Feasibility study for removing calcified material using a planar rectangular ultrasound transducer

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Abstract

Background The aim of the proposed study was to conduct a feasibility study using a flat rectangular (3 mm × 10 mm) MRI compatible transducer operating at 5.3 MHz for destroying calcified material in an in vitro model. The proposed method can be used in the future for treating atherosclerosis plaques of the coronary, carotid or peripheral arteries.

Methods The system was tested initially on calcium rods. Another test was performed in a hydroxyapatite–polylactide model.

Results A parametric study was performed where the mass of calcified material removed was studied as a function of intensity, pulse repetition frequency (PRF), duty factor (DF) and presence of bubbles.

Conclusions The amount of calcified material removed is directly related to the intensity, PRF and DF. It was found that the presence of bubbles accelerates the removal of calcified material. In order to ensure that pure mechanical mode ultrasound was used, the protocols were designed so that the temperature does not exceed 1 °C.

Keywords Ultrasound · Atherosclerotic · Plaque · Rabbit

Sommario

Scopo Scopo dello studio è stato quello di valutare la fattibilità della distruzione di materiale calcifico, in un modello in vitro, con un trasduttore da 5.3 MHz., rettangolare, piatto (3 mm x 10 mm), compatibile con la MRI. Il metodo proposto potrebbe essere utilizzato in futuro per il trattamento di placche aterosclerose di coronarie, carotidi o arterie periferiche.

Materiale e metodi Il sistema è stato testato inizialmente su barre di calcio. Un altro test è stato eseguito su un modello di idrossiapatite-polylactide (HA- / PLA). E' stato eseguito uno studio parametrico in cui la massa di materiale calcificato rimossa è stata studiata in funzione di intensità, frequenza di ripetizione degli impulsi (PRF), fattore di utilizzo (DF) e presenza di bolle.

Risultati La quantità di materiale calcificato rimossa è direttamente legato a intensità, PRF e DF. Si è riscontrato che la presenza di bolle accelera l'asportazione di materiale calcificato.

Conclusioni Questa tecnologia potrebbe essere utilizzata in futuro nella pratica clinica quotidiana principalmente per il trattamento di placche calcificate della carotide.

Introduction

Atherosclerosis also known as arteriosclerotic vascular disease (ASVD) is a condition in which fatty material collects along the walls of arteries. This fatty material thickens, hardens (forms calcium deposits), and may eventually block the arteries [1]. The plaque is composed of distinctly morphological features including a fibrous cap comprised of smooth muscle cells and fibrotic tissue, and lipid core containing fat-laden macrophages and

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extracellular lipids [1]. In the advanced stage, atherosclerotic plaque contains large amounts of calcium salt or hydroxyapatite (HA) [2], which significantly increases the size of the plaque. Histology studies have also led to the recognition that plaque structure influences the risk of plaque rupture. Specifically, a plaque with a thin fibrous cap and a large lipid core is more prone to rupture [3].

Lifestyle changes, such as eating a healthy diet and exercising, are often the best treatment for atherosclerosis. But sometimes, medication or surgical procedures may be recommended as well [4]. Over the years researchers were involved in clinical research to develop medication treatments and approaches to reduce the risk of heart attack and other medical problems caused by atherosclerosis (for example Angiotensin II receptor blockers (ARBs) [5], Calcium Channel Blockers [5], Cholesterol Medications [6], and Diuretics [7]).

Atherosclerosis treatment may require special surgical procedures such as Balloon Angioplasty [8–11], Balloon Angioplasty and Stenting [12, 13], Cutting Balloon [14–19], Atherectomy [20, 21], and Surgical Bypass [22–27] to open an artery and improve blood flow. Endarterectomy is the main treatment for the carotid artery [28–30].

A group in the University of Minnesota [31] recently developed a new HIFU technology that performs noninvasive, real-time ultrasonic imaging and localized treatment using thermal HIFU. A HIFU exposure was applied to a very small, localized treatment area, usually as small as a grain of rice.

In this paper, pulsed ultrasound was utilized for removing calcified material. In order to ensure that non-thermal ultrasound was used, the protocols were designed so that the temperature does not exceed 1 °C. Hydroxyapatite-poly(lactide) (HA-PLA) was investigated as a possible material for atherosclerotic plaque [32]. Recently an ablation experiment was performed on an HA-PLA composite using a high-speed rotational ablation tool [32]. In this particular research, a rotational atherectomy technique was used in which a small grinder is inserted into the coronary arteries to ablate plaque and increase blood flow to the heart. However, to our knowledge, no prior studies have been reported on ablation of calcified material using mechanical mode HIFU.

This paper describes a feasibility study that investigated the effectiveness of a therapeutic protocol in removing calcified material using pulsed ultrasound with a planar unfocused transducer operating at 5.3 MHz. In order to achieve this, the effect of various parameters such as intensity, pulse repetition frequency (PRF), duty factor (DF), and the presence of bubbles were explored. Thus, in vitro experiments were conducted using mainly cylindrical chalks and HA-PLA composites.

Materials and methods

Experimental setup

Figure 1 shows the schematic diagram of the high intensity ultrasound system. The samples under sonication were placed in an acrylic tank containing filtered, degassed, and de-ionized water. The apparatus is divided into two primary systems: (1) high intensity ultrasound generation, and (2) passive cavitation detection (a hydrophone was employed to monitor cavitation activity). A 5.3 MHz sinusoidal input was generated by a function generator (Agilent 33120 15 MHz Function/Arbitrary Waveform Generator, Englewood, CO, USA). The electrical signal is amplified by an RF amplifier (500 W, AR, Souderton, PA, USA), and then delivered through an impedance matching network designed exclusively for this particular transducer.

The active size of the transducer is 3 mm × 10 mm. The transducer material is P762-type PZT piezoceramic (Quartz & Silice, Nemours, France) with air backing, operating at 5.3 MHz. Figure 2a shows the transducer holder manufactured using Acrylonitrile Butadiene Styrene (ABS). The ABS parts of the transducer were designed using Computer-Aided Design (CAD) software (Microstation V8, Bentley Systems, Inc.). The files were then exported to Computer-Aided Manufacturing (CAM) software (Insight V. 6.4.1, Stratasys Inc.). The files were sent to a 3D printer (FDM400, Stratasys, 7665 Commerce Way, Eden Prairie, Minnesota, 55344, USA) for production. This structure contains two inlets for transducer cooling and two inlets for the transducer wiring. Figure 2b shows the drawing of the transducer holder indicating the water inlets and wiring inlets. Figure 2c shows the final assembly of the transducer inside the plastic holder. Figure 2d shows the pressure field for this transducer with 6 W applied using the simulation model proposed by Lafon et al. [33]. Because in future clinical trials the transducer will be incorporated in a catheter that is guided through arteries (1–3 mm wide), the transducer element must be as compact as possible. If a spherically focused technology will be used, then the size of the transducer will increase and therefore it will not fit in the catheter. Since the catheter will be inserted in the body, after the treatment, then the catheter is not reusable (i.e., it is considered consumable). Thus, a spherically focused technology has the additional disadvantage that will increase the cost substantially. Besides as it will be seen in the results section, a flat transducer produces enough plaque destruction.

RF connections were made via a miniaturized 10 m long, 50 Ω coaxial cable with a 0.9-mm outer diameter. The outer ground conductor was connected to the external face of the transducer. The inner conductor reached the

Fig. 1 Diagram of the pulsed high intensity ultrasound system which includes a generator/amplifier, a temperature reader, and a passive cavitation detector

Fig. 2 **a** Transducer holder manufactured using ABS. This structure contains two inlets for transducer cooler and two inlets for the transducer wires. **b** Drawing of the transducer holder indicating the

water inlets and wiring inlets. **c** Final assembly of the transducer inside the plastic holder. **d** Simulated pressure field for this transducer with 6 W applied

internal face of the transducer through the lumen of the tube. To limit energy loss during transmission of the electric signal, a connection with a capacitor–inductor network was included to match the transducer. Using the acoustic balance technique 0, the electroacoustic efficiency

of the applicator was measured (55 % at 5.3 MHz). The external face of the transducer was cooled by a continuous flow of degassed water circulating within of the transducer. The cooling water serves as coupling medium between the transducer and the ablated tissue. The water cooling circuit

was maintained at 15 °C and was driven by a Masterflex peristaltic pump (Cole Parmer Instrument Co., Chicago, IL) at a flow of 0.15 L/min.

Sonication parameters

The Spatial Average intensity was estimated, by dividing the power with the area of the transducer. The PRF was varied from 5 to 100 Hz. The duty factor varied from 5 to 40 %. The sonication duration was set to 30 min. The bubbles from the cylindrical chalk were removed by immersing the chalks in the water container of the degassing system for 1 h. With this method, the voids within the chalk are filled with degassed water and thus the bubble influence is minimized. If the effect of bubbles was needed, then the chalk samples were not immersed in the degassed water bath, and therefore, the bubbles in the voids of the chalk are preserved.

Cavitation detection

The cavitation activity was monitored using a hydrophone (Specialty Eng. Associates, California, USA) which is placed perpendicularly to the transducer. The signal from the hydrophone was fed to a custom made amplifier (20× amplifications), and was high-pass filtered using custom made filter. Fast Fourier Transform (FFT) spectra of the acoustic emission signals were acquired using a PC-card (Gage, Lockport, USA). The hydrophone is aligned perpendicular to the sample under investigation.

In vitro experiments

Twenty in vitro experiments were carried out initially in cylindrical chalks with dimensions of 80 mm in length and 9 mm in diameter. The efficacy of pulsed ultrasound was also investigated in vitro during experiments on artificial materials that have elastic moduli similar to those of calcified plaque, such as HA–PLA composite. HA–PLA was used in this research because of the high HA content of calcified plaque. The PLA (4032D, NatureWorks, Minnetonka, MN, USA), 40 wt%, was dissolved in Dimethyl-formamide (A.J. Vouros Ltd, Nicosia, Cyprus) at 60 °C, and then HA powder (Medisell, Nicosia, Cyprus), 60 wt%, was dispersed in the mechanical stirring for 1 h and sonication for 20 min. Then the solution was poured into a mold and cured for 3 days at 40 °C.

Particle size distribution

The particle size distribution after a specific sonication protocol was measured using a laser diffraction particle size analyzer (SALD-2300, SHIMADZU CORPORATION,

Kyoto, Japan). At the end of the experiment, the water of the container was left in the sun until the water evaporated. Thus the debris remained in the bottom of the container and was collected.

Temperature measurement

A data acquisition board (6251 DAQ, National Instruments, Texas, USA) was used to measure the temperature in the chalk. An analog input of the data acquisition board was used to capture the temperature. An Omega (M2813-1205, OMEGA Engineering, INC. Stamford, Connecticut, USA) voltage to temperature converter was used to measure temperature using a software written in MatLab (The Mathworks Inc., Natick, MA). A thermocouple (Omega engineering) was placed inside the chalk in order to measure temperature elevation. The size of the thermocouple was chosen to be 50 µm, so that the interaction with the ultrasound field is minimized.

Results

First, the effect of the intensity on the erosion of cylindrical chalk was investigated. Various chalks were exposed to different spatial average, temporal average (SATA) intensity varying from 5.5 to 20 W/cm², with the DF and PRF kept constant to 10 % and 100 Hz, respectively. Figure 3a shows the picture of the cavities generated on the chalk (degassed) for two different SATA intensities (5.5 and 11 W/cm²) for 30 min. We believe that erosion appeared mostly in areas with trapped bubbles. In areas, with no bubbles, the effect of erosion was minimal. Figure 3b shows the weight loss of degassed chalk versus intensity (SATA) with 10 % DF and 100 Hz PRF. At SATA intensity above 5.5 W/cm², the temperature increases beyond 1 °C. Figure 3c shows the spectral power measured by the cavitation detector during the exposure with SATA intensity of 5.5 W/cm², 10 % DF and 100 Hz PRF. The sub-harmonic emission indicated the appearance of stable cavitation. These harmonic emissions appeared, during all the exposures evaluated in Fig. 3b. Although the chalks were degassed, the cavitation detector showed cavitation activity. It seems even if the chalks are degassed, still some bubbles remain in the chalks. The size of the removed calcified material by the ultrasonic transducer in a plane parallel to the transducer face is slightly less (8.5 mm × 3 mm) than the transducer area (10 mm × 3 mm).

The next step was to investigate the effect of the PRF on the erosion rate of the cylindrical chalk (degassed). Four chalks were exposed to SATA intensity of 5.5 W/cm² for 30 min, varying the PRF from 5 to 80 Hz with the DF kept constant to 10 %. Figure 4a shows the weight loss at

Fig. 3 **a** Picture of cavities generated on chalk at two different SATA intensities (5.5 and 11 W/cm²) for 30 min. DF and PRF were kept constant to 10 % and 100 Hz, respectively. **b** Weight loss as a function of SATA intensity ($f = 5.3$ MHz, DF = 10 %, PRF = 100 Hz), and **c** Spectral power measured by the cavitation detector during the exposure with SATA intensity of 5.5 W/cm², 10 % DF and 100 Hz PRF

different PRF for intensity (SATA) of 5.5 W/cm² and DF of 10 %. During these experiments, the temperature did not exceed 1 °C.

The next step was to investigate the effect of the DF on erosion of the chalk. The chalk was exposed to a spatial average, pulse average (SAPA) intensity of 55 W/cm² for 30 min, with varying DF from 5 to 40 % (while PRF was kept constant to 100 Hz (Fig. 4b). With DF above 20 % the temperature exceeded 1 °C indicating, that the exposure is no longer in mechanical mode. With a DF of 10 % (SATA

intensity is 5.5 W/cm²) the temperature elevation is approximately 1 °C, and increases linearly to 4 °C with a DF of 40 %. This temperature increase does not result in drastic thermal effects, that justify the increased mass reduction. Therefore, the increased mass reduction is attributed to cavitation, since with increased DF, the probability of the occurrence of cavitation possibly increases.

The effect of the presence of bubbles or not on the erosion of the chalk is shown in Fig. 5 for DF of 20 %,

Fig. 4 **a** Weight loss vs. PRF. ($f = 5.3$ MHz, $I_{\text{SATA}} = 5.5$ W/cm², DF = 10 %, 30 min), **b** Variation of weight loss of each chalk versus DF ($f = 5.3$ MHz, $I_{\text{SATA}} = 5.5$ W/cm² PRF = 100 Hz)

Fig. 5 Variation of weight loss of chalk without bubbles and with bubbles. ($f = 5.3$ MHz, $I_{\text{SATA}} = 5.5$ W/cm², for 30 min, PRF = 100 Hz, DF = 20 %)

PRF = 100 Hz and intensity (SATA) of 5.5 W/cm² for 30 min. With the presence of bubbles, the cavitation activity was increased as recorded by the cavitation detector.

In another experiment, the goal was to visualize the chalk's debris after pulsed ultrasound exposure. A chalk

was exposed to intensity (SATA) of 10 W/cm² for 30 min, with DF of 10 % and PRF of 100 Hz. Particles of mean diameter of 35 nm (standard deviation = 19 nm) were measured.

HA–PLA composite was exposed to the intensity (SATA) of 11 W/cm² for 30 min, with the DF and PRF kept at 10 % and 100 Hz, respectively. Figure 6a shows the HA–PLA before the sonication and Fig. 6b shows the erosion of HA–PLA after this ultrasonic exposure. With this transducer and protocol we were able to remove HA–PLA material up to a depth of 3 mm (1664 mg) in just 30 min.

Conclusions

This paper includes a feasibility study that investigates the effectiveness of pulsed ultrasound in removing calcified material. A previous study [33] utilized thermal HIFU which might cause damage to the artery. Using mechanical mode ultrasound, avoids thermal damage to the artery, and yet it is possible to remove efficiently calcified plaque. This feasibility study includes a parametric study of the effect of intensity, PRF, DF, and the presence amount of bubbles. Various in vitro experiments were carried out, in chalk pieces and HA–PLA composite. The protocols used resulted into temperatures less than 1 °C (safe temperature). It was demonstrated in a set of experiments, that if the DF is increased, then the safe temperature is exceeded. Another parameter that increases the temperature is the intensity. In these experiments, the intensity used was carefully chosen, and, therefore did not cause any temperature elevation above 1 °C.

The removed calcified material as expected increases with the intensity, PRF, and DF. It was found that the removal of calcified material increases with the presence of bubbles. This may be attributed to the effect of cavitation. During the application of any exposure, sub-harmonic emissions were detected by the cavitation detector indicating the presence of cavitation. Even when the chalk material was degassed, stable cavitation activity was recorded due to the synergy with bubbles trapped inside the chalk. Perhaps, the non-degassed chalk possibly includes more bubbles and, therefore the mass removal increases drastically compared to the degassed chalk.

Very promising results were obtained in carrying out experiments on HA–PLA composites using this planar transducer. With this transducer and protocol we were able to remove HA–PLA material up to a depth of 3 mm in just 30 min. This type of technology looks promising for the removal of atherosclerotic plaque in humans, provided that the dissolved material from the plaque is collected so that it does not flow from the blood stream to other arteries, thus

Fig. 6 **a** HA–PLA composite before sonication, and **b** HA–PLA composite after ablation ($f = 5.3$ MHz, $I_{\text{SATA}} = 11$ W/cm², for 30 min, DF = 10 %, PRF = 100 Hz)

causing the blockage of arteries. Although we have shown that the particle size of the removed material is very small, care should be taken to collect this material. For example in studies involving atherectomy [34, 35] suction mechanism was used to collect the removed particles. Such suction technology can also be incorporated with this ultrasound technology to remove the residual particles. Another possible complication of this technology is possible endothelial damage due to the ultrasonic pressure applied under microbubble flow. The effect of pressure on the endothelium which is well described by Li et al. [36], needs to be controlled. Therefore, further studies are needed that determines the safe acoustic pressure that can be used.

It is possible that if the particle size is too small, then there is no need to collect the residual particles and, therefore, the deployment of ultrasound technology would be more feasible. Yet clinical studies need to be done in order to reveal how small this residual particle must be. This specific device with this size can be used probably in peripheral arteries or in the carotid. Special design of the device needs to be done so as not to block the artery. For the application in the cardiac arteries, the device must be scaled down to possibly 1 mm.

The in vitro test was performed to derive an ultrasonic protocol that completely avoids thermal effects. It seems that the presence of bubbles in the chalk is responsible for the mass removal due to stable cavitation.

This technology can be used in the future for clinical trials primarily to treat calcified plaques in the carotid.

Unstable plaques in the carotid are a major source of plaques that can reach the brain and cause stroke [37]. The device can be attached to a catheter of appropriate size and the catheter can be guided intravenously to the carotid for ultrasonic treatment. Care will be taken to avoid the escape of debris reaching the brain, thus causing stroke. This technology can also be used for other stenotic conditions such as the femoral artery especially for superficial targets. Currently, this condition is under clinical evaluation using other technologies such as directional atherectomy [37].

This technology potentially can be used for the treatment of intracranial atherosclerosis [38] diseases that may also cause stroke. The current technology has to be scaled down to smaller dimensions so that it can reach vessels in the brain using microcatheters. Another potential application is to treat plaques that rupture from the carotid and reach the brain [39]. This can be done intracranially using a small transducer attached to a microcatheter or by focused ultrasound transducer transcranially.

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Compliance with ethical standards

Conflict of interest C. Damianou, A. Couppis declare that they have no conflict of interest.

Ethical standard This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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