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Research Paper

Ultrasound Imaging of Nonlinear Media Response Using a Pressure-Dependent Nonlinearity Index

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It has been shown that within the range of acoustic pressures used in ultrasound imaging, waveforms are distorted during propagation in tissue due to the physically nonlinear behavior of the tissue. This distortion leads to changes in the spectrum of the received ultrasound echoes, causing the transfer of signal energy from the fundamental frequency to higher harmonics. Interestingly, adipose tissue exhibits up to 50 % stronger nonlinear behavior compared to other soft tissues. The tissue nonlinearity parameter B/A is typically measured ex vivo using an ultrasound method in transmission mode, which requires extensive receiving systems. Currently, there is no improved ultrasound method for measuring the B/A nonlinearity parameter in vivo, which could be used in assessing the degree of fatty liver disease.

We propose a new, simple approach to estimating nonlinear tissue properties. The proposed method involves transmitting ultrasound waves at significantly different acoustic pressures, recording echoes only in the fundamental frequency band at various depths, and introducing a nonlinearity index (NLI) based on specific echo amplitude ratios.

The NLI at a given depth is calculated using the ratio of two dimensionless parameters. The first parameter is a predetermined constant obtained by dividing the total echo values from transmitting a signal at higher sound pressure by those from a signal at lower sound pressure, summed over a small tissue sample volume located near the transducer. The second parameter is calculated at a fixed distance from the transducer, determined by dividing the total echo values from transmitting a signal at higher sound pressure by those from a signal at lower pressure, summed over a small tissue volume of the tissue at that distance from the transducer. The reliability of the proposed measurements for assessing tissue nonlinearity has been substantiated through experimental confirmation of the existing correlations between the values of NLI and B/A in water, sunflower oil, and animal liver tissue samples with oil-enriched regions. The NLI was more than 15 % higher in sunflower oil than in water. The NLI in bovine liver sample below the area with injected oil (mimicking "steatosis") was more than 35 % higher than in regions without oil. This method represents a promising modality for the nonlinear characterization of tissue regions in vivo, particularly for diagnosing fatty liver disease.

Keywords: ultrasound imaging; abdominal ultrasound; nonlinear propagation; tissue harmonic imaging; nonlinearity index.

1. Introduction

Ultrasound imaging has become a cornerstone of modern medicine, offering a safe, portable, and cost-effective method to visualize internal organs and structures. Modern ultrasonography relies on linear and nonlinear properties (such as tissue harmonic imaging) of ultrasound wave propagation in tissue. By analyzing these nonlinearities, physicians can gather additional information about tissues, potentially providing deeper insights into physiological processes and disease states.

A broad overview of the current state of research and challenges in estimating the B/A nonlinearity parameter is presented in (Panfilova *et al.*, 2021). So far, with a very wide range of B/A measurements, none of the methods has been successfully implemented in real-time ultrasound. One significant challenge lies in the limited bandwidth of linear arrays and convex type of ultrasonic transducers, which does not exceed 60 %–70 %. This narrow bandwidth significantly limits the reception of second harmonic echoes, consequently limiting the ability to estimate the B/A parameter in real time along the propagation path. The first attempts to reconstruct B/A profiles were made using the pump wave method (Ichida *et al.*, 1983; 1984). Another approach, using parametric array tomography was described in (Gong *et al.*, 2004; Wang *et al.*, 2003). The finite amplitude method, called FAM (Gong *et al.*, 2004; Akiyama, 2000; Toulemonde *et al.*, 2015) might be considered as an inspiration for our method. However, to the best of our knowledge, none of the B/A estimation/reconstruction techniques have yet been applied to real-time US imaging.

The phenomenon of nonlinear propagation of ultrasonic waves is used in tissue harmonic imaging (THI) because it increases the resolution of ultrasound images of examined organs (Varray *et al.*, 2010; Van Wijk, Thijssen, 2002). Several methods have been developed to measure this nonlinear echo, including amplitude modulation, pulse inversion, and second harmonic inversion (Simpson *et al.*, 1999). However, THI is far from being optimal in the sense that only half of the available transducer bandwidth is used for image formation – the lower half for transmission and the upper half during reception. The importance of reduced dynamic range and penetration encountered in THI was also pointed out (Averkiou *et al.*, 1997; Averkiou, 2001). Since images are formed with only the first harmonic components, which are usually at least 20 dB below the fundamental, the dynamic range is limited. Additionally, Coila and Oelze (2020) conducted a study on the influence of nonlinear propagation in tissue on the estimation of attenuation/absorption in specific tissue regions.

The linearized pressure-density equation of state has a form:

$$p = P - P_0 = (\rho - \rho_0)\left(\frac{\partial P}{\partial \rho}\right)_{\rho_0}, \tag{1}$$

where P is the total pressure, which is the sum of the equilibrium pressure P_0 and the acoustic pressure p; ρ_0 and ρ are the equilibrium density and the small increase in density produced by the sound, respectively. Equation (1) is applicable when the speed of sound (c) is much greater than the local flow velocity (v), $c \gg v$, i.e., when the Mach number (M) is much less than one, $\mathrm{M} = v/c \ll 1$.

In the context of ultrasonic pressures, typically ranging from hundreds of kilopascals to several megapascals, tissue volume experiences compression and stretching, leading to pressure-dependent changes in the speed of sound.

At sufficiently high pressure magnitudes, wave propagation ceases to be linear, necessitating the inclusion of additional nonlinear terms to the fluid equation of state. These terms account for both the tissue elasticity (A) in the linear regime of density changes and the higher-order elasticity coefficient (B) as the first correction taking into account nonlinear (quadratic) changes in density (Hamilton, Blackstock, 2008).

Consequently, the pressure-density relation $p = f(\rho)$ can be approximated by a Taylor series expansion of the adiabatic equation of state:

$$\begin{aligned} p &= (\rho - \rho_0)\left(\frac{\partial P}{\partial \rho}\right)_{\rho_0} + \frac{(\rho - \rho_0)^2}{2}\left(\frac{\partial^2 P}{\partial \rho^2}\right)_{\rho_0} + \cdots \\ &= A\left(\frac{\rho - \rho_0}{\rho_0}\right) + \frac{B}{2}\left(\frac{\rho - \rho_0}{\rho_0}\right)^2 + \cdots \end{aligned} \tag{2}$$

After truncating Eq. (2) to the second-order term, the ratio of B/A and the nonlinearity coefficient of the medium $\beta = 1 + (1/2)B/A$ can be estimated, where $A = \rho_0(\partial P/\partial \rho)_{\rho=\rho_0}$, and $B = \rho_0^2(\partial^2 P/\partial^2 \rho)_{\rho=\rho_0}$. The parameter A corresponds to the elasticity coefficient of increases and hence the speed of sound propagation increases. The nonlinear parameter B/A carries information about the distortion of the propagating wave, resulting in the transfer of some energy to the second and higher harmonics.

In the domain of linear acoustics, specifically in a lossless linear medium, the neglect of wave distortions and the emergence of higher harmonics result in $B/A = 0$. However, in real materials, B/A assumes finite values. Documented B/A values for various fluids and biological media were outlined in (Duck, 2002): for water at 20 °C and 40 °C, $B/A = 4.96$ and 5.38, respectively; for 3.5 % saline at 20 °C, $B/A = 5.25$; for blood plasma at 30 °C, $B/A = 5.74$; for whole blood (26 °C) $B/A = 6.1$; for nonfat soft tissues $B/A = 6.3$–8.0; and for fatty soft tissues $B/A = 9.6$–11.3 (Varray *et al.*, 2010). Dong *et al.* (1999) provided the ultrasonic nonlinearity parameter B/A for nine versions of water-based, macroscopically uniform ultrasonically tissue-mimicking (TM) nonfat and fat materials. Notably, the B/A parameter is 1.5 to 2 times greater in adipose compared to other tissues, thereby partially elucidating the advantages of utilizing harmonic imaging in challenging cases involving excess body fat.

In what follows, we describe a preliminary investigation focused on evaluating the nonlinearity of the medium by comparing echoes from selected areas subjected to various scanning signals with differing amplitudes. In a linear medium, the magnitude of the echoes should be directly proportional to the amplitude of the

transmitted signals. Any deviation from the linear relationship between the transmitted signal's amplitude and the backscattered amplitude is contingent upon the physically nonlinear properties of the tissue area under scrutiny.

The rest of the paper is organized as follows: the next section presents a brief overview of the proposed method, the results obtained using proposed method are presented in Sec. 3, and the discussion is presented in Sec. 4.

2. Materials and methods

In the linear model of ultrasound propagation, the echoes from reflectors or biological tissue for different sound pressures measured at the same depth should vary proportionally to the transmitted sound pressures. However, in the case of nonlinear wave propagation, part of the acoustic energy is transferred to higher harmonics. This transfer increases with increasing acoustic pressure, resulting in a real decrease in echo amplitudes for the first harmonic.

We propose a new, straightforward approach to quantifying the nonlinear properties of tissue by analyzing the ratio of the energy of scattered echoes from a tissue/medium with different nonlinear ultrasound propagation characteristics using different acoustic pressures during transmission.

This new approach involves using several consecutive wave transmissions of identical waveform but with significantly different acoustic pressures (varying by several times), along with successive recordings of ultrasound images in the baseband of the head (only the first harmonic is recorded). Images of "linear" tissues will differ only in amplitude, which will be proportional to the amplitude of the transmitted wave. Therefore, the ratios of the echoes' amplitudes recorded for the sequence of low- and high-pressure transmission (after compensating for different transmit pressures) should be close to one. If there are areas in the imaging space with different B/A nonlinearity ratio, the amplitude ratios will differ from one and this value should increase with increasing nonlinearity coefficient of the imaged tissue.

The Verasonics Vantage 256 (Verasonics, USA) and us4R-lite ultrasound research system (us4us ltd., Poland) with a convex probe (ATL C4-2) were used for the measurements. The research was carried out in three stages: hydrophone measurements in water and sunflower oil, reflection measurements in water and sunflower oil, and backscatter measurements in tissue in vitro. First two steps were performed the using us4R-lite system, while the measurements in the liver sample were conducted with the Verasonics Vantage 256. In all three experiments, all transducer elements were activated simultaneously. For this purpose, short pulses (two sine cycles) at a nominal frequency of 3.125 MHz and a sampling rate of 62.5 MHz were generated, with amplitudes corresponding to various sound pressures (see discussion below).

In the first step of the evaluation, three pulses with different driving voltages were successively transmitted into water. The corresponding peak-to-peak pressure amplitudes were measured with a needle hydrophone with a sensor diameter of 0.075 mm (Precision Acoustics, UK) at a distance of 0.5 cm from the face of the transmitting transducer. The measured amplitudes P_1, P_2, and P_3 were equal to 0.19 MPa, 0.39 MPa, and 1.55 MPa, respectively. Then, for each of these transmission pressures, the amplitudes of the first and higher harmonics were measured in both water and sunflower oil. The hydrophone was positioned at depths of 1 cm, 2 cm, 3 cm, 4 cm, 5 cm, and 6 cm from the transducer.

In the second step of our research, we used the same transmission pressures, to measure the echoes' amplitudes from a thread phantom made of thin (0.2 mm) nylon threads spaced 1 cm apart, immersed in both water and sunflower oil.

In the last step, we performed backscattered ultrasound measurements in a fresh beef liver sample. At a depth of 4 cm from the surface of the sample, 1 cm^3 of sunflower oil was injected into the sample to mimic fatty tissue. Then, we determined the average amplitude of echoes in selected areas along the radiation axis of the examined tissue. We used regions of interest (ROIs) in the shape of a scan stripe with an arbitrarily selected width of 0.5 cm (10 image lines) and 25 RF samples along each line corresponding to 0.5 cm in depth (Fig. 1). The averaged echoes' amplitudes were calculated for each of the applied sound pressures P_1–P_3.

Finally, the echo amplitude values were normalized, i.e., divided by the transmitted pressures, and these values are denoted in this article as E_{P1}–E_{P3}. Theoretically, for purely linear propagation, such normalized backscattered echoes' amplitudes E should be the same across all applied pressures throughout the penetration depth. The pressures reported in the experiments are given as peak-to-peak values. The corresponding mechanical indices (MI) calculated for peak negative pressures at a nominal frequency of 3.125 MHz are given in Table 1. For all applied pressures, the MI remains below the FDA regulated limits for diagnostic ultrasound, MI < 1.9.

Table 1. MI values for pressures used in the experiments.

Peak-to-peak pressure [MPa]	Peak negative pressure [MPa]	MI
0.19	0.096	0.049
0.39	0.196	0.1
1.55	0.68	0.345

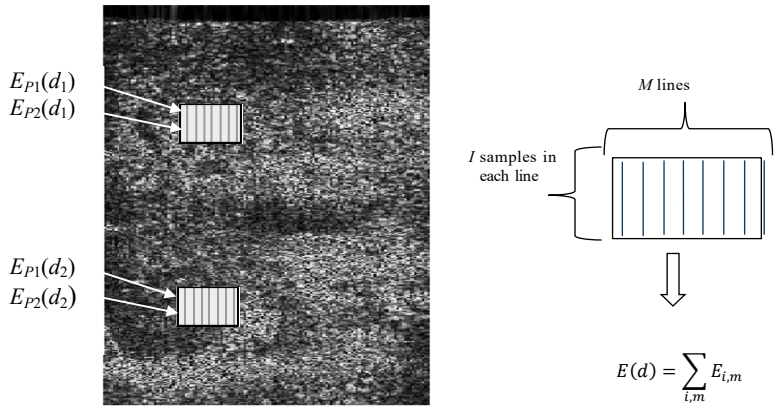

Fig. 1. Principle of calculating the average amplitude of echoes $E_{P1}(d_1)$, $E_{P2}(d_1)$ and $E_{P1}(d_2)$, $E_{P2}(d_1)$ at different depths d_1 and d_2 of the examined tissue and for two different pressures P_1 and P_2 of the transmitted ultrasonic wave. The echo amplitude $E(d)$ in each region is calculated as the sum of amplitudes of I samples in M lines.

We introduce the nonlinearity index (NLI) in the form of the quotient of two average echo amplitudes $E_{Pi}(d)$ and $E_{Pj}(d)$ measured at depth d for two different transmitted acoustic pressures P_i (lower pressure) and P_j (higher pressure):

$$\mathrm{NLI}(d; P_i, P_j) = \mathrm{NR}\frac{E_{Pi}(d)}{E_{Pj}(d)}, \qquad (P_j > P_i). \tag{3}$$

The ratio of echo amplitudes $E_{Pi}(d)$ and $E_{Pj}(d)$ for both transmitted pressures is normalized by the factor NR, which is the ratio of the echo amplitudes E_{Pj} (for the higher pressure P_j) and E_{Pi} (for the lower pressure P_i) measured 0.5 mm below the transducer face. In our experiments, NR was equal to 9.3 for the pressures of 1.55 MPa and 0.19 MPa, and 4.4 for the pressures of 1.55 MPa and 0.19 MPa, respectively.

The instantaneous amplitude of the ultrasound echo signals was obtained using Hilbert transform-based envelope detection of the ultrasound radiofrequency (RF) signals (Hahn, 1996).

3. Results

As stated in the previous section, the measurements were carried out in three stages. First, we determined the intrinsic first harmonic levels in water and sunflower oil using a needle hydrophone placed at various depths from the face of the scanning head, ranging from 1 cm to 6 cm. Then, the amplitudes of backscattered echoes from thin threads immersed in both water and sunflower oil were measured. In the last stage of the research, the NLI was determined in areas of the beef liver sample with the "steatosis" area introduced by injecting 1 ml of sunflower oil.

3.1. Hydrophone axial field measurements in water and sunflower oil

The Fourier spectra (up to the third harmonic) of the acoustic pressures measured with a needle hydrophone in water and sunflower oil at depths of 10 mm and 60 mm are shown in Figs. 2a–b and Figs. 3a–b,

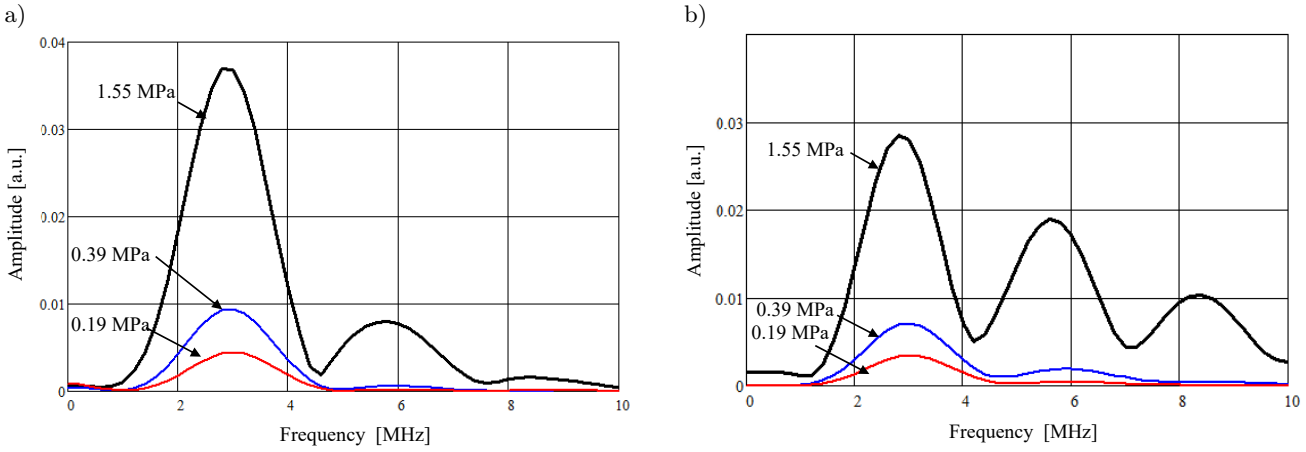

Fig. 2. Amplitudes of the first three harmonics 1 through 3 measured in water with a needle hydrophone (along the radiation axis) at depths of 1 cm (a) and 6 cm (b) from the transducer face. The transmitted pressures ranged from 0.19 MPa to 1.55 MPa.

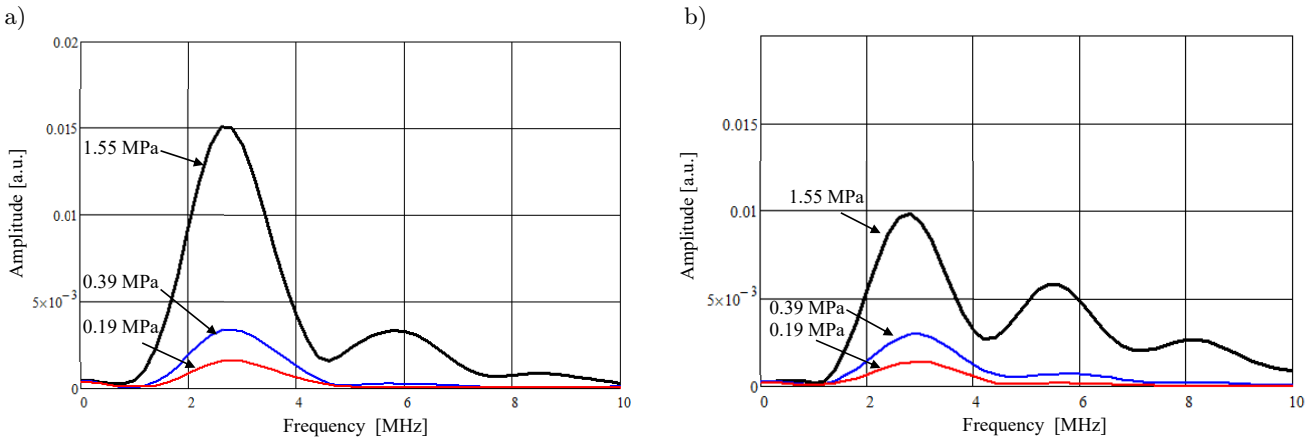

Fig. 3. Amplitudes of the first three harmonics measured in sunflower oil with a needle hydrophone (along the radiation axis) at depths of 1 cm (a) and 6 cm (b) from the transducer face. The transmitted pressures ranged from 0.19 MPa to 1.55 MPa.

respectively. The transmitted pressure amplitudes measured at a depth of 5 mm were recorded at values of 0.19 MPa, 0.39 MPa, and 1.55 MPa.

In water, at a depth of 1 cm, the amplitude of the first harmonic is 0.0382 (in arbitrary units – a.u.) for a pressure of 1.55 MPa, and at a depth of 6 cm, its value is 0.0285. For a pressure of 0.39 MPa, the amplitudes of the first harmonics are 0.0094 and 0.0071 at depths of 1 cm and 6 cm, respectively. For a pressure of 0.19 MPa, the amplitudes of the first harmonics are 0.0041 and 0.0037 at depths of 1 cm and 6 cm, respectively.

In sunflower oil, at a depth of 1 cm, the amplitude of the first harmonic for a pressure of 1.55 MPa is 0.015 (in a.u.), while at a depth of 6 cm its value is 0.0098. For a pressure of 390 kPa, the amplitudes of the first harmonics are 0.0034 and 0.0029 at depths of 1 cm and 6 cm, and for a pressure of 190 kPa, the amplitudes of the first harmonics are 0.0016 and 0.0014 at depths of 1 cm and 6 cm, respectively.

Figure 4 shows the dependence of NLIs defined by Eq. (3) on depth in both water and sunflower oil based on hydrophone data.

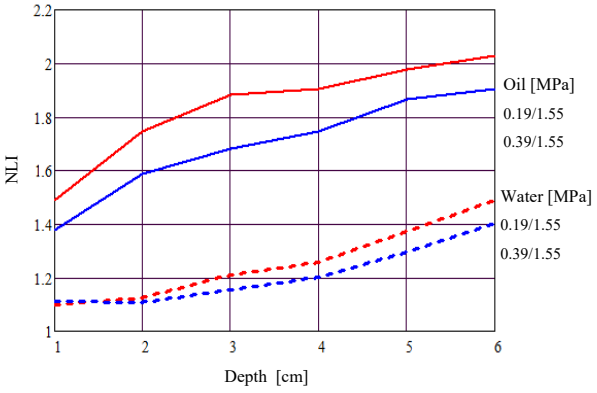

Fig. 4. Plots of NLIs in water and oil based on hydrophone data for pressures of 0.39 MPa and 0.19 MPa, using a reference pressure of 1.55 MPa (see Figs. 2 and 3).

The amplitude of the first harmonic for the reference pressure of 1.55 MPa decreases with increasing depth faster in sunflower oil than in water, particularly when comparing to the first harmonic at lower pressures of 0.39 MPa and 0.19 MPa. This is consistent with the fact that the nonlinearity coefficient B/A is larger for oil than for water (water ≈5, sunflower oil >8). As a result, starting from a depth of 2 cm, the NLI increases up to 2.02 in oil and 1.5 in water, at a depth of 6 cm for the applied pressures of 1.55 MPa and 0.19 MPa. This shows that higher values of the NLI correspond to higher values of B/A parameter, describing the nonlinear propagation characteristics of the medium. The corresponding NLI values for the reference pressures of 1.55 MPa and 0.39 MPa in oil and water were about 20 % lower, i.e., 1.9 and 1.4, respectively.

3.2. Thread phantom experiment

The NLI for echoes from the threads placed at depths of 1 cm, 2 cm, 3 cm, 4 cm, 5 cm, and 6 cm from the transducer head in both water and sunflower oil, using transmitted pressures of 190 kPa, 0.39 MPa, and a reference pressure of 1.55 Pa, is shown in Fig. 5.

The NLI is approximately 15 % greater in oil than in water for depths below 2 cm. However, the value of NLI in oil flattens out above 5 cm due to much greater attenuation – over 60 times greater than in water at 3 MHz (0.07 dB/cm for water and close to 4.5 dB/cm for oil). In practice, attenuation in water can be neglected.

3.3. In vitro measurements

A B-mode image of the fresh beef liver sample with three marked areas for NLI determination: area 1 – 2.5 cm from the surface; area 2 – 4.5 cm from the surface; area 3 – 6.5 cm from the surface, is shown in Fig. 6.

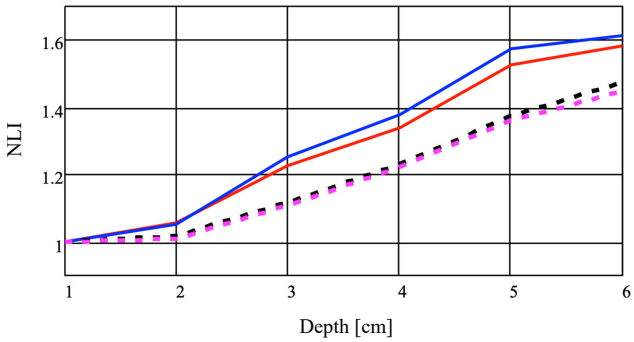

Fig. 5. NLIs for reflections from the nylon threads in oil and water. Threads are placed every 1 cm. The blue and red solid lines correspond to the NLI for sunflower oil at pressures of 0.19 MPa/1.55 MPa (solid blue line) and 0.39 MPa/1.55 MPa (solid red line). The blue and red dashed lines represent the NLI in water for pressures of 0.19 MPa/1.55 MPa (blue dashed line) and 0.39 MPa/1.55 MPa (red dashed line).

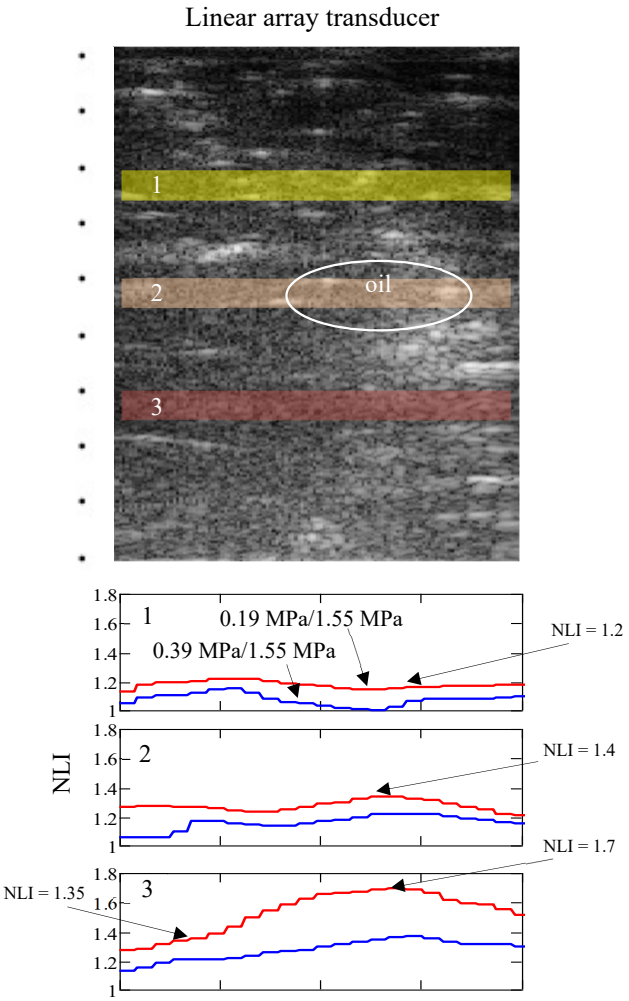

Fig. 6. *B*-mode image of a beef liver sample with three areas marked for NLI determination. The red lines correspond to pressures 0.19 MPa/1.5 MPa, while the blue lines correspond to pressures 0.39 MPa/1.5 MPa.

As shown in Fig 6, there is a significant increase in NLI to approximately 1.7 in area 3, at a depth of 5.5 cm, which is approximately 1.5 cm below the region where sunflower oil was injected. The results presented in Fig. 6 show that the NLI strongly depends on "steatosis" within the tissue. In the case of normal tissue (on the left side of the *B*-mode image of the sample) aside of the region with the injected oil, the NLI at a depth of about 6 cm does not exceed the value of 1.35, while it undergoes an increase of 20 % under the oil-injected region.

4. Discussion and conclusion

The nonlinear properties of the tissue cause the transfer of energy from the transmitted wave not only to the second harmonic component but also to the third, fourth, and higher harmonics. However, this energy transfer is ignored in THI. In the proposed technique for determining the nonlinear coefficient of the tested medium, the losses of the signal transferred to all higher harmonics are automatically taken into account – the amplitude of the recorded echoes at the first harmonic is smaller than the actual amplitude of the returning signals reflecting the energy loss to the second, third and higher frequency components. Moreover, since the proposed technique does not require the recording of the second and higher harmonics, the entire transducer bandwidth can be used for both transmission and reception.

In our preliminary experiments, we demonstrated that, both in water and sunflower oil, the relative decrease in echo amplitude with penetration depth is greater at higher initial pressures of the transmitted wave. Specifically, the quotient of the amplitude of the first harmonic for low and high transmit acoustic pressures increases faster in oil than in water. This result is consistent with what was expected, given that the nonlinearity coefficient B/A is over 1.5 times higher in oil than in water (water ≈5, sunflower oil >8).

Furthermore, the NLI at depths exceeding 2 cm in oil is approximately 15 % larger than in water. However, the NLI growth curve in oil begins to flatten out slightly beyond 5 cm (Fig. 5). This phenomenon is attributed to much greater attenuation of ultrasound in oil – over 60 times than in water. Specifically, at 3 MHz, the attenuation is 0.07 dB/cm for water and close to 4.5 dB/cm for oil. Practically, attenuation in water can be practically ignored.

The preliminary in vitro experiment using a beef liver sample, where a small region of the liver tissue was modified by injecting 1 ml of sunflower oil, confirmed the ability to assess the "steatosis" mimicking area by measuring the NLI.

The introduced NLI strongly depends on "steatosis" of the media where nonlinearity accumulation accelerates, and reaches maximum below this region. This is

confirmed in Fig. 6 where below the steatotic tissue (on the right side of the sample, the region with injected oil), the NLI at the depth of 6 cm reached 1.7 which is almost 35 % higher than the NLI value of 1.3 observed below normal tissue (on the left side of the sample).

The proposed method currently serves as a qualitative one and only allows the identification of areas in the examined tissue with smaller or larger nonlinear properties. At this stage, it does not allow for a quantitative correlation of the proposed NLI with the commonly established B/A nonlinearity parameter. However, the B/A ratio can only be determined in tissues prepared in vitro, while our method is suitable for direct application in vivo.

The nonlinearity parameters for healthy liver and fatty liver tissues are (according to the existing literature) 7 and over 10, respectively (Zhang, 2001). We expect that the proposed NLI index could significantly help in the assessment of pathological changes in the examined tissue.

There is a number of key issues that we will address in our future research. First, we will extend the depth of NLI analysis (depth limitation is currently limited due to attenuation) and we will validate the proposed methodology using focused transmission techniques. We also plan to modify the presented approach for a more localized assessment of medium nonlinearity. Finally, our goal is to develop a methodology that will enable quantitative imaging of tissue nonlinear properties based on the introduced NLI.

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