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Uncertainty of High Intensity Therapeutic Ultrasound (HITU) Field Characterization with Hydrophones: Effects of Nonlinearity, Spatial Averaging, and Complex Sensitivity

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Abstract

Reliable acoustic characterization is fundamental for patient safety and clinical efficacy during high intensity therapeutic ultrasound (HITU) treatment. Technical challenges, such as measurement uncertainty and signal analysis still exist for HITU exposimetry using ultrasound hydrophones. In this work, four hydrophones were compared for pressure measurement: a robust needle hydrophone, a small PVDF capsule hydrophone and two different fiber-optic hydrophones. The focal waveform and beam distribution of a single element HITU transducer (1.05 MHz and 3.3 MHz) were evaluated. Complex deconvolution between the hydrophone voltage signal and frequency-dependent complex sensitivity was performed to obtain pressure waveform. Compressional pressure, rarefactional pressure, and focal beam distribution were compared up to 10.6/–6.0 MPa (p_+ and p_-) (1.05 MHz) and 20.65/–7.20 MPa (3.3 MHz). In particular, the effects of spatial averaging, local nonlinear distortion, complex deconvolution and hydrophone damage thresholds were investigated. This study showed an uncertainty of no better than 10–15% on hydrophone-based HITU pressure characterization.

Keywords

HITU; Hydrophone; Uncertainty; Nonlinearity; Complex deconvolution; Spatial averaging

INTRODUCTION

In recent years, high intensity therapeutic ultrasound (HITU) has re-emerged as a minimally-invasive and non-ionizing therapeutic modality for the treatment of a variety of diseased tissues, including uterine fibroid, prostate, breast, and brain (Jolesz et al. 2005). Newer biomedical applications, such as neural stimulation (Sassaroli and Vykhodtseva 2016), drug delivery (Hynynen 2008) and histotripsy (Maxwell et al., 2012; Khokhlova et al. 2015), are also being actively explored from fundamental bio-effect mechanisms to investigational clinical trials. Pioneering studies have demonstrated that HITU, with a high acoustic pressure amplitude between 5 MPa and 40 MPa at the beam focus, can produce deep, localized necrotic lesions in tissue through either thermal coagulation or cavitation erosion under the guidance of magnetic resonance imaging (MRI) or diagnostic ultrasound imaging (Bailey et al. 2003).

Despite these encouraging clinical achievements, measurement standards and regulatory guidelines to determine the safe and effective exposimetry of such therapeutic devices are still in their infancy. In order to develop exposimetry techniques, validate theoretical models, and characterize specific HITU devices, accurate and repeatable pressure measurement should be obtained in the free field first (IEC 601601-2-62, 2013). Relevant engineering (*in vitro*) or animal (*in vivo*) bench testing can then be conducted before larger scale clinical trials are performed. Even though acoustic hydrophones are used extensively for exposimetry, complex technical challenges still exist due to the sharply focused, intense, and nonlinear HITU fields. Moreover, many studies quoted pressure measurements without uncertainty ranges because the experimental accuracy is typically unknown. Therefore, in order to interpret, compare, and reproduce bench testing results for device development and regulatory reviews, a better understanding of hydrophone performance and pressure measurement uncertainty is needed.

In the past decade, several groups have developed hydrophone technology and measurement methods to address these engineering challenges. A piezoelectric-based needle hydrophone was specifically designed as a robust sensor to measure acoustic pressures up to peak-positive and peak-negative (p_+/p_-) values of 15 MPa/−4 MPa (Zanelli and Howard 2006). Wideband fiber optic hydrophones have been evaluated for shock wave lithotripsy and HITU dosimetry studies (Staudenraus and Eisenmenger 1993; Wilkens and Koch 1999; Morris et al. 2009). In order to reduce the cavitation damage and artifacts under high pressure radiation, a novel protective thin film layer was coated around the sensing elements of either a membrane hydrophone (Bessonova and Wilkens 2013; Wilkens et al. 2016) or a fiber optic probe (Gopinath et al. 2009; Martin et al. 2015). Haller et al. (2012) characterized HITU fields by comparing three hydrophones up to 51.5 MPa/−13.4 MPa around 2 MHz. Only the fiber optic hydrophone survived their strong ultrasound exposure, while the reported intensity measurements varied up to 50% among the three hydrophones. A custom-designed fiber optic probe was reported to withstand the short pulse histotripsy fields up to 76 MPa/−21 MPa without cavitation interference during histotripsy application (Parsons et al. 2006). More recently, to mitigate the experiment and modelling challenges, an acoustic holography technique has been proposed by combining low pressure near field hydrophone scanning and nonlinear simulation (Sapozhnikov et al. 2015). This method has been used to quantify the complex acoustic field of a clinical phased-array HITU system (Kreider et al. 2013), and it has been included in IEC 62556 technical specification (2014). All this pioneering research clearly demonstrates that reliable and accurate pressure measurements for HITU dosimetry present an important and challenging task for both academia and industry.

In this study, four acoustic hydrophones were selected for comparing measurement uncertainty and signal analysis methods. These include the HITU needle hydrophone mentioned above, a small PVDF capsule hydrophone, and two wideband fiber-optic acoustic hydrophones. The focal pressure waveform and field distribution of a single element HITU transducer were measured and compared in both linear and nonlinear regimes.

Complex deconvolution (Wilkens and Koch 2004; Hurrell 2004; Wear et al. 2014; Eichstadt et al. 2016) between the hydrophone output signal and the hydrophone frequency-dependent complex sensitivity was performed to obtain pressure waveforms. With increasing acoustic

power output, the deconvolved waveform, compressional pressure, rarefactional pressure, and lateral focal beam profile were compared and reasons for experimental variations were evaluated. In particular, the effect of complex deconvolution, spatial averaging and local nonlinear parameters were discussed.

This work aimed to investigate HITU hydrophone measurement uncertainty and damage threshold, including the effect of complex deconvolution. The results will improve the understanding of measurement uncertainties during HITU device characterization and also facilitate the metrology standardization process.

DEVICES AND METHODS

A. Ultrasound hydrophones

Four commercial ultrasound hydrophones were evaluated for HITU acoustic field characterization, including a robust needle hydrophone, a small PVDF capsule hydrophone and two broadband fiber-optic hydrophones.

The needle hydrophone (Needle) consists of a miniature piezo-ceramic sensing element encased in a 20–70 μm thin metallic coating (HNA-400, Onda Corporation, Sunnyvale, CA). The effective diameter of the sensing element is within 10% of its nominal geometric diameter of 400 μm and, as demonstrated later in this work, should provide reasonable spatial resolution for low frequency HITU measurements (Howard and Zanelli 2006). This hydrophone is specifically developed as a robust sensor to withstand the high acoustic temporal-average intensity (up to $I_{\text{TA}} = 715 \text{ W/cm}^2$) and potential damage by inertial cavitation. Due to the protective coating and internal structure, the frequency response of this needle hydrophone is not uniform, resulting in distortion of nonlinear HITU measurements. For both in-house sensitivity calibration and pressure measurement, this needle hydrophone was used with a unity voltage gain pre-amplifier (Harris 1988) due to the hydrophone's high output impedance.

The capsule hydrophone (Capsule) is designed with a small and solid construction using polyvinylidene fluoride (PVDF) material (HGL-85, Onda Corporation, Sunnyvale, CA). Encased in a rounded housing to reduce diffraction, the capsule hydrophone has a very small effective aperture (85 μm), coupled with a uniform and broad frequency sensitivity from the PVDF membrane ($\pm 3 \text{ dB}$ from 250 KHz up to 20 MHz). Due to the low sensitivity of its small element, this hydrophone was used together with a 20 dB pre-amplifier (AH-2020, Onda Corporation, Sunnyvale, CA) throughout the in-house complex sensitivity calibration and measurements.

The first fiber optic probe hydrophone (FO-1) was originally designed to measure high pressure pulses from shock wave lithotripsy (FOPH2000, RP Acoustics, Leutenbach, Germany). With a 100 μm active diameter for better spatial resolution, this hydrophone measures the pressure-induced refractive index change by analyzing the reflected laser light from the glass fiber tip in water. When the fiber tip is damaged by the high intensity heating or cavitation, a new tip can be easily prepared by stripping and cleaving the remaining fiber.

The second fiber optic hydrophone (FO-2) operates from the Fabry-Perot interferometric principle by detecting acoustically-induced thickness changes of a thin polymer film coated at the tip of the optical fiber (Precision Acoustics Ltd, Dorchester, UK). This hydrophone has high sensitivity, an optical element size of 10 μm , pressure measurement range of 15 MPa, MR compatibility, and it can be implanted into tissues for simultaneous pressure and temperature measurement (Morris et al. 2009; Bull et al. 2013). If the fiber tip is damaged by the high pressure or cavitation, a replacement fiber probe can be purchased from the manufacturer. However, this broadband hydrophone has non-uniform frequency response, varying by a factor of 5 to 10 over the range from 1 to 50 MHz (Wear et al. 2015).

The physical and acoustic hydrophone properties are further listed for comparison in Table 1, including the individual amplitude sensitivities (mV/MPa) at both 1.05 MHz and 3.3 MHz. It should be noted that FO-2 was the most sensitive (~ 200 mV/MPa) while the FO-1 was the least sensitive hydrophone (~ 2 mV/MPa) selected for this study.

B. Experimental setup

The HITU source was a spherically focused single element piezo-ceramic transducer (H101, Sonic Concepts Inc., Bothell, WA), which has been used in several bio-effects and dosimetry studies (Canney et al. 2008; Bessonova and Wilkens 2013; Martin et al., 2015). This air-backed transducer has a 64 mm active element diameter and 62.6 mm geometric focus ($F\# = 0.98$). In this study, the transducer was driven at either the fundamental frequency 1.05 MHz or its third harmonic 3.3 MHz, with the corresponding matching box, from an arbitrary function generator (AFG3102, Tektronix Inc., Beaverton, OR) and linear power amplifier (AG1017L, T&C Power Conversion Inc., Rochester, NY). The emitted sinusoidal signals were tone bursts of 50 cycles at 100 Hz pulse repetition rate (*i.e.*, low duty cycle). This pulsing sequence allowed the pulse to reach a steady state within the first 20 cycles, at which point 10 or more cycles of steady-state response were recorded to simulate an equivalent continuous wave situation (Sapozhnikov et al. 2015). The tone burst signal was pulsed at a low duty cycle in order to minimize the potential hydrophone tip heating and avoid temporal overlap between the initial radiated radio frequency (RF) signal (main bang) and the actual acoustic signal. The HITU transducer was mounted on a 3D fixture horizontally, which also allowed its 2D angular orientation to be adjusted. The hydrophone was attached to a three-axis computer-controlled positioning system for alignment (20 μm spatial resolution) and RF data acquisition (Acertara Acoustics Lab, Longmont, CO). All the measurements were performed in a large low-density polyethylene (LDPE) water tank, which avoided interference from tank wall reflections. The tank was filled with deionized degassed water (oxygen content < 3 ppm) at room temperature (22 $^{\circ}\text{C}$). The received hydrophone RF signals were averaged 256 times and recorded using a digital oscilloscope (Tektronix TDS 3054B, 500 MHz bandwidth, 10k pts, 5Gs/s, Tektronix Inc., Beaverton, OR). Eight increasing electrical driving levels were applied across the transducer at both 1.05 MHz and 3.3 MHz. Driving voltages were monitored by a high impedance X10 voltage probe connected to the output of the power amplifier. Considering the potential nonlinear distortion effect at higher output levels, the hydrophone signal was spatially aligned toward the maximum pulse intensity integral *p_{ii}* (IEC 62127-1, 2013), rather than p_+ or p_- , during the 3D focal search

procedure. Alignment in the axial direction (Z-axis) with the acoustic beam axis followed a similar protocol described in Haller et al. (2012).

C. Complex Deconvolution

Three of the four hydrophones, *i.e.* the Capsule, the Needle and the FO-2, were specifically calibrated for their complex sensitivity (both amplitude and phase responses) up to 40 MHz using our in-house ultrasonic time delay spectrometry (TDS) system via a substitution calibration method (Wear et al. 2011). We found that our calibration variation of the magnitude sensitivity averaged 8.0% at 3 MHz and 7.4% at 20 MHz and that of phase sensitivity averaged 3.3° at 3 MHz and 3.1° at 20 MHz (Wear et al. 2014). The FO-2 hydrophone response has high-pass filter characteristics up to about 15 MHz and becomes variable beyond that. This high-pass filtering, which boosted harmonics relative to the fundamental frequency (*i.e.*, the acoustic working frequency = f_{awf}), could result in waveforms with sharp transitions. Therefore, complex deconvolution was performed between each individual hydrophone RF signal and the measured hydrophone impulse response (the inverse Fourier transform of the complex sensitivity) in order to reduce distortions due to non-uniform hydrophone sensitivity. When deconvolving a measured voltage spectrum, $X(f)$, with hydrophone sensitivity, $M_L(f)$, the ratio $Y(f) = X(f) / M_L(f)$ can be unstable for frequencies where $M_L(f)$ is very low. This problem can be suppressed using a low pass filter, $L(f)$, so that $Y'(f) = X(f) L(f) / M_L(f)$ (Wear et al. 2015; Eichstadt 2016). For the Needle, Capsule, and FO-2 hydrophones, a Gaussian low-pass filter, $L(f) = \exp(-f^2/2\sigma^2)$ with $\sigma = 25$ MHz, was used and all data analyses were completed off-line using MATLAB (MathWorks, Natick, MA). For the FO-1 hydrophone, the measured photodiode RF waveforms were deconvolved with the hydrophone impulse response using a proprietary algorithm from the manufacturer to obtain the pressure waveforms.

D. Local distortion parameter (σ_q)

Nonlinear propagation, also known as finite amplitude effects, is described as increasing waveform distortion due to the increased medium nonlinearity, operating frequency, acoustic pressure and propagation distance (Szabo 2014). During HITU pressure measurements, as the acoustic output level increases, the measured RF signals could evolve from their original sinusoidal shape to approaching a saw-tooth waveform containing higher harmonic due to nonlinear propagation. As part of acoustic beam characterization, both the ultrasonic hydrophone standard IEC 62127-1 (2013) and HITU technical specification IEC 62556 (2014) define a local distortion parameter (nonlinear propagation parameter) σ_q as:

$$\sigma_q = Z_p P_m \omega \beta / (\rho c^3 F_a^{1/2}) \quad (1)$$

z_p is the axial location; p_m is the arithmetic mean acoustic pressure; β is the nonlinearity parameter ($\beta = 3.5$ for water); ω is the angular frequency; F_a is the local area factor (a measure of focusing gain); ρ and c are the medium density and sound speed.

This index represents the nonlinear distortion level in a free ultrasound field by considering a specific spatial location with corresponding acoustic pressure. Furthermore, IEC 62556

(2014) states that only a focal acoustic field of $\sigma_q < 0.5$ (quasi-linear condition) is applicable to its outlined hydrophone measurement protocols for reporting the focal acoustic parameters, such as peak pressure (p_+ or p_-), acoustic working frequency and -6dB beam dimension. Therefore, in this study, we would like to better understand how high a focal pressure can be achieved in practice at relevant HITU frequencies (1.05 or 3.3 MHz) before the $\sigma_q = 0.5$ condition is reached and how this quasi-linear requirement will affect HITU hydrophone measurement limit and uncertainty. Specifically, we calculated the local distortion parameter based on the measured acoustic focal pressures for all four hydrophones at all eight output levels. The averaged σ_q was further correlated with the pressure deconvolution analysis, harmonic contents and pressure ratio (p_+/p_-) at different output levels. This assessment helped to determine whether the hydrophones were providing adequate measurement bandwidth for high amplitude nonlinear pressures and also the pressure level at which the quasi-linear status ($\sigma_q < 0.5$) is surpassed during a typical HITU dosimetry testing.

E. Spatial averaging correction

With a finite sensing area, an ultrasound hydrophone is a phase sensitive detector that spatially integrates the acoustic pressure over its active surface. Therefore, without particular measurement guidance for the strongly focused nonlinear HITU field, spatial averaging effects may result in underestimation of the actual acoustic field up to 30%, especially for the peak compressional pressure and temporal-average intensity (Haller et al. 2012). As currently recommended in IEC 62556 (2014), the criterion for the maximum effective radius $a_{\max}$ of a hydrophone for a focusing ultrasound field is given by:

$$a_{\max} = \lambda \left(Z_{\text{foc}}^2 + R_{\text{xdt}}^2 \right)^{1/2} / (8R_{\text{xdt}}) \quad (2)$$

Z_{foc} is the focal length, R_{xdt} is the output transducer radius, and λ is the acoustic wavelength.

However, because of practical considerations such as adequate signal-to-noise ratio or limited availability of suitable hydrophones, sometimes the maximum recommended effective radius is exceeded. In these cases, spatial averaging corrections may be necessary.

Following the protocol in Annex E (IEC 62127-1, 2013), if the received signal decreases more than 1 dB when translating the hydrophone laterally from the transducer focus by a distance equal to the effective hydrophone radius, then a spatial averaging correction should be applied. Specifically, the pressure correction factor K'_{sa} for moderate nonlinear wave approximation is defined as:

$$K'_{\text{sa}} = \left(3 - 2\beta' \right) \quad (3)$$

$\beta' = (\text{signal at half a hydrophone radius from the axis})/(\text{signal on axis})$ and should not be confused with β in Equation 1. This equation may be more valid than other options for

nonlinear propagation, provided that the pressure varies radially according to a quadratic form (IEC 62127-1, 2013). In this work, we first compared the maximum suitable hydrophone radius with the reported effective radius of all four investigated hydrophones to understand their measurement limitations at 1.05 MHz and 3.3 MHz. Then, by examining the lateral beam profile within the focal plane, we could determine and implement the spatial averaging correction process as described above to evaluate its impact on hydrophone measurement uncertainty.

RESULTS

A. Measurement repeatability

Before comparing pressure values obtained from different hydrophones, it is fundamental to first understand the RF voltage measurement repeatability from a single hydrophone before the more sophisticated deconvolution and signal processing. The sources of variation within the experimental system include mechanical alignment tolerance, driving/receiving electronics, and operator procedures. Long term stability of both HITU system output and hydrophone sensitivity are other critical factors to be evaluated. To this end, the Needle hydrophone was chosen to track the same weak nonlinear ultrasound field over a four-year period (2011–2014). The electrical driving voltage across the HITU transducer monitored by the X10 voltage probe was found to fluctuate within 1% over this study period. As summarized in Table 2 for both 1.05 and 3.3 MHz, the RF signals for positive (V+), negative (V−) and RMS (Vrms) voltages varied around 5% (Coefficient of Variation, COV) over the four-year study period. The V− voltages fluctuated a little more than V+ voltages at both 1.05 MHz (6.03% vs 4.05%) and 3.3 MHz (3.95% vs 3.26%). These single hydrophone results demonstrated a reasonably repeatable measurement system and provided intrinsic baseline information to further evaluate pressure measurement uncertainty.

B. Acoustic beam profiles

Lateral and axial beam profiles across the transducer focal plane were first measured using the Needle hydrophone at 1.05 MHz (Fig. 1a) and 3.3 MHz (Fig 1b). At both frequencies the normalized pressure plots stayed the same (Fig.1) as the acoustic signal level increased from relatively linear (level 1) to highly nonlinear (level 8) condition. Both the lateral side-lobe pressure distribution in the focal plane and the pre-focal axial distribution became more variable as the frequency was increased from 1.05 MHz to 3.3 MHz, presumably due to the shrinking beam size. The plots showed a −6 dB beam dimension (full-width half-maxima) of 1.97 mm (lateral) × 13.25 mm (axial) at 1.05 MHz and 0.63 mm × 4.30 mm at 3.3 MHz with a focal length of 62.6 mm. These dimension measurements are comparable with previously reported values of 1.92 mm × 12.74 mm at 1.06 MHz and 0.62 mm × 4.08 mm at 3.3 MHz (Bessonova and Wilkens 2013).

Next, under relatively linear ultrasound exposure (level 1), the lateral beam profiles including the side lobes were measured by the four hydrophones and compared on both logarithmic (dB) and linear scales (Fig. 2). Based on the previous results (Fig. 1), the scanning range for hydrophone comparison was chosen as ±4.5 mm (0.3 mm step size) for 1.05 MHz and ±2.0 mm (0.1 mm step size) for 3.3 MHz. It is clear in Figure 2 that one fiber

optic hydrophone (FO-1) was not able to depict the detailed side-lobes profiles outside the -6 dB main beam area, which is due to its lower acoustic sensitivity. This result suggested that the FO-1 hydrophone could be used as a pressure sensor at the focus, but not for general HITU beam profile characterization away from the focus. The other three hydrophones measured similarly symmetric beam profile distributions, up to the 2nd or 3rd side-lobes down to -40 dB, at both 1.05 and 3.3 MHz (Fig. 2). In particular, the capsule hydrophone and FO-2 hydrophone had relatively small sensor sizes (Table 1) and provided better resolution on the dB scale at several spatial minimum locations. Overall, three out of the four hydrophones provided comparable lateral beam profiles down to -40 dB and were able to provide sufficient spatial resolution to differentiate several side-lobes.

C. Compressional and rarefactional pressure

Representative focal waveforms measured by the FO-1 hydrophone are plotted for both 1.05 MHz (Fig. 3a) and 3.3 MHz (Fig. 3b) as the output levels were increased from level 1 to level 8. Due to the finite amplitude propagation at higher output levels, the complex deconvolved waveforms evolved from the symmetrical sinusoidal profile (level 1) to a distorted nonlinear shape (level 8), referred to as “shock development” in the previous study by Haller et al. (2012). In this study, the highest focal pressure measured by the FO-1 hydrophone was calculated to be 10.6/–6.0 MPa at 1.05 MHz and 20.65/–7.20 MPa at 3.3 MHz, which are lower than the highest pressure measured by a similar fiber-optic sensor (80/–15 MPa at 2 MHz) in Canney et al. (2008).

In order to estimate measurement variations, Figure 4 compares the deconvolved focal pressure waveforms (one cycle) measured by all four hydrophones at output level 1, level 4 and the highest level 8. For both 1.05 MHz (Fig. 4a) and 3.3 MHz (Fig. 4b), variation in waveform shape and pressure amplitude can be clearly seen among the four hydrophones even at the lowest level 1 output, which is still under the relatively linear condition. As the measured waveforms began to show nonlinear distortion with higher pressure amplitude at level 4 (Fig. 4, middle row), the FO-2 hydrophone reached its measurement limit at 3.3 MHz while the other three hydrophones were still able to measure mostly comparable waveforms. At the highest output level 8, the measured waveforms from Needle and FO-1 hydrophones clearly demonstrated the nonlinear distortion with comparable pressure amplitude and temporal profile (Fig. 4, bottom row). It should be noted that the Needle and the FO-1 are the only two probes that survived all the frequency/output combinations in this study without showing any problems such as intermittent oscilloscope display, distorted and shaking waveform, sudden amplitude reduction, and disappearance. When these artifacts were observed, the output level could be reduced sometimes to restore the waveform and avoid permanent hydrophone damage.

To further quantify the pressure variation and hydrophone limit, Table 3 summarizes and compares the individual compressional (p_+) pressure, rarefactional (p_-) pressure and corresponding coefficient of variation (COV) at every output level. Even though the Capsule and FO-2 hydrophones did not survive all the exposure conditions, it is actually valuable to know their measurable pressure ranges at both HITU frequencies. The measurement limit for the Capsule hydrophone was found to be 11.22/–6.92 MPa at 1.05 MHz and 10.09/–5.85

MPa at 3.3 MHz. For the FO-2 hydrophone, the damage threshold was 6.67/−4.11 MPa (1.05 MHz) and 4.62/−4.57 MPa (3.3 MHz). It is interesting to note that, for each hydrophone (Capsule and FO-2), the pressure damage threshold did not vary significantly between the two ultrasound frequencies.

The inter-hydrophone variation and uncertainty during HITU pressure measurement is another important aspect to assess. In Table 3, the COV % column provided p_+ or p_- variation percentage among four hydrophones at each output level. At 1.05 MHz, the COV of p_- is a slightly higher than that of p_+ at each output level (for example, 16.45% vs 12.68% at level 4). As the output level increases, the COV for either p_+ or p_- creeps up slowly, from approximately 11% up to 17% (except when some hydrophones failed at Level 8 and therefore COV values were not as reliable). At 3.3 MHz, even though hydrophones failed at lower output levels due to stronger nonlinearity effect, the general observation about measurement uncertainty is similar to the 1.05 MHz. Specifically, we found that the COV, at each output level, is comparable between p_+ and p_- . With increasing output levels, the COV for both p_+ and p_- are also rising gradually from 7.15% to 13.32% (first three levels). These result showed that the increasing output levels lead to a higher pressure measurement uncertainty. However, higher frequency did not significantly affect our measurement variation and yielded overall comparable uncertainty about 10–15% for both p_+ and p_- .

D. Local distortion parameter (σ_q)

In Figure 3, pressure waveforms from the FO-1 hydrophone clearly demonstrate the distortion process from a sinusoidal waveform (level 1) into a highly nonlinear waveform (level 8) at both HITU frequencies. The Figure 5 inserts indicate the most nonlinear focal pressure waveforms recorded by the FO-1 and Needle hydrophones at 1.05 MHz (10.6/−6.0 MPa) and 3.3 MHz (20.7/−7.2 MPa). Figure 5 further presents the corresponding Fast Fourier Transform (FFT) spectra for these highly distorted waveforms, which reveal their harmonic content up through the fifth harmonic (5.5 MHz) at 1.05 MHz and eighth harmonic (26.4 MHz) at 3.3 MHz. The latter represents the highest harmonic generation recorded in our study. To quantify the nonlinear distortion, Table 4 shows local distortion parameter σ_q averaged from four hydrophone measurements at each output level. The COV change of σ_q among the four hydrophones is about 10–20% at each level. For 1.05 MHz, the averaged σ_q value increased from 0.07 ± 0.01 at level 1, 0.27 ± 0.04 at level 4 and 0.54 ± 0.04 at level 8. Consequently, the majority of the 1.05 MHz measurements were under the quasi-linear condition ($\sigma_q < 0.5$) and therefore the standard measurement protocols described in IEC 62556 (2014) are applicable. On the other hand, at 3.3 MHz the σ_q was already beyond 0.5 above level 3 and reached 1.75 ± 0.07 at output level 8. At this highest level, the FO-1 hydrophone recorded only eight harmonics, and the averaged pressure amplitude reached 19.37/−7.67 MPa with a p_+/p_- ratio of 2.53. In contrast, at 1.05 MHz, the highest σ_q value was 0.54 (close to quasilinear condition) while five harmonics were recorded (Figure 5b), and the peak pressure was 10.07/−5.67 MPa with a p_+/p_- ratio of 1.78. When the p_+/p_- ratio between 1.05 MHz and 3.3 MHz is comparable (1.24 vs 1.21) at level 3, the corresponding σ_q are much different (0.19 vs 0.57). Similarly, when the p_+/p_- pressure amplitudes are comparable (9.27/−5.59 MPa at level 7 of 1.05 MHz vs 9.19/5.42 MPa at level 5 of 3.3 MHz), the corresponding σ_q are also quite different (0.51 vs 1.69). Therefore, these

observations indicate harmonic content, pressure amplitude and p_+/p_- ratio did not correlate well with the local distortion parameter in terms of defining the extent of nonlinearity. These calculations and comparisons provided a direct evaluation for the degree of distortion presented in HITU measurements and the complex relationships among nonlinearity, spatial beam shape, frequency, pressure amplitude and p_+/p_- ratio.

E. Spatial Averaging Correction

According to Eqn. 2, the recommended maximum radius $a_{\max}$ values at 1.05 MHz (392 μm) and 3.3 MHz (125 μm) are both larger than majority of the listed sensor radii of the four hydrophones (Table 1). Therefore, those hydrophones are suitable for the our HITU focal field evaluation and spatial averaging correction is not needed, at least at lower output levels (higher harmonics is negligible) based upon current hydrophone measurement standard (IEC 62127-1, 2013). The only exception is that the effective radius of the Needle hydrophone (200 μm) is still larger than the recommended maximum hydrophone radius of 125 μm at 3.3 MHz and hence a spatial averaging correction is recommended. To further confirm this observation, the lateral focal beam pressure distribution (Figure 1) was examined in detail at both frequencies. Figure 1 reveals that the normalized pressure drops by 1 dB (12% amplitude) near 450 μm (1.05 MHz) and 120 μm (3.3 MHz) laterally. These values are greater than the hydrophone sensitive element radii for this study except that the Needle hydrophone radius exceeds the 1 dB reduction point at 3.3 MHz. Therefore, a spatial averaging correction factor of $K'_{\text{sa}} = 1.123$ was subsequently calculated for the Needle hydrophone at 3.3 MHz following the procedure outlined in Methods section. The spatial averaging correction increased the Needle hydrophone pressure values by 12.3% ($K'_{\text{sa}} = 1.123$) and hence corrected the pressure at level 8 to 20.3 MPa (p_+) and -9.13 MPa (p_-).

Figure 6 plots both the original p_+ pressure from all hydrophones, together with the spatial averaging (SA) corrected p_+ values of Needle hydrophones. Compared to the original Needle hydrophone (200 μm radius) measurement (light blue * line), the corrected higher pressure values (red line) are not necessarily always closer to the measurement results of other hydrophones with smaller sensor diameter, *i.e.*, the 85 μm Capsule hydrophone (dark black line), 10 μm FO-2 hydrophone (purple line) and 100 μm FO-1 hydrophone (green line). A similar situation was also seen from the p_- data plot (not shown). This observation was further quantified in Table 5 by comparing the overall pressure COV. Using the p_- as an example, the COV before (original) and after (corrected) SA correction is 7.15% vs 12.13% at level 1, 10.05% vs 8.3% at level 4 and 6.07% vs 11.82% at level 8. Therefore, in this study, spatial averaging correction did not necessarily reduce the overall experimental variation and improve measurement accuracy. This might be because other sources of uncertainty were comparable to or greater than the effect of spatial averaging correction.

DISCUSSION AND CONCLUSION

A reliable characterization of acoustic pressure is fundamental for both patient safety and device efficacy during clinical HITU applications. In order to facilitate pre-clinical bench testing and metrology standardization, this study evaluated hydrophone measurement uncertainty, robustness and signal analysis protocols for nonlinear HITU waveforms. Using

four different ultrasound hydrophones, including a robust needle hydrophone, a small PVDF capsule hydrophone and two broadband fiber optic hydrophones, the focal pressure waveform and field distribution of a single element HITU transducer was characterized over a range of output levels and frequencies.

A single element dual-frequency transducer (H101, Onda Corporation, Sunnyvale, CA) was chosen because it has been used as a prototype HITU transducer in various academic laboratories and clinical institutes (Khokhlova et al. 2013; Haworth et al. 2013). This bowl-shaped transducer is able to generate clinical relevant acoustic pressure up to 10.6/–6.0 MPa at 1.05 MHz and 20.65/–7.20 MPa at 3.3 MHz in our study. Such a systemic pressure measurement using a representative HITU source at specified driving voltage aimed to provide meaningful and clinically-relevant dosimetry information for other bio-effect studies and future inter-laboratory comparison.

In order to evaluate the individual hydrophone's measurement range and damage threshold, the HITU driving voltages (Table 3) were carefully increased until pressure measurement failure was observed. The PVDF capsule hydrophone (Capsule) was found to reach its pressure limit at 10.1/–7.32 MPa (1.05 MHz) and 13.42/–6.66 MPa (3.3 MHz), at which point unstable, shaking, and diminishing waveforms were seen on the oscilloscope. Similarly, the Fabry-Perot fiber optic hydrophone (FO-2) achieved a pressure measurement limit of 7.14/–4.32 MPa (1.05 MHz) and 6.04/–4.7 MPa (3.3 MHz) before optical fiber was eventually damaged. In general, the FO-2 probe is relatively easy to be damaged by high acoustic pressures, likely due to the sophisticated interferometer coating film at the tip of the fiber (Martin et al. 2015). Presumably due to cavitation or mechanical stress within the hydrophone itself, both hydrophones showed a similar signal corruption or pressure damage thresholds between 1.05 MHz and 3.3 MHz. Overall, these data provided experimental evidence for the hydrophone pressure measurement limit, which at present are not provided by the manufacturers.

As an important parameter for measurement uncertainty, the COV % (Table 3) essentially represents a combination of various error sources from system electronics, hydrophone calibration, mechanical hardware, and human factors. At both 1.05 MHz and 3.3 MHz, the COV among the four hydrophones did increase gradually with higher amplitude and nonlinear distortion, except when some hydrophones reached measurement limits and therefore COV values were not as reliable. However, at each output level, the COV between p_+ and p_- always stay on comparable uncertainty value. Overall, with complex deconvolution, the pressure measurement accuracy for high intensity, nonlinear conditions was around 10–15%, comparable with low pressure (< 5 MPa) linear measurements. We should mention that hydrophone amplitude sensitivity calibration itself demonstrated a typical 10% experimental variation mostly due to the sensitivity calibration system and process (Preston et al. 1988). During our inter-hydrophone comparison, the COV values provide accuracy information for HITU pressure characterization uncertainty.

Finite amplitude distortion (local distortion parameter σ_q) is affected by frequency, propagation distance, pressure amplitude, harmonic content and focusing gain (Bessonova and Wilkens 2013). The limitations for the σ_q calculation include the plane wave

assumption, Gaussian beam approximation, and even signal overshoot in the detection electronics (Bacon 1984). According to Table 4, the distortion parameters σ_q at 1.05 MHz were essentially always smaller than 0.5 (quasi-linear condition) even though the FFT spectrum analysis (Fig. 5a) revealed up to the 5th harmonic content. In contrast, the σ_q at 3.3 MHz exceeded 0.5 (quasi-linear condition) above output level 3 and reached 1.75 at level 8 where the FFT analysis (Fig. 5b) revealed only up to the 8th harmonic. It should be mentioned that, because FO-1 is less sensitive, the harmonics beyond the 8th might have been generated but difficult to measure. These data indicate that neither the p_+/p_- ratio, pressure amplitude (Table 4) nor the harmonic content (Fig. 5) present a good correlation with σ_q by defining the degree of waveform nonlinearity. The relative merits of p_+/p_- and other parameters for characterizing nonlinearity have also been studied in several previous publications (Szabo et al. 1999; Duck 1999; Bigelow and O'Brien 2002).

For nonlinear HITU measurement, inadequate complex deconvolution at both the low and high end of the signal spectrum could contribute to the pressure error (Wilkins and Koch 1999; Wilkins and Koch 2004; Hurrell 2004; Wear et al. 2015). To better understand the significance of complex deconvolution for obtaining accurate HITU pressure measurements. Figure 7 plotted the pressure percentage change due to deconvolution (vs linear conversion at f_{awf}) as a function of local distortion parameter σ_q . Specifically, the percentage change due to complex deconvolution corrections (averaged from four hydrophones) at 1.05 MHz for p_+ went from 2.65% to 17.07% as the corresponding nonlinearity parameter σ_q increased only to 0.54 (still within the quasi-linear regime). Furthermore, at the first three output levels of 3.3 MHz (quasi-linear regime), the p_+ percentage change after deconvolution already increases from 14% to 23%. When the σ_q grew to 1.75, the pressure change is even greater, up to 36.09% at level 8. Similarly, the percentage change on p_- also rose with increasing nonlinearity parameter, although at a lower level (up to 11.04% at level 8 of 3.3 MHz) compared to the p_+ change. Based on these results, broadband nonlinear measurement definitely needs to be considered in this study, including hydrophone bandwidth uniformity, phase response and deconvolution analysis. Even though the narrow band approximation was satisfied when $\sigma_q < 0.5$, it is still not sufficient to consider only the hydrophone sensitivity value at the working frequency (linear conversion) for accurate pressure calculation. The quasi-linear characterization protocols prescribed in IEC 62556 (2014) may not be applicable for our experiment, especially at 3.3 MHz due to considerable nonlinear distortion. We recommend that both the f_{awf} and σ_q are important factors to consider when determining whether complex deconvolution is necessary, especially for the compressional pressure p_+ .

Following the recommendation in IEC 62127-1 (2013), a spatial averaging correction of 12.3% was applied for the Needle hydrophone (200 μm radius) due to the small lateral beam width (0.63 mm) at 3.3 MHz. The inherent accuracy of the spatial averaging correction process is between 10% to 30% for a nonlinear distortion parameter σ_q of 0.5~1.5 (IEC 62127-1, 2013), which happened to be the primary nonlinear regime encountered in this study. Such correction uncertainty is basically comparable to the overall measurement variation between hydrophones and therefore may not essentially improve experimental accuracy. It should be noted that this correction equation may be approximately valid for

moderately nonlinear fields, but not for general nonlinear fields, if the pressure varies according to the quadratic assumption.

During the axial beam profile characterization, the focus location didn't shift as the pressure output levels increased for either the 1.05 MHz or 3.3 MHz measurements (Fig.1), similar to the previous study by Haller et al. (2012). Such a spatial change might be expected based on numerical simulations (Khokhlova et al. 2013), where the focal location shifts axially towards the transducer due to nonlinear propagation effect at higher pressure levels. One possible reason no shift was seen in this study is that the pressure levels were not high enough. Another possibility is that our 3D alignment process was conducted to maximize the pulse intensity integral instead of pressure amplitude. These explanations should be investigated further by measuring even higher pressure levels in our future research.

Another limitation of this work is that the frequency selection (1.05 MHz and 3.3 MHz) is still a subset of the clinical HITU frequency range, which may vary from 400 KHz (transcranial HITU) up to 8 MHz (aesthetic/ophthetetic HITU) (Szabo 2014). Both the lower and higher frequency HITU field measurements will pose unique and interesting challenges for hydrophone measurements. Some issues could be similar to those examined in the present study, including alignment precision, spatial averaging, complex deconvolution, and damage threshold.

In summary, we demonstrated an overall uncertainty no better than 10–15% on hydrophone-based HITU pressure measurements. This study could facilitate intelligent hydrophone selection, improve deconvolution analysis, and optimize operation guidance for device quality assurance and HITU regulatory evaluation in order to benefit patient safety and clinical efficacy.

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Figure 1.
Lateral and axial RMS acoustic pressure beam distribution at (a) 1.05 MHz and (b) 3.3 MHz measured by Needle hydrophone at output level of 1, 4 and 8

Figure 2.

Lateral acoustic beam distribution comparison in logarithmic (left) and linear (right) scale at (a) 1.05 MHz and (b) 3.3 MHz measured by different hydrophones

Figure 3.
Deconvolved focal pressure waveform at (a) 1.05 MHz and (b) 3.3 MHz measured by FO-1 hydrophone from output level 1 to 8

Figure 4.
Pressure waveform comparison for (a) 1.05 MHz and (b) 3.3 MHz measured by different hydrophones at output levels 1, 4 and 8

Figure 5.

Waveform spectrum analysis at the highest output level 8 for (a) 1.05 MHz and (b) 3.3 MHz with corresponding time waveforms (insert)

Figure 6.

Comparison of spatial averaging (SA) corrected p+ pressure measured by Needle hydrophone with all other hydrophones

Figure 7. Pressure change percentage between complex deconvolution and scaled linear conversion (at working frequency) as a function of nonlinearity parameter at both 1.05 MHz and 3.3 MHz

Table 1

Parameters comparison of the four hydrophones

Model	ONDA HGL-85	ONDA HNA-400	FOPH 2000	FOPH PA
Abbreviation	Capsule	Needle	FO-1	FO-2
Material	PVDF	Ceramic	Fiber-optic	Fiber-optic
Sensor diameter (μm)	85	40	100	10
Calibration bandwidth (Amplitude, MHz)	40	40	100	40
Calibration bandwidth (Phase, MHz)	40	40	100	40
Pre-amplifier	20 dB	Unity Gain	Internal	Internal
Sensitivity (mV/MPa) (1.05 MHz/3.33 MHz)	58/38	31.9/50	~2.0	151/236

Table 2
Repeatability of the Needle Hydrophone Voltage Measurements (2011 to 2014)

	1.05 MHz			3.3 MHz		
	V ₊ (mv)	V ₋ (mv)	V _{rms} (mv)	V ₊ (mv)	V ₋ (mv)	V _{rms} (mv)
2011	29.4	28.1	21.0	-	-	-
2012	32	24.7	20.1	72.3	64.5	48.6
2013	29.7	28	20.2	70.5	61.3	45.2
2014	29.6	27.8	20.3	75.2	66.3	50.4
Average	30.4 ± 1.22	26.9 ± 1.64	20.4 ± 0.41	72.7 ± 2.37	64.0 ± 2.53	48.1 ± 2.64
COV %	4.05%	6.03%	2.00%	3.26%	3.95%	5.49%

Table 3

Pressure comparison of the four Hydrophones at both 1.05 MHz (a) and 3.33 MHz (b)

(a) Driving voltage _{pp} (V)	p ₊ , Compressional pressure (MPa)					p ₋ , Rarefactional pressure (MPa)				
	Capsule	Needle	FO-1	FO-2	COV %	Capsule	Needle	FO-1	FO-2	COV %
22 (Level 1)	1.18	0.89	1.07	0.93	11.32%	1.14	0.86	0.82	0.86	13.92%
44 (Level 2)	2.42	1.77	2.09	2.02	11.18%	2.21	1.57	1.67	1.51	15.94%
66 (Level 3)	3.76	2.8	2.98	3.07	11.55%	3.24	2.3	2.4	2.24	15.93%
88 (Level 4)	5.46	3.96	4.35	4.24	12.68%	4.32	3.02	3.22	2.94	16.45%
110 (Level 5)	7.49	5.17	5.62	5.45	15.40%	5.24	3.61	3.84	3.56	16.93%
132 (Level 6)	9.53	6.42	6.84	6.67	17.09%	6.17	4.28	4.49	4.11	17.30%
154 (Level 7)	11.22	7.97	8.62	–	15.15%	6.92	4.8	5.06	–	16.88%
176 (Level 8)	–	9.53	10.6	–	5.32%	–	5.34	6.00	–	5.82%

(b) Driving voltage _{pp} (V)	p ₊ , Compressional pressure (MPa)					p ₋ , Rarefactional pressure (MPa)				
	Capsule	Needle	FO-1	FO-2	COV %	Capsule	Needle	FO-1	FO-2	COV %
15 (Level 1)	1.62	1.82	1.46	1.58	8.00%	1.56	1.68	1.42	1.42	7.15%
30 (Level 2)	3.43	3.78	2.63	3.14	12.98%	3.09	3.23	2.4	2.88	10.84%
45 (Level 3)	4.78	5.88	4.45	4.57	11.52%	3.55	4.58	3.49	4.62	13.32%
60 (Level 4)	7.31	6.49	6.15	–	7.32%	5.36	4.35	4.37	–	10.05%
75 (Level 5)	10.09	8.8	8.67	–	6.98%	5.85	5.31	5.1	–	5.83%
90 (Level 6)	–	11.42	11.53	–	0.48%	–	6.2	5.85	–	2.90%
115 (Level 7)	–	15.56	16.14	–	1.83%	–	7.4	6.68	–	5.11%
130 (Level 8)	–	18.08	20.65	–	6.64%	–	8.13	7.2	–	6.07%

Table 4

Averaged local distortion parameters σ_b , averaged p_+ and p_- pressure amplitude, and corresponding p_+/p_- ratio from four hydrophones. ($\sigma_b > 0.5$ are labeled in red)

	1.05 MHz			3.3 MHz		
	σ_b	p_+/p_- [MPa]	p_+/p_- Ratio	σ_b	p_+/p_- [MPa]	p_+/p_- Ratio
Level 1	0.07±0.01	1.02/0.92	1.11	0.20±0.03	1.62/1.52	1.07
Level 2	0.13±0.02	2.08/1.74	1.19	0.39±0.07	3.25/2.90	1.12
Level 3	0.19±0.03	3.15/2.55	1.24		4.92/4.06	1.21
Level 4	0.27±0.04	4.50/3.38	1.33		6.65/4.69	1.42
Level 5	0.34±0.06	5.93/4.06	1.46		9.19/5.42	1.69
Level 6	0.41±0.08	7.37/4.76	1.55		11.48/6.03	1.90
Level 7		9.27/5.59	1.66		15.85/7.04	2.25
Level 8		10.07/5.67	1.78		19.37/7.67	2.53

Table 5

COV of p+ and p- pressure between four hydrophone with (Corrected) and without (Original) spatial averaging correction

3.3 MHz (Needle)	p+ COV (%)		p- COV (%)	
	Original	Corrected	Original	Corrected
Level 1	8.00	13.09	7.15	12.13
Level 2	12.98	17.35	10.84	14.69
Level 3	11.52	17.17	13.32	16.80
Level 4	7.32	7.85	10.05	8.30
Level 5	6.98	6.54	5.83	6.79
Level 6	0.48	5.31	2.90	8.68
Level 7	1.83	3.97	5.11	10.88
Level 8	6.64	0.83	6.07	11.82