

Generation and measurement of acoustic streaming in limited space

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The aim of this work was to use the streaming phenomena to assist clot dissolution in blood vessel. Such treatment is called sonothrombolysis. Acoustic streaming is a steady flow in a fluid driven by the acoustic wave propagating in a lossy medium. It is a non-linear effect and it depends on ultrasound intensity, and sound absorption in the media.

The source of ultrasound was a flat piezoceramic disc generating long pulses at 1 MHz frequency and 0.2 W/cm^2 I_{TA} acoustical intensity. The streaming was generated in a vessel simulating free space, and next repeated in a multi-well cell culture plate, and in the limited space inside the 8 mm diameter silicone tube positioned perpendicular to the ultrasonic beam. The tube was filled with a mixture of water, glycerol, and starch, so with acoustic properties similar to blood. The streaming velocity was recorded either by the Siemens Acuson Antares ultrasonic scanner operating in the color Doppler mode at 8.9 MHz, or by the custom built 20 MHz pulsed Doppler flowmeter.

The results obtained using both systems were very similar. The recorded streaming velocities were 3.2 cm/s, 6.1 cm/s and 0.3 cm/s, respectively. They were an order of magnitude smaller than that calculated theoretically. However, the results obtained confirm existence of streaming, even very close to the source, in the limited space. This effect will be explored in in-vitro experiments of blood clot dissolution within the tube simulating a blood vessel.

Keywords: ultrasound, radiation force, blood, thrombolysis

1. Introduction

The acoustic waves propagated in liquid comply with the general hydrodynamics law. The Euler equation is valid in ideal, frictionless, liquids for plane waves with finite displacement amplitude propagating in Newtonian liquids with shear viscosity μ and volume viscosity $\xi = \lambda + 2/3\mu$, where λ is the Lamé constant. For a wave that only propagates in z direction the Navier-Stokes equation applies:

$$\rho \left(\frac{\partial v}{\partial t} + v \cdot \frac{\partial v}{\partial z} \right) = - \frac{\partial p}{\partial z} + \left(\xi + \frac{4}{3} \mu \right) \frac{\partial^2 v}{\partial z^2} \quad (1)$$

where ρ is the medium density, v is the particle velocity, and p is the pressure.

In a nonlinear medium, the impedance varies in time and the acoustic pressure is $p = \rho cv$, where $p = P - P_0$, P corresponds to instantaneous pressure, and P_0 to hydraulic ambient pressure. A constant component of the mean pressure value \bar{p} is equal to:

$$\bar{p} = \frac{1}{T} \int_0^T p dt = \Pi = \frac{1}{2} \rho_0 v_0^2 \quad (2)$$

where ρ_0 is the mean density of the medium, v_0 is the amplitude of the particle velocity and Π is the radiation pressure. In analogy to electric circuits, it may be said that a nonlinear medium acts as a pressure rectifier. Waves with finite amplitudes are accompanied by such events as radiation pressure and streaming.

For a linear, sinusoidal wave, the intensity I in the medium is equal to the energy E contained in a rectangular block with a unit base and height of c , where c is the wave propagation velocity in the medium:

$$I = E \cdot c = \frac{1}{2} \rho_0 c v_0^2 \quad (3)$$

The radiation pressure gradient causes constant streaming. Nyborg solved the Navier-Stokes equation using second order approximations [1]. This solution assumes that the particle velocity may be represented in the form of the sum $v = v_1 + v_2$, where v_1 is a first-order approximation to solution (2) for a steady-state v . The term v_2 introduces a time-independent correction for the total v and is related to the constant medium streaming.

For a plane wave the mass force (N/m^3) is called the acoustic radiation force F :

$$F = \frac{2\alpha I_{TA}}{c} \quad (4)$$

where I_{TA} is a time averaged intensity in a given space point and α is the absorption coefficient.

Tjøtta [2] introduced a simple formula in which the streaming velocity was proportional to the absorption coefficient α , the beam width $2a$ and the acoustic intensity I_{TA} as well as inversely proportional to the medium viscosity μ and the sound velocity in the medium c :

$$v_2 = \frac{8\alpha I_{TA} a^2}{\mu c} \quad (5)$$

After adopting relevant assumptions, we have obtained the correct solution to the Nyborg equation for a linear plane wave [3]:

$$v_{2z}(0,0,z) = \frac{\alpha I_{TA} a^2}{\mu c} \int_0^\infty e^{-2\alpha a s} \left[\sqrt{1 + \left(\frac{z-s}{a}\right)^2} - \sqrt{1 + \left(\frac{z+s}{a}\right)^2} + \left(\frac{z+s}{a}\right) - \left|\frac{z-s}{a} - s\right| \right] ds \quad (6)$$

where s is the integration variable on z axis.

The aim of the study was to evaluate the process of thrombolysis by the interaction of the drug and the ultrasonic wave. Alexandrov et al [4] have found that the process of thrombolysis can be accelerated by administration to a clot of a dissolving drug, and simultaneous insonifying of the occluded region with ultrasound. Synergic action of drugs and ultrasounds speeds up revascularization, reducing the time and lowering the dose, of the drug therapy compared with standard procedure [3]. The effectiveness of the combined drug-ultrasound method, called sonotrombolysis has been confirmed in the laboratory, and in clinical studies, by many researchers. However, the origin of the phenomenon of ultrasound wave interaction and the thrombolytic drug, remains unknown. Presumably, the mechanism supporting the accelerating process of clot dissolution effect, is the phenomenon related to the acoustic streaming microflow in the vicinity of the thrombus.

The aim of this work is to attempt streaming generation in limited space conditions - corresponding to *in vitro* and *in vivo* experiments - as well as an attempt to measure the flow velocity generated by streaming.

The example of the streaming generated, and velocity measured, by 32 MHz ultrasonic pulsed Doppler flowmeter is presented in Fig.1.

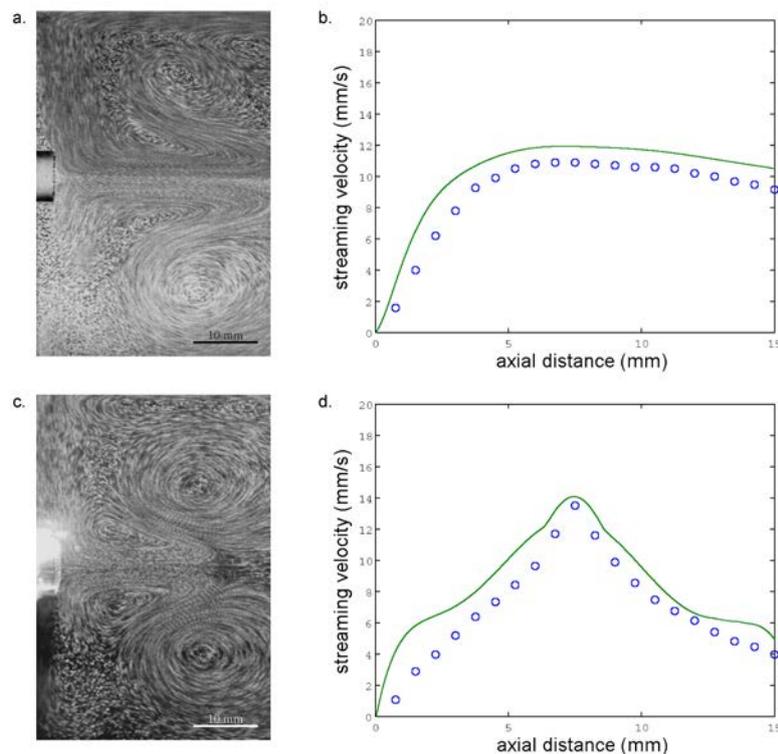


Fig. 1. Optical image of the acoustical streaming generated in the free field by the flat LiNb ultrasonic transducer 4 mm diameter, 32 MHz frequency and 11 mW/cm^2 of I_{TA} intensity, powered by a custom-built 32 MHz pulsed Doppler (a). Measured by pulsed Doppler (circles), and calculated from the equation (6) streaming velocity along the transducer axis (z axis) (b). Acoustical streaming generated by focused ultrasonic transducer, focus $f = 8 \text{ mm}$, other parameters as above. Optical image (c), measured and calculated [3] streaming velocity (d). Based on the experiment described in detail in [3].

2. Materials and Methods

A flat, 1 MHz, 25 mm diameter disc, transducer (Pz28 piezoceramics, Megitt, Denmark) was used for the streaming generation. The transducer was driven by an ENI 3100LA radio frequency amplifier (ENI, USA) controlled by a 33250A arbitrary function generator (Agilent, USA). Transducer generated 1000 cycle tone bursts repeated every 2.5 ms (0.4 duty cycle), as in our previous experiments [5]. The emitted acoustical power was measured using ultrasound power meter UPM-DT-1E (Ohmic Instruments, USA) and was equal to 1 W. This power corresponds to 0.2 W/cm^2 I_{TA} ultrasonic intensity. The streaming was generated in a large vessel, simulating open space, and in the limited space of the single well of the multiwell Cell Culture Plate, and inside the silicone tube. The blood-mimicking fluid, with acoustic properties similar to human blood ($\alpha = 1.15 \text{ Np/m}$, $\mu = 4.0 \cdot 10^{-3} \text{ Pa}\cdot\text{s}$, $c = 1570 \text{ m/s}$) was used in the experiments [6]. The liquid consisted of 79% distilled water, 20% glycerol and 1% of rice starch.

The measurements were conducted in two different setups. In the first, the streaming velocity was recorded using Siemens Acuson Antares (Siemens, USA) ultrasound scanner with linear array probe VF 13-5, operated in Color Doppler mode at 8.9 MHz. The 1 MHz streaming generating transducer was positioned on the bottom of the container at a distance of 45 mm from the imaging transducer. Walls of the container (2 l volume) were coated with silicone rubber absorbing ultrasound. The recordings of the streaming velocity maps are shown in Fig.2.

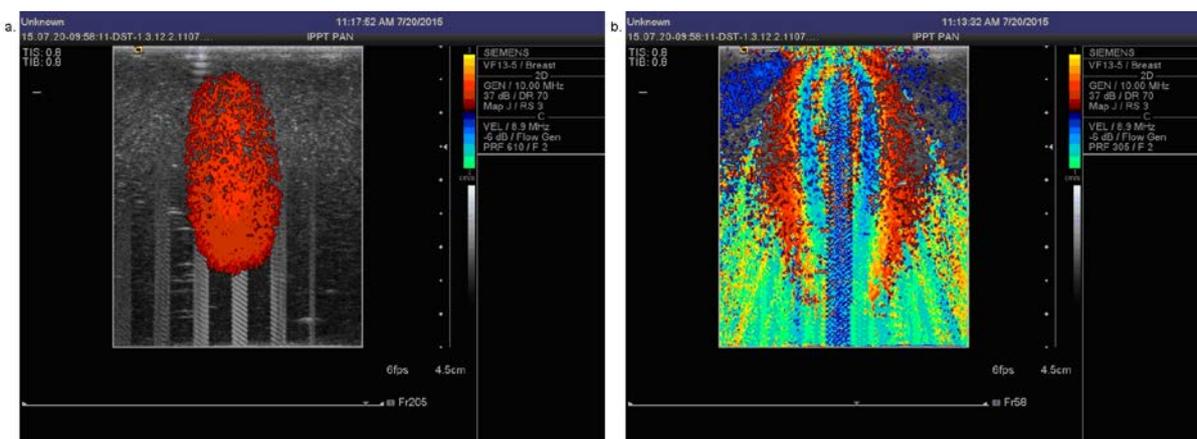


Fig. 2. 2D images of the streaming velocity generated by 1 MHz ultrasonic transducer positioned on the bottom of the vessel and radiating upward. (a) Streaming flow going upward (red), velocity range $\pm 3 \text{ cm/s}$. (b) Returned flow going into sides (blue) visible at velocity range reduced to $\pm 1 \text{ cm/s}$. Aliasing visible on the center of image.

In the second measurement setup the 20 MHz ultrasonic Doppler flowmeter, connected to the acquisition card in the PC was used (Fig.3). The system recorded flow in 128 gates and analyzed the velocity profile using the GASP software [7]. For the measurement, the 20 MHz 2 mm diameter flat (unfocused) Doppler receiving transducer was used.

The streaming was generated in three vessels. First, in a relatively large container with 2 l volume, simulating open space (Fig.4). The distance between the streaming and Doppler transducers was 24 mm.

The streaming experiment was carried out in the well of the 665-180 12 Well Cell Culture Plate (Cellstar, USA) (Fig.5) with 22 mm internal diameter, filled with the blood-mimicking fluid to 10 mm height, simulating in vitro conditions (Fig.6b). The total distance

between the transducers was 20 mm. And finally, the streaming was generated inside of the 8 mm internal diameter silicone tube (Fig.6), simulating in vivo conditions. In the tube was an opening, so Doppler transducer had direct contact with the blood-mimicking fluid (Fig.6b).



Fig. 3. Streaming measurement setup with the 20 MHz Doppler flowmeter connected to PC, using the GASP software (right). In the red circle, the 2 mm 20 MHz Doppler transducer was on top, silicone tube from Fig.6b was in the center (vessel removed), and 25 mm 1 MHz streaming generating transducer was at the bottom. The ENI 3100LA power amplifier and 33250A arbitrary function generator were on the left.

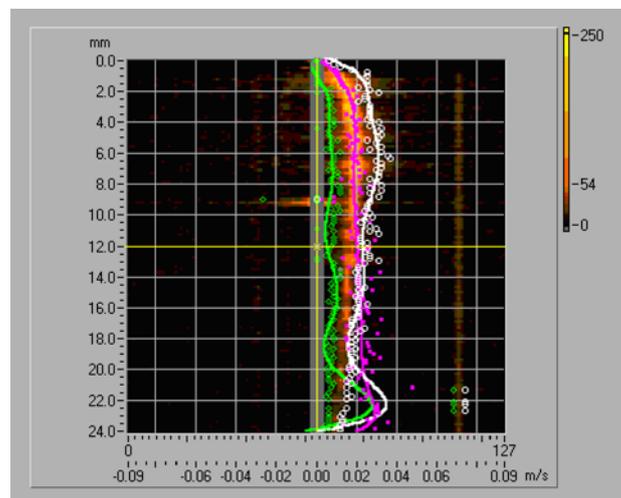


Fig. 4. Streaming velocity profile recorded in 2 l container. Doppler transducer was positioned on top (0 mm), and streaming generating transducer was at the bottom (24 mm). The blood-mimicking fluid was forced to flow upwards. The flow profiles calculated from the 128 Doppler gates were presented in white (maximum velocity), magenta (mean velocity), and green (minimum velocity). The maximum value of the mean velocity was 3.2 cm/s, recorded at 18 mm distance from the source – the streaming generating 1 MHz transducer.

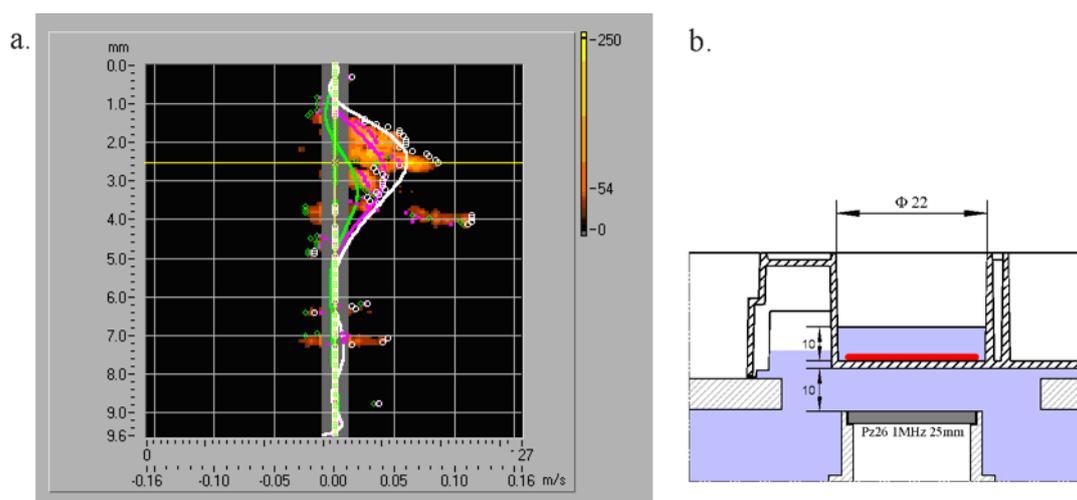


Fig. 5. Streaming velocity profile recorded in the single well of 12 Well Cell Culture Plate simulating *in vitro* conditions (a). The cross-section of a single well is presented in (b). Doppler transducer was positioned on top (0 mm) and streaming generating transducer was at the bottom (9.6 mm). Blood-mimicking fluid was forced to flow upwards. Flow profiles were presented in white (maximum velocity), magenta (mean velocity), and green (minimum velocity). The maximum value of the mean velocity was 6.1 cm/s, recorded at 7.5 mm distance from the bottom of the well.

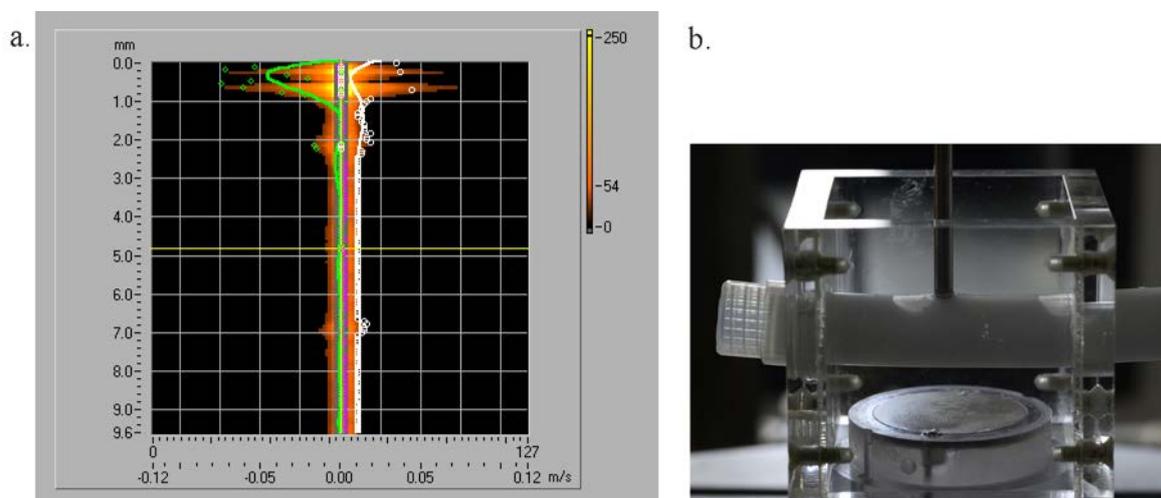


Fig. 6. Streaming velocity profile recorded inside the 8 mm internal diameter silicone tube (a), simulating *in vivo* conditions. In the tube was an opening, so Doppler transducer had direct contact with the blood-mimicking fluid (b). Total distance between transducers was 19 mm. Flow profiles were presented in white (maximum velocity), magenta (mean velocity), and green (minimum velocity). The maximum value of the mean velocity was 3.0 cm/s, recorded at a 6.5 mm distance from the opposite wall of the silicon tube. The acoustic intensity was raised to 2 W/cm^2 .

3. Results

The streaming velocity, calculated from the equation (5) for the boundary conditions: $\alpha = 1.15 \text{ Np/m}$, $I_{TA} = 0.2 \text{ W/cm}^2$, $a = 1.25 \text{ cm}$, $\mu = 0.004 \text{ Pa}\cdot\text{s}$ and $c = 1570 \text{ m/s}$ is equal to 46cm/s. However, in our *in vivo* simulating experiment, in the limited space inside the 8 mm

diameter tube ($a = 0.4$ cm), the estimated streaming velocity was much lower, being equal to 4.7 cm/s only. The maximum streaming velocity forced by a flat 1 MHz transducer, measured with 20 MHz Doppler, was 3.2 cm/s at a distance of 18mm from the source (Fig.4). The measurement executed under the same conditions, but using an ultrasound scanner, recorded a velocity of around 3 cm/s (Fig.2). The color scale of scanner did not allow accurate measurement of velocity, but only its estimation. In the limited space, in the single well of 12 Well Cell Culture Plate, simulating in vitro conditions, the maximum streaming velocity was 6.1 cm/s, recorded at 7.5 mm distance from the bottom of the well (Fig.5). In the simulated in vivo conditions, inside the 8 mm internal diameter silicone tube, the maximum streaming velocity was 3 cm/s, recorded at 6.5 mm distance from the opposite wall of the tube (Fig.6), at acoustic intensity increased to 2 W/cm^2 . In accordance with formula (5), the streaming velocity depends linearly on the intensity, so for the 0.2 W/cm^2 intensity, the streaming velocity inside the silicon tube would be 0.3 cm/s.

4. Conclusions

In the three measurement setups, the recorded streaming velocities were 3.2 cm/s, 6.1cm/s and 0.3 cm/s. They were an order of magnitude lower than that calculated from equation (5). Presumable cause of the low streaming velocity was limited space, even in a 2 l volume container and 45 mm distance between the transducers. According to equation (6), the streaming velocity was zero at the source (transmitter surface or flow-stopping baffle), and increasing with distance from the source. Such was the case in the 2 l container, and inside the silicone tube. In the case of the multiple-well cell culture plate, the acoustic wave reflected from the water-air boundary, and returned downwards to the streaming generating transducer. Then the streaming velocity reached a maximum at a distance of 7.5 mm from the bottom of the well, and was rapidly reduced near the water-air boundary.

However, the results obtained confirm that developing of the streaming phenomena was possible, even very close to the source, in limited space. This effect will be explored in in-vitro experiments of blood clot dissolution within the tube, simulating a blood vessel. The results obtained using both systems were very similar.

Acknowledgments

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