spot (i.e. 0.8 mm) (Fig. 3). The simulated pressure amplitude is the response in the fluid at a chosen node; it has been verified that the responses of the neighbouring nodes are comparatively the same. Fluid medium was modelled by two dimensional linear fluid elements surrounding the solid, and one dimensional linear absorbing elements at the external surface simulating the outgoing propagation effects of a domain that extends to infinity. Absorbing elements avoid

reflections, thus interference with vibrations of the solid. The titanium seed (Young's modulus 116 GPa, Poisson's ratio 0.36, density 4506 Kg/m³) was modelled by two dimensional linear solid elements. The total number of nodes and elements is 1154 and 2010, respectively. The pressure evaluated at a particular node was the angle of incidence was varied from 90° down to 20° in 5° increments.

2.2.2. Multiple seed imaging experiment

2.2.2.1. Experimental setup: To investigate and compare the effect of seed orientation angle on VA imaging, three different types of seeds oriented at various angles were used. The seed types evaluated were standard seeds (OncoSeed™), corrugated seeds (EchoSeed™), and seeds in absorbable vicryl suture (RAPID Strand™), (Fig. 4) all from Amersham, Inc. In these studies, ten seeds of each type were used. Seeds were placed in three parallel rows on a stretched latex rubber membrane in such a manner that the membrane and adhesive were acoustically translucent. Seeds were placed 1 cm apart from center-to-center along each row. The seeds and membrane were suspended in a water tank. The seeds attached to the membrane were rotated with a precision optical rotation stage for scanning at various angles. The VA imaging system that was used was described previously in Section 2.2.1 and displayed in Fig. 2.

2.2.2.2. Pulse-echo ultrasound (PE-U) imaging experiment: The procedure for the PE-U experiments is similar to the one previously described in [10] to which the reader should be referred for complete explanation. Conventionally, the clinical data are displayed in a B-scan format. However, the previously published data [10] were PE-U images in a C-scan format that will be compared with VA images. In these experiments, however, the angle of incidence was varied from 90° down to 20° in 5° increments. At 90°, the long axis of the seeds was oriented perpendicular to the incident ultrasound beam and thus produced the maximum backscattered signal. The sensitivity of the incremental step has been tested previously [10] by using an incremental step of 1°. The previously published data showed a crossover point at 86°, or 4° away from perpendicular incidence (Fig. 5). Measurements at angles less than 20° angle of incidence were difficult to obtain due to experimental limitations with the system.

The AnalyzeAVW [26] software was used to examine the images through an integrated optical density (IOD) method [27]. The procedure is also described in [10] to which the reader should be referred for complete explanation.

2.2.2.3. VA imaging experiment: The set of seeds was scanned by the VA system at $\Delta f = 50$ kHz using the CW mode. Images with pixel dimensions of 0.2 mm by 0.2 mm were produced for incident angles from 90° (beam perpendicular to the seed axis) to 20° in 5° increments. Image dimensions are 525 by 200 pixels (10.5 cm by 4 cm). Because VA results were almost invariant with respect to angle, there was no need to perform the first 5° in 1° increments. An IOD analysis, similar to the one already performed for the B-mode ultrasound images, was also conducted on the VA images. A square and uniform region centered on each seed, 1 cm by 1 cm, was analyzed by computing the IOD for each region of interest (ROI). The IOD is the sum of all pixel values in the ROI [27]. It provides a quantitative means to compare the VA signal strength between seed types and varying angles of incidence of the beam.

3. Results and discussion

Fig. 6 shows a comparison of theoretical and FE versus experimental results of the PE-U and VA sensitivities for the one single seed. This figure reveals that VA is far less sensitive to angle than B-mode ultrasound. Particularly, experimental results correlate well with theoretical predictions.

Figs. 7 and 8 show a series of PE-U images of the seeds at 5 MHz and 7.5 MHz, respectively. Each panel in these figures includes three rows of seeds: OncoSeed™ (top row), EchoSeed™ (middle row), and RAPID Strand™ (bottom row). It is evident that seed orientation and type can significantly affect the ability to localize a given seed. Note that the standard seeds (OncoSeed™) start to break up and each become like two separate dots, or “corner echoes” [28], at incidence angles greater than 4° away from perpendicular incidence, which is an indication of high sensitivity of pulse-echo imaging to seed orientation. This result demonstrates why TRUS often fails detecting the standard seeds. Fig. 5 shows that the corrugated seeds EchoSeed™ (middle row) appear as broken dots at 90°, 86° and 85°, however they appear continuous at 89°, 88°, 80° down to 55° (Figs. 7 and 8) but they start to break again below 55°. This effect is related to the acoustic backscattering of obliquely incident waves from a corrugated seed having a particular uneven shape [29]. Due to the wavy shape, the appearance of corrugated seeds also depends on the ultrasound frequency. These results indicate that the corrugated seeds may not be detected by TRUS at some angles. The RAPID Strand™ seeds appear poorly at acute angles. It is important to know the seed location; knowing where the strand is, is not enough. In addition, it is anticipated that detection of all types of seeds (including corrugated) would become considerably more difficult when the seeds are implanted in the prostate. The broken and spotty appearance of the seeds at off normal angles would blend into the speckle pattern of the soft tissue, making seed delineation very difficult.

Fig. 9 shows the VA images of the seeds from 90° to 20°. This figure demonstrates the capability of VA in displaying all the seeds at all angles – a capability that justifies application of VA for PPB imaging. All three types of seeds are clearly visible as continuous structures (not broken dots) in all angles. It is also of interest that the RAPID Strand™ seeds and the Vicryl suture sleeve can be delineated from each other. The shadowing in some of the panels may be due to acoustic reverberations (or multipath artifact as described in Ref. [18]) in the water tank, which manifests as a low spatial frequency variation in the image. This reverberation pattern is strongly dependent on the temporal frequency of the acoustic emission. Reverberations are sensitive to seed orientation because changing its position (by rotation) induces a new stationary field at the low frequency which interferes with the acoustic emission of the seed.

To evaluate the image quality versus angle in a quantitative manner, IOD values of the three seeds were normalized with respect to their corresponding values at 90°. Fig. 10 shows the resulting plots for the OncoSeed™ and EchoSeed™. This figure shows that VA IOD stays relatively constant at different angles down to 20°, where as pulse-echo IOD is very sensitive to angle. Thus these quantitative data confirm the interpretation of VA and pulse-echo images.

4. Conclusion

PE-U and VA experiments were conducted on three types of PPB seeds and images were compared. Results of experiments conducted under well-controlled conditions in a water tank on a series of seeds indicate that VA is capable of imaging PPB seeds at any orientation. However, PE-U is very sensitive to the seed orientation, and fails to detect the seeds at various angles. It is concluded by quantitative analysis that VA is superior to PE-U for the detection of PPB seeds.

Future work should focus on testing VA performance in human prostates *in vitro* and *in vivo*. Should the results of an *in vivo* setting study prove to be in favor of VA, this method could be very promising in monitoring prostate brachytherapy treatment.

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Fig. 1.
Normal and oblique incidence in PE-U.

Fig. 2.

VA system setup. The system includes a focused confocal transducer, consisting of a center disk and an outer ring. Two continuous wave generators drive these elements at slightly different frequencies. The transducer is focused on the seeds attached to the membrane, with the beams interacting at the joint focal point to produce an oscillating radiation force on the object at the difference frequency. This force causes the seeds to vibrate and as a result an acoustic emission field is produced in the surrounding medium. This field is detected by the hydrophone and filtered by a bandpass filter centered at the difference frequency. The amplitude of the resulting signal is used to modulate the intensity of the image at a point corresponding to the position of the beam on the object. The image is formed by raster scanning of the object. The experiments take place in a water tank containing the transducer, hydrophone and the seeds.

Fig. 3. Finite-element mesh of the axisymmetric model. The applied oscillatory force (shown by arrows) is applied on the nodes attached to the seed over a distance corresponding to the lateral resolution of the transducer (i.e. 0.8 mm).

Fig. 4. Photograph of the three types of BT seeds investigated in this study: OncoSeed™ (standard), EchoSeed™ (corrugated), and RAPID Strand™. (Published with permission from The International Journal of Radiation Oncology, Biology, Physics [10]).

Fig. 5. PE-U images generated at 5 MHz of the three rows of seeds as a function of angle incidence from perpendicular (90°) to 85° away from the perpendicular in 1° increments. The top row is the OncoSeedTM (standard), the middle is the EchoSeedTM (corrugated), and the bottom row is the RAPID StrandTM in Vicryl suture material. (Published with permission from The International Journal of Radiation Oncology, Biology, Physics [10]).

Fig. 6. Comparison of angle sensitivity in VA and PE-U imaging. One particularly notices the good agreement between experimental and theoretical results.

Fig. 7.
The same as in Fig. 5 but the angle of incidence was varied from perpendicular (90°) to 20° away from the perpendicular in 5° increments.

Fig. 8.
The same as in Fig. 7 but the ultrasound frequency was set at 7.5 MHz.

Fig. 9.

VA images at 20 kHz of the three rows of seeds as a function of angle incidence from perpendicular (90°) to 20° away from the perpendicular in 5° increments. The top row is the OncoSeed™ (standard), the middle is the EchoSeed™ (corrugated), and the bottom row is the RAPID Strand™ in Vicryl suture material. This figure shows that VA is capable of imaging BT seeds at any orientation, and the resulting images are speckle free.

Fig. 10.
Normalized IOD plots for OncoSeed™ and EchoSeed™ in PE-U and VA.