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INVESTIGATION OF INTENSITY THRESHOLDS FOR ULTRASOUND TISSUE EROSION

Zhen Xu^{*}, J. Brian Fowlkes^{*,†}, Achi Ludomirsky[‡], and Charles A. Cain^{*}

^{*} Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA

[†] Department of Radiology, University of Michigan, Ann Arbor, MI, USA

[‡] Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA

Abstract

Our previous studies have shown that short intense pulses delivered at certain pulse repetition frequencies (PRF) can achieve localized, clean erosion in soft tissue. In this paper, the intensity thresholds for ultrasound induced erosion and the effects of pulse intensity on erosion characterized by axial erosion rate, perforation area and volume erosion rate were investigated on *in vitro* porcine atrial wall tissue. Ultrasound pulses with a 3-cycle pulse duration and a 20-kHz PRF were delivered by a 788-kHz single element focused transducer. I_{SPPA} values of 1000 to 9000 W/cm² were tested. Results show the following: (1) the estimated intensity threshold for generating erosion was at I_{SPPA} of 3220 W/cm²; (2) the axial erosion rate increased with higher intensity at $I_{SPPA} \leq 5000$ W/cm², while decreased with higher intensity at $I_{SPPA} \geq 5000$ W/cm²; and (3) the perforation area and the volume erosion rate increased with higher intensity.

Keywords

Cavitation; Therapeutic ultrasound; Pulsed ultrasound; Tissue erosion; Intensity; Cardiac applications

INTRODUCTION

The overall motivation for this research is the development of a noninvasive procedure to perforate the atrial septum as the first step to treat neonates with hypoplastic left heart syndrome (HLHS) and an intact or restrictive atrial spectrum. HLHS is a congenital heart defect characterized by a dysfunctional left ventricle. It is usually fatal within 2 wk after birth if not treated. The preferable treatment is reconstructive surgery. The only way to extend patient survival until reconstructive surgery is to generate a temporary flow channel between the two atria, (*i.e.*, perforation of the atrial septum, which is the membrane separating the two atria).

Current procedures to create this trans-atrial communication all involve catheter-based septostomy, *e.g.*, trans-septal puncture, balloon atrial septostomy, blade septostomy and Brockenbrough atrial septoplasty or stenting (Atz et al. 1999). They are all invasive, either unsuccessful or have high mortality (~50%) (Andrews and Tulloh 2002; Vlahos et al. 2004).

We have developed an ultrasonic technique (termed “histotripsy”) to achieve mechanical breakdown of soft tissue using a number of short, high intensity pulses delivered at certain

repetition frequencies (PRF) (Cooper et al. 2004; Parsons et al. 2004; Xu et al. 2004). At a fluid-tissue interface, this modality results in localized tissue erosion, which has been applied to create clearly defined holes in atrial septa and atrial wall (Xu et al. 2004). We believe that histotripsy may be developed into a noninvasive surgical alternative to the current invasive procedure to perforate the neonatal atrial septum in the treatment of HLHS.

Although the physical basis for histotripsy is not completely understood, our results have suggested cavitation as the primary mechanism. An enhanced and temporally fluctuating acoustic backscatter from the erosion zone has been observed during tissue erosion, “initiation” of which is required for generating erosion (Xu et al. 2005). This backscatter pattern is often regarded as a signature of cavitation (Fairbank and Scully 1977; Roy et al. 1985; Atchley et al. 1988; Holland and Apfel 1990; Madanshetty et al. 1991; Everbach et al. 1997; Poliachik et al. 1999; Kripfgans et al. 2000; Chen et al. 2002). Additional evidence is provided by the significant change in erosion rate of tissue in fluid with different gas concentrations (Xu et al. 2004).

The purpose of this paper is to explore the intensity thresholds for ultrasound tissue erosion and the effects of pulse intensity on erosion characteristics. Acoustic intensity has long been considered as the acoustic parameter of primary importance in the study of cavitational biological tissue effects and investigated by numerous researchers, *e.g.*, tissue ablation in brain tissue, prostate tissue, breast tissue, liver tissue, kidney tissue and muscle tissue creating lung hemorrhage, etc. (Fry et al. 1970; Dunn and Fry 1971; Frizzell et al. 1983; ter Haar et al. 1986; Fowlkes et al. 1991; Hynynen 1991; Chapelon et al. 1992; Coleman et al. 1995; O’Brien et al. 2003; Tran et al. 2003; Poliachik et al. 2004).

For the investigation of erosion characteristics, axial erosion rate, perforation area and volume erosion rate are chosen as output indices. The axial erosion rate is chosen because erosion in the axial direction contributes the most to perforation with the primary acoustic beam perpendicular to the target tissue, which is the configuration of the *in vitro* experiment. This configuration should be achievable in the clinical situation based on the echocardiography of HLHS and normal neonatal patients. The echocardiography suggests that a subcostal acoustic window exists for the atrial septal insonation, such that the transducer can be positioned with the primary beam axis perpendicular to the atrial septum. Area of perforation is selected, because it indicates useful information related to the erosion mechanism, which will be discussed in detail in the discussion section. Finally, volume erosion rate is included as an evaluation of the overall erosion effect.

This study is conducted under *in vitro* conditions, because *in vitro* experimentation enables exploration of a very large parameter space rather quickly and at low cost compared to *in vivo* experiments. Since the previous canine experiment (Xu et al. 2004) demonstrated that *in vivo* atrial septal erosion is at least qualitatively similar to the *in vitro* results, acoustic parameters developed *in vitro* can serve as a workable starting point for future *in vivo* experiments. Most importantly, understanding the physical basis for the erosion process *in vitro* will allow optimal utilization of experimental animals in the *in vivo* experiments.

METHODS

Sample materials

The preparation of the tissue samples has been described previously in detail (Xu et al. 2004). A total of 20 pieces of fresh porcine atrial wall were used in the *in vitro* experiments. The part of the porcine atrial wall we chose is similar to the atrial septum in both structure and geometry. Resembling atrial septa, the porcine atrial wall consists of two layers of thin membrane and soft tissue between the layers. The thicknesses of the porcine atrial wall samples

were 1 to 3 mm. In comparison, the atrial septa of human neonates are approximately 1 to 1.5 mm thick. The difference between the two tissues is that the atrial wall is more uniform and has a larger surface area to work with, which is ideal for experimental purposes. Porcine atrial wall tissues were obtained from a commercial abattoir (Jackson, MI) and used within 24 h of harvesting.

Ultrasound transducers and calibration

Ultrasonic exposures were delivered by a 788-kHz single element focused transducer (f number = 1, Etalon Inc., Lebanon, IN, USA) to generate erosion in tissue samples positioned at its focus. The 788-kHz transducer has an 8.8-cm focal length, an 8.8-cm o.d., and a 3.7-cm diameter hole in the center for a monitoring transducer. All ultrasound exposures occurred in a 61-cm long $\times$ 28-cm wide $\times$ 30.5-cm high polycarbonate tank containing water degassed (Kaiser et al. 1996) to a desired level before the experiment. The 788-kHz transducer was mounted to a frame suspended from the tank. Figure 1 shows the experimental set-up.

The acoustic field of the 788 kHz transducer was measured in degassed water with a bilaminar-shielded PVDF membrane hydrophone (Model IP056, Marconi Research Center, Chelmsford, UK). The hydrophone was calibrated by Sonic Consulting, Inc. (Wyndmoor, PA, USA) in the frequency range of 0.25 to 20 MHz. Spatial peak pulse average intensities (I_{SPPA}) were measured by integrating the pulse intensity at the spatial maximum and dividing the pulse duration defined in AIUM standards (1998). The peak rarefactional pressure, peak compressional pressure, pulse duration (in μ s) and beam cross-sectional area in mm^2 at I_{SPPA} values of 1000 to 9000 W/cm^2 were also measured and listed in Table 1. Beam cross-sectional area is defined as the area consisting of all the points where the pulse intensity integral is greater than 25% of the maximum pulse intensity integral in the focal plane (AIUM 1998). Both pulse duration and beam cross-sectional area decrease with increasing I_{SPPA} , as the nonlinear propagation becomes more prominent at higher intensity.

Acoustic backscatter for monitoring cavitation

Inside the inner hole of the 788-kHz transducer, a 5-MHz, 2.5-cm diameter single element focused transducer (Valpey Fisher Corporation, Hopkinton, MA, USA) with a 10-cm focal length was mounted coaxially with the 788-kHz transducer to receive the acoustic backscatter from the focal zone to monitor the cavitation activity that induces erosion. In our recent report, an enhanced and temporally variable backscatter, regarded as an indicator of cavitation, was always observed during erosion (Xu et al. 2005). The initiation and extinction of this variable backscatter is correlated with the start and suspension of cavitation. We have developed statistical criteria to detect both initiation and extinction of the variable backscatter signals. The criteria were based on the significantly increased temporal backscatter variability when "initiation" occurs and significantly reduced temporal backscatter variability when "extinction" occurs. The criteria, procedures and set-up to detect the initiation and extinction phenomena were detailed in our previous paper (Xu et al. 2005). It was noted that when tissue was perforated, the backscatter variability greatly decreased and was detected as extinction based on our criteria. Therefore, the extinction of the variable backscatter was used as the basis for perforation detection. Perforation time is defined as the interval between the onset of acoustic pulses and the last extinction detected when perforation was visually observed. The acoustic backscatter signal and the tissue echo (used for measuring tissue thickness described later) were recorded and displayed as time traces by a digital oscilloscope (Model 9354TM, LeCroy, Chestnut Ridge, NY, USA). The recorded waveforms were then transferred through GPIB and processed by the Matlab program (Mathworks, Natick, MA, USA).

Tissue thickness measurement

In addition to perforation time, the thickness of the tissue needs to be measured to calculate axial erosion rate. An 3-mm diameter single element unfocused transducer with a 20-MHz center frequency (Model V316-SU, GE Panametrics, Waltham, MA, USA) was used to measure the thickness of the tissue sample at the location where the 788-kHz transducer was focused (*i.e.*, location of perforation). To make such measurement, the 20-MHz transducer was aligned coaxially with and facing the 788-kHz transducer through a miniature 2D translation stage (Model M-DS25-XY, Newport Corporation, Irvine, CA, USA), to which the 20-MHz transducer was attached. The miniature 2D translation stage and the 788-kHz transducer were both mounted to a frame suspended from the water tank. The tissue clamped to a tissue holder was placed between the 788-kHz transducer and the 20-MHz transducer.

Before each treatment, the tissue was placed approximately 3-cm in front of the 20-MHz transducer. The 20-MHz transducer was pulsed and the tissue echo was received using a pulser-receiver (Panametric, Model PR 5072, Waltham, MA, USA). The tissue thickness was then calculated from the time of flight between the front and rear surface of tissue and the speed of sound in porcine atrial wall (1.519 mm/ μ s at 21°C measured in our lab). A figure demonstrating the measurement of the tissue thickness was given in Fig. 2 of our previous paper (Xu et al. 2004). At a 3-cm distance and with the 20-MHz transducer in pulse-echo mode, the -3dB beam widths of echo intensity are 0.39 mm from the simulation using an ultrasound field simulation software Field II (Technical University of Denmark, Lyngby, Denmark) and 0.61 mm from the actual measurement. The discrepancy between these values may be due to an effective element diameter smaller than 3 mm.

The speed of sound in the porcine atrial wall was measured using the method developed by Kuo et al. (1990), which derives the speed of sound in a specimen by using the reference of the speed of sound in the fluid medium in which the specimen is placed. For this measurement, the 20-MHz transducer was placed parallel to a flat stainless steel reflector in a water bath. A porcine atrial wall sample was positioned parallel to and between the transducer and the reflector. The speed of sound in the tissue is calculated using eqn (1):

$$c_m = [(T_w - T_m)/(t_2 - t_1) + 1]c_w$$

where c_w and c_m are the sound speeds in the water and porcine atrial wall tissue, respectively. T_m and T_w are the time of flight from the transducer to the reflector with and without the sample and back, respectively. t_1 and t_2 are the time of flight from the transducer to the front face and the rear face of the sample back, respectively. This method yields a sound speed of 1.519 ± 0.009 mm/ μ s (mean $\pm$ standard deviation) at $21 \pm 0.2^\circ\text{C}$ from 10 measurements, using a c_w of 1.485 mm/ μ s at 21°C (Del Grosso and Mader 1972). The edge of the echo reflected from the reflector was determined by maximizing the superimposed transmitted pulse and time-shifted reflected echo (Martin and Spinks 2001). No filtering or shaping was performed to define water-tissue interface because the impedance mismatch between the two was not strong enough to cause an unambiguous change. But using this method, even 10% error in $t_2 - t_1$ will result in less than $\pm 1\%$ error in c_m . For example, a $(t_2 - t_1)$ of 2.0 μ s, a $(T_w - T_m)$ of 0.046- μ s, and a c_w of 1.485 mm/ μ s yield c_m of 1.519 mm/ μ s. Adding $\pm 10\%$ error to $t_2 - t_1$ results in c_m of 1.516 mm/ μ s and 1.523 mm/ μ s using $(t_2 - t_1)$'s of 2.2- and 1.8- μ s, respectively, both of which result in less than 0.3% error in c_m . Typically, the actual measurement error of $t_2 - t_1$ should be smaller than 10%. Our measured value of sound speed in porcine wall (1.519 mm/ μ s at 21°C) is close to the speed of sound measured by Gong et al. (1989) in fresh porcine bulk heart tissue (1.572 mm/ μ s at 23°C).

During each ultrasound treatment, tissue was positioned at the focus of the 788-kHz transducer. The tissue holder was mounted and adjusted by a 3-axis positioning system to precisely locate three to four perforations in each sample separated by at least 1-cm. An angled sound absorber (40 Durometer, Sorbothane, Inc., OH, USA) was placed between the tissue and the 20-MHz transducer to reduce the sound reflection from the transducer and the side of the tank.

Output indices

Axial erosion rate, perforation area and volume erosion rate were chosen as the output indices, as described in the Introduction section. The axial erosion rate and the volume erosion rate were calculated when perforation occurs. When erosion occurs without perforation, the erosion area is often equal to or smaller than the focal beam width of the 20 MHz transducer. As a result, the 20-MHz transducer is unable to provide an accurate measurement of the on-axis thickness of tissue eroded.

Axial erosion rate is calculated using the tissue thickness eroded divided by the perforation time (expressed in $\mu\text{m/s}$) as tissue is positioned perpendicular to the primary beam axis. The tissue thickness at the focus of the 788-kHz transducer before erosion was measured by the 20-MHz transducer. The time to perforate the tissue was determined based on the extinction of the acoustic backscatter received by the 5-MHz transducer and visual observation detailed in another section. To calculate the perforation area, an elliptical form is assumed. The short diameter and long diameter of perforation were measured with a caliper (0.05 mm accuracy). The volume erosion rate is defined by volume of tissue eroded divided by the perforation time and estimated using the multiplication of the axial erosion rate and the perforation area (expressed in mm^3/s). For example, using 2 min to erode a 1.0-mm deep, 2.0-mm short diameter and 2.5-mm long diameter hole, the three output indices are calculated as follows: the axial erosion rate is $1.0 \text{ mm}/120 \text{ s} = 8.3 \mu\text{m/s}$; the perforation area is $\pi \times (2.0 \text{ mm}/2) \times (2.5 \text{ mm}/2) = 3.9 \text{ mm}^2$ and the volume erosion rate is $8.3 \mu\text{m/s} \times 3.9 \text{ mm}^2 = 32.4 \times 10^{-3} \text{ mm}^3/\text{s}^{-1}$.

Experimental parameters

The following parameters were used in all ultrasound exposures: a pulse duration (PD) of 3 cycles, a PRF of 20 kHz and a gas concentration range of 39% to 49%. This set of parameters was chosen because it achieved the highest axial erosion rate at I_{SPPA} of 9000 W/cm^2 and a gas concentration range of 40% to 55% in our previous studies (Xu et al. 2004). I_{SPPA} values of 1000, 2000, 3000, 3500, 4000, 5000, 7000 and 9000 W/cm^2 were tested. PD is defined as the number of cycles in the waveform at the output of the function generator. PD values (in μs) at the above I_{SPPA} values are presented in Table 1. The actual ultrasound waveforms with a PD of three cycles and I_{SPPA} values of 1000, 3000, 5000 and 9000 W/cm^2 delivered by the 788 kHz transducer recorded by a membrane hydrophone were shown in Fig. 6 of our previous work (Xu et al. 2005). When tested in the experiments, the acoustic parameters were randomized. The partial pressure of oxygen (PO_2) in air was used as our metric for gas concentration, and the PO_2 level was measured with YSI Dissolved Oxygen Instruments (YSI 5000, Yellow Springs, OH, USA).

RESULTS

A total of 75 ultrasound treatments were applied to 20 pieces of 1 to 3 mm thick porcine atrial wall, at $\sim 21^\circ\text{C}$. Tissue erosion was observed in 41 of 75 treatments. In these 41 treatments, tissue perforation was generated in 36 treatments. Here, tissue erosion is defined as obvious tissue removal that can be distinguished from the surrounding tissue by unaided visual observation. The sample size for each combination of parameters is from 8 to 12 as listed in Table 2.

Intensity thresholds of generating erosion and perforation

Probability of erosion and probability of perforation estimated at I_{SPPA} of 1000 to 9000 values W/cm^2 are reported in Table 2. Results show that erosion was never observed in any of the 24 treatments at $I_{SPPA} \leq 2000 W/cm^2$ ($Pr = 0$). At I_{SPPA} of $3000 W/cm^2$, erosion was observed in 4 of 11 treatments ($Pr = 0.364$). At $I_{SPPA} \geq 4000 W/cm^2$, erosion was generated in 32 of all 32 treatments ($Pr=1$). A logistic regression model was used to estimate the intensity threshold for erosion, yielding an estimated intensity threshold for erosion (defined by $Pr = 0.5$) at I_{SPPA} of $3220 W/cm^2$ (Fig. 2a).

Perforation was never observed in any of the 35 treatments at $I_{SPPA} \leq 3000 W/cm^2$ ($Pr = 0$). At I_{SPPA} of $3500 W/cm^2$, perforation was observed in 4 of 8 treatments ($Pr = 0.5$). At $I_{SPPA} \geq 4000 W/cm^2$, perforation was generated in 32 of all 32 treatments ($Pr=1$). Although the logistic regression model worked well for erosion, the model failed to fit the probability of perforation data attributable to inadequate data points of probability between 0 and 1. Fortunately, our raw data has provided an estimation of intensity threshold for perforation defined by $Pr = 0.5$ at I_{SPPA} of $3500 W/cm^2$ (Fig. 2b).

Axial erosion rate vs. intensity

As shown in Fig. 3, the axial erosion rate increased with higher intensity at $I_{SPPA} \leq 5000 W/cm^2$. The mean axial erosion rates were 4.82 , 8.01 and $15.44 \mu m/s$ at I_{SPPA} values of 3500 , 4000 and $5000 W/cm^2$, respectively ($p < 0.05$; t -test for each pair; Table 3 and Table 4). However, the axial erosion rate decreased as intensity increased at $I_{SPPA} \geq 5000 W/cm^2$ within the range of I_{SPPA} values tested. The mean axial erosion rates were 15.44 , 12.35 and $10.10 \mu m/s$ at I_{SPPA} values of 5000 , 7000 and $9000 W/cm^2$, respectively ($p < 0.05$; t -test for each pair; Table 3 and Table 4).

We also calculate the axial erosion rate using perforation time as cavitation active time (initiated time), indicated as the periods of time when the variable backscatter was observed between the onset of insonation and perforation. Taking into account only the time when ultrasound pulses are actively inducing cavitation and subsequently causing tissue erosion, such estimation of the axial erosion rate may provide information concerning the actual efficiency of ultrasound pulses during erosion. If calculated using the initiated time, the axial erosion rates at I_{SPPA} values of 4000 and $5000 W/cm^2$ were comparable. The axial erosion rate was $14.80 \pm 4.18 \mu m/s$ (mean $\pm$ standard deviation; Table 5) at I_{SPPA} of $4000 W/cm^2$ and $15.67 \pm 3.66 \mu m/s$ (mean $\pm$ standard deviation; Table 5) at I_{SPPA} of $5000 W/cm^2$ ($p = 0.73$; t -test of axial erosion rate for I_{SPPA} values at 4000 and $5000 W/cm^2$). This suggests that during erosion acoustic pulses at 4000 and $5000 W/cm^2$ are almost equally efficient. In comparison, axial erosion rates calculated using initiated time at $I_{SPPA} \geq 5000 W/cm^2$ still decreased with higher intensity.

Perforation area vs. intensity

The perforation area increased with increasing intensity (Fig. 4). For example, the mean values of perforation area were 0.61 , 1.30 and $5.97 mm^2$ at I_{SPPA} of 3500 , 5000 and $9000 W/cm^2$ ($p < 0.05$; t -test for each pair; Table 3, Table 4). Figure 5 demonstrates graphically the erosion and perforation in porcine atrial wall tissue produced by ultrasound pulses at I_{SPPA} values of 3000 , 3500 , 4000 , 5000 , 7000 and $9000 W/cm^2$, respectively. At I_{SPPA} of $3000 W/cm^2$, erosion was generated, although tissue was not perforated (Fig. 5a). At $I_{SPPA} \geq 3500 W/cm^2$, perforation was generated, and the perforation area was larger as intensity increased (Fig. 5b, c, d, e and f).

It is not surprising that the perforation area increases with higher intensity. With higher I_{SPPA} , the area where the pulse intensities are greater than the erosion threshold (I_{SPPA} of $\sim 3220 W/cm^2$) is larger and, therefore, exposing larger area of tissue to high intensity pulses and

producing larger perforations. If this is the major factor, the perforation area would be similar to the area of tissue exposed to pulses with intensity greater than the erosion threshold (beam cross-sectional area $>3220 \text{ W/cm}^2$). The beam cross-sectional area $>3220 \text{ W/cm}^2$ is marked as a square in Fig. 4 to compare with perforation area. The supposition holds true for the perforation area results at $I_{\text{SPPA}} \leq 5000 \text{ W/cm}^2$. However, at I_{SPPA} values of 7000 and 9000 W/cm^2 , the perforation area is significantly larger than the beam cross-sectional area $>3220 \text{ W/cm}^2$. To measure the beam cross-sectional area $>3220 \text{ W/cm}^2$, a radial symmetry of the beam cross-section was assumed for the 788-kHz circular aperture transducer. 1-D transverse beam plots in the focal plane were measured by a bilaminar-shielded PVDF membrane hydrophone (Model IP056, Marconi Research Center, Chelmsford, UK) to achieve the diameter of the beam cross-sectional area $>3220 \text{ W/cm}^2$. 1-D transverse beam plots of the 788 kHz transducer in the focal plane at I_{SPPA} values of 3000, 3500, 4000, 5000, 7000 and 9000 W/cm^2 are shown in Fig. 6.

Volume erosion rate vs. intensity

As shown in Fig. 7, the volume erosion rate increased with increasing intensity. For example, the mean volume erosion rates were 2.97×10^{-3} , 19.13×10^{-3} , $50.49 \times 10^{-3} \text{ mm}^3/\text{s}$ at I_{SPPA} values of 3500, 5000 and 9000 W/cm^2 , respectively ($p < 0.001$; t -test for each pair; Table 3 and Table 4).

DISCUSSION

The primary goals of this study were to estimate the intensity thresholds of ultrasound induced erosion in cardiac tissue (*e.g.*, atrial wall) and to investigate the effects of pulse intensity on erosion characterized by axial erosion rate, perforation area and volume erosion rate. Within a total of 8 min of ultrasound exposure, our results show that the estimated threshold I_{SPPA} (defined as $\text{Pr} = 0.5$) for generating erosion in atrial wall is 3220 W/cm^2 , and the estimated threshold I_{SPPA} (defined as $\text{Pr} = 0.5$) for generating perforation in atrial wall is 3500 W/cm^2 . Although intensity threshold for erosion and perforation may vary with different environments (*e.g.*, *in vivo*, different gas concentrations and viscosities) and acoustic parameters (*e.g.*, different PDs and PRFs) and needs further investigation, we believe that the intensity thresholds estimated here can serve as feasible reference points.

Results show that the axial erosion is faster with higher intensity at $I_{\text{SPPA}} \leq 5000 \text{ W/cm}^2$. However, at $I_{\text{SPPA}} \geq 5000 \text{ W/cm}^2$, axial erosion is slower with increasing intensity. This is contradictory to the common expectation that the axial erosion rate would increase with increasing I_{SPPA} because higher I_{SPPA} results in more propagated energy as the same PD and PRF were used in all the exposures. This decrease in axial erosion rate may be due to “shadowing” effects. Supposing each pulse creates a cloud of spatially and temporally changing microbubbles, the number of microbubbles and overall size of the cloud generated by each ultrasound pulse will most likely increase at higher intensity. If the intensity is too high and a dense bubble cloud forms (including perhaps large but ineffectual bubbles), “shadowing” may occur wherein ultrasound energy is scattered or absorbed before it reaches the target tissue.

The same principle may explain the results showing that the perforation area is significantly larger than the area where tissue is exposed to pulses with intensity greater than the erosion threshold at $I_{\text{SPPA}} \geq 7000 \text{ W/cm}^2$. Although shadowing in the central portion of the beam slows the erosion at high intensity, a large number of bubbles may increase local scattering and, therefore, increase peripheral erosion beyond the beam cross-sectional area, defined at $> 3220 \text{ W/cm}^2$.

The increase in the perforation area may roughly compensate for the reduction in the axial erosion rate, resulting in an overall trend toward an increasing volume erosion rate with increasing intensity. Additional investigations will be required to determine the origins of changes in axial erosion rates and area of erosion at high intensities.

We are aware that the gas concentration of 39% to 49% employed here is lower than the gas concentration in the human venous and arterial blood, which is approximately 90%. We used a lower gas concentration for the experiment for two reasons. First, the ultrasound induced erosion is qualitatively the same at different gas concentrations. However, the process is faster and the perforation boundary is sharper under lower gas concentration (Xu et al. 2004). Second, this ideal gas concentration in the blood could be achieved clinically by making patients breathe in only oxygen to reduce the nitrogen level. Since nitrogen constitutes approximately 80% of the gas in the blood and oxygen only constitutes 20%, it is possible to reduce the gas concentration to a level between approximately 20% and 90%, *in vivo*, to make the erosion process more efficient. In general, understanding of the physical basis for erosion is critical if we are to have a rational basis for optimization of the process *in vivo*. One advantage of *in vitro* experiments is the possibility of extending environmental parameters beyond what is possible *in vivo* and, thus, allowing a deeper understanding of the mechanisms of tissue interaction.

CONCLUSIONS

The intensity thresholds for generating erosion and perforation were investigated, yielding estimated threshold I_{SPPA} values (defined as $Pr = 0.5$) for generating erosion and perforation in atrial wall at 3220 W/cm² and 3500 W/cm², respectively. The axial erosion rate increases with higher intensity at $I_{SPPA} \leq 5000$ W/cm², however decreases with higher increasing at $I_{SPPA} \geq 5000$ W/cm². Both the perforation area and the volume erosion rate increase with increasing intensity.

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Fig. 1.

Experimental set-up. The 788 kHz transducer, the 5-MHz transducer and the 20-MHz transducer were positioned coaxially with each other. Connection A was used before the ultrasound treatment to measure the tissue thickness at the focus of the 788-kHz transducer. Connection B was used during the ultrasound treatment to receive the acoustic backscatter from the erosion zone. The sound absorber was placed between the tissue and the 20-MHz transducer during the ultrasound treatment to reduce the sound reflection, but removed for the measurement of tissue thickness.

Fig. 2.

(a) A logistic regression model (curve) was employed to fit the experimental data (filled circles), to estimate the intensity threshold for erosion. The estimated intensity threshold for erosion (defined as $Pr = 0.5$) is at I_{SPPA} of 3220 W/cm^2 . (b) The raw data provides an estimation of intensity threshold for perforation defined by $Pr = 0.5$ at I_{SPPA} of 3500 W/cm^2 .

Fig. 3.

Axial erosion rate is plotted vs. I_{SPPA} by mean and standard deviation values. The erosion rate is only calculated when perforation occurs. The probability of perforation is marked above each data point for the same set of parameters. I_{SPPA} of 1000, 2000, 3000, 3500, 4000, 5000, 7000 and 9000 W/cm² were tested. A PD of 3 cycles, a PRF of 20 kHz and a gas concentration range of 39% to 49% were used for all the ultrasound exposures. The sample size is listed in Table 2.

Fig. 4.

Perforation area was plotted vs. I_{SPPA} by mean and standard deviation values. The square indicates the beam cross-sectional area >3220 W/cm² for each I_{SPPA} value. The probability of perforation is marked above each data point for the same set of parameters. I_{SPPA} of 1000, 2000, 3000, 3500, 4000, 5000, 7000 and 9000 W/cm² were tested. A PD of 3 cycles, a PRF of 20 kHz and a gas concentration range of 39% to 49% were used for all the ultrasound exposures. The sample size is listed in Table 2.

Fig. 5.

Pictures of erosion and perforation in porcine atrial wall tissue generated by ultrasound pulses. (a), (b), (c), (d), (e) and (f) depict the tissue effects generated at I_{SPPA} values of 3000, 3500, 4000, 5000, 7000 and 9000 W/cm^2 , respectively. Ultrasound pulses with a PD of 3 cycles, PRF of 20 kHz and a gas concentration range of 39% to 49% were used. (a) At I_{SPPA} of 3000 W/cm^2 , erosion was generated, although tissue was not perforated. (b), (c), (d), (e) and (f) At $I_{SPPA} \geq 3500$ W/cm^2 , tissue perforation was generated and the perforation area increased with higher intensity.

Fig. 6.

1-D transverse beam plot of the 788 kHz transducer in the focal plane at I_{SPPA} values of 3000, 3500, 4000, 5000, 7000 and 9000 W/cm². Pulsed average intensity (I_{PA}) values are plotted along lateral axis. I_{PA} values were measured by integrating the pulse intensity and dividing the duration of the pulse defined in AIUM standards (AIUM). The horizontal line in each figure marks 3220 W/cm². The I_{PA} values are calculated from actual acoustic waveforms as recorded by a PVDF membrane hydrophone.

Fig. 7.

Volume erosion rate was plotted vs. I_{SPPA} by mean and standard deviation values. The probability of perforation is marked above each data point for the same set of parameters. I_{SPPA} of 1000, 2000, 3000, 3500, 4000, 5000, 7000 and 9000 W/cm² were tested. A PD of 3 cycles, a PRF of 20 kHz and a gas concentration range of 39% to 49% were used for all the ultrasound exposures. The sample size is listed in Table 2.

Table 1

Exposure parameters

I_{SPPA} (W/cm ²)	p^+ (MPa)	p^- (MPa)	Pulse duration (μ s)	Cross-sectional beam area (mm ²)
1000	7.8	5.2	3.77	5.06
2000	11.7	6.6	3.74	4.98
3000	15.2	7.5	3.71	4.81
3500	16.7	7.9	3.56	4.67
4000	18.3	8.3	3.41	4.57
5000	21.4	9.0	3.37	4.49
7000	27.3	10.1	3.32	4.30
9000	36	11.6	3.32	4.03

I_{SPPA} = spatial peak, pulse average intensity; p^+ = peak compressional pressure; p^- = peak rarefractional pressure.

Table 2
Number and probability of erosion and perforation at different I_{SPPA} values

I_{SPPA} (W/cm ²)	Erosion			Perforation		
	Number of treatments	Number eroded	Probability	Number perforated	Probability	Probability
1000	12	0	0	0	0	0
2000	12	0	0	0	0	0
3000	11	4	0.364	0	0	0
3500	8	5	0.625	4	0.5	0.5
4000	8	8	1	8	1	1
5000	8	8	1	8	1	1
7000	8	8	1	8	1	1
9000	8	8	1	8	1	1

Table 3

Mean and standard deviation (SD) values of axial erosion rate, perforation area and volume erosion rate

I_{SPPA} (W/cm²)	Axial erosion rate (μm/s)	Perforation area (mm²)	Volume erosion rate (10⁻³ mm³/s)
	Mean ± SD	Mean ± SD	Mean ± SD
3500	4.82 ± 1.50	0.61 ± 0.28	2.97 ± 1.59
4000	8.01 ± 2.70	0.74 ± 0.26	5.83 ± 2.90
5000	15.44 ± 3.82	1.30 ± 0.66	19.13 ± 8.35
7000	12.35 ± 2.48	3.45 ± 0.52	42.16 ± 8.08
9000	10.10 ± 1.17	5.97 ± 0.55	50.49 ± 8.91

Table 4

P values (t-test) of comparing axial erosion rate, perforation area and volume erosion rate at different I_{SPPA} pairs

I _{SPPA} pair	Axial erosion rate	Perforation area	Volume erosion rate
3500 and 4000	0.036	0.212	0.050
3500 and 5000	<0.001	0.037	<0.001
3500 and 7000	<0.001	<0.001	<0.001
3500 and 9000	<0.001	<0.001	<0.001
4000 and 5000	<0.001	0.026	0.001
4000 and 7000	0.002	<0.001	<0.001
4000 and 9000	0.340	<0.001	<0.001
5000 and 7000	0.038	<0.001	<0.001
5000 and 9000	<0.001	<0.001	<0.001
7000 and 9000	<0.001	<0.001	0.035

Table 5

Mean and standard deviation (SD) values of axial erosion rate, perforation area and volume erosion rate (calculated by initiated time)

I_{SPPA} W/cm²	Axial erosion rate (μm/s)	Perforation area (mm²)	Volume erosion rate (10⁻³ mm³/s)
	Mean ± SD	Mean ± SD	Mean ± SD
3500	8.36 ± 3.16	0.61 ± 0.28	5.15 ± 3.33
4000	14.80 ± 4.18	0.74 ± 0.26	10.67 ± 4.53
5000	15.67 ± 3.66	1.30 ± 0.66	19.48 ± 8.47
7000	12.35 ± 2.48	3.45 ± 0.52	42.16 ± 8.08
9000	10.10 ± 1.17	5.97 ± 0.55	50.46 ± 8.94