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Evaluation of a small flat rectangular therapeutic ultrasonic transducer intended for intravascular use

N. Papadopoulos [a], G. Menikou [a], M. Yiannakou [b], C. Yiallouras [b,c], K. Ioannides [d], C. Damianou [b,*]

[a] Department of Bioengineering, City University, London, UK
[b] Electrical Engineering Department, Cyprus University of Technology, Cyprus
[c] R&D, MEDSONIC LTD, Limassol, Cyprus
[d] Radiology, Ygia Polyclinic, Limassol, Cyprus

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ABSTRACT

Background: The aim of the proposed study was to evaluate the performance of a flat rectangular (2×10 mm^2) transducer operating at 4 MHz. The intended application of this transducer is intravascular treatment of thrombosis and atherosclerosis.
Methods: The transducer's thermal capabilities were tested in two different gel phantoms. MR thermometry was used to demonstrate the thermal capabilities of this type of transducer.
Results: Temperature measurements demonstrated that this simple and small transducer adequately produced high temperatures, which can be utilized for therapeutic purposes. These high temperatures were confirmed using thermocouple and MR measurements. Pulsed ultrasound in combination with thrombolytic drugs and microbubbles was utilized to eliminate porcine thrombi.
Conclusions: The proposed transducer has the potentials to treat atherosclerotic lesions using the thermal properties of ultrasound, since high temperatures can be achieved in less than 5 s. The results revealed that the destruction of thrombi using pulsed ultrasound requires long exposure time and high microbubble dosage.

1. Introduction

Atherosclerosis is a condition in which fatty material collects along the walls of arteries. This fatty material thickens and may eventually block the arteries [1]. Atherosclerosis treatment may require special surgical procedures such as Balloon Angioplasty and Stenting [2,3], Cutting Balloon [4], Atherectomy [5,6] and Surgical Bypass [7], to open an artery and improve blood flow.

Another technological modality with therapeutic capabilities is ultrasound. Therapeutic ultrasound was clinically utilized on prostate carcinoma utilizing ultrasound imaging [8–10]. The two dominant clinically available systems using transrectal high intensity focused ultrasound (HIFU) are Ablatherm (EDAP-TMS, Lyon, France) and Sonablate 500 (Focal Surgery, Milpitas, CA now SonaCare Medical, Charlotte, North Carolina). In the nineties, therapeutic ultrasound was combined with magnetic resonance imaging (MRI) guidance [11], which offers monitoring of the thermal effects of ultrasound. The first clinical success that employs therapeutic ultrasound with MRI was the technology introduced by the Israeli company InSightec [12]. This technology resulted in the first commercial system for the treatment of uterine fibroids, which received approval by the Food and Drug Administration (FDA) in 2004. This system is incorporated in the table of a General Electric MRI scanner.

HIFU has an active role for thrombolysis. One of the first clinical studies using sonothrombolysis was the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial US and Systemic tissue plasminogen activator (rt-PA) (CLOTBUST) trial [13]. The purpose of CLOBUST trial was to evaluate the effects of Transcranial Doppler (TCD) ultrasonography in combination with rt-PA, on thrombolysis. Study results have shown that the combination of rt-PA with 2 h of continuous TCD increased recanalization rates compared with rt-PA alone.

In another clinical trial, called the TRanscranial low-frequency US-Mediated thrombolysis in Brain Ischemia (TRUMBI), the aim was to treat stroke patients with either rt-PA alone or with rt-PA in conjunction with 90 min of low frequency ultrasound (300 kHz). However, the TRUMBI trial was stopped prematurely due to very high rate of symptomatic intracranial haemorrhage in stroke patients [14]. Since then, clinical trials are restricted to

* Corresponding author.
E-mail address: cdamianou@cytanet.com.cy (C. Damianou).

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the use of high frequencies (MHz range) and low intensities, similar to that used for diagnostic purposes.

The use of small transducers has been reported in several studies. Diederich et al. [15] utilized 3.5 mm tubular transducers operating at 7.5 MHz for ablating prostate tissue using a transurethral approach. The same concept was applied by the group of Chopra [16], also ablating prostate tissue using a transurethral approach with a $4 \times 20\ mm^2$ planar MRI-compatible transducer. Couppis et al. [17] use rectangular flat transducer to ablate heart tissue under MRI guidance. In another study [18], a planar MRI compatible unfocussed ultrasound transducer of $15 \times 8\ mm^2$ in size was developed with the intend to treat esophageal cancer. The active part of the transducer was covered by a latex balloon, and made contact with the target during treatment. When the transducer was rotated on its axis, sector-based or cylindrical volumes of necrosis could be produced, matching the shape of esophageal tumors.

In this paper a flat rectangular ($2 \times 10\ mm^2$), MRI compatible transducer, operating at a frequency of 4 MHz was used. The aim was to evaluate the thermal and mechanical capabilities of such transducer. Two different gel phantoms were used to test the efficacy of this transducer.

2. Materials and methods

2.1. Transducer design

The active size of the transducer was $2 \times 10\ mm^2$. The transducer material was made out of P762-type piezoceramic (Ferroperm, Kvistgaard, Denmark), operating at 4 MHz (±5%). The thickness of the transducer was 0.5 mm. A backing material (epoxy) of 2 mm thickness was used. No matching layer was used in front of the transducer. The cabling of the transducer was soldered for 3 s using lead-containing solder at 250 °C. This soldering temperature ensured that no damage was caused to the piezoelectric material. The transducer's impedance was matched to 50 Ω. The efficiency of this transducer was 30%. Because of high temperatures produced in the transducer element (close to 100 °C), a cooling system was used that circulates cold water (15 °C) on the transducer's face using a peristaltic pump (Cole Parmer, 7518-40, Vernon Hills, IL, USA). Fig. 1A shows the design details of the planar transducer. Fig. 1B shows the transducer holder manufactured using Acrylonitrile Butadiene Styrene (ABS). The ABS parts of the transducer holder were produced by a 3D printer (FDM400, Stratasys, 7665 Commerce Way, Eden Prairie, Minnesota, 55344, USA). This internal structure includes a cavity to accommodate the 1 mm thick coaxial cable. In future clinical trials the transducer will be incorporated in a catheter which will be inserted intravascular (1–3 mm wide), and therefore the transducer element must be as compact as possible.

2.2. Gel phantom for lesion visualization

Experiments in gel phantom were carried out in order to visualize the lesions created by this transducer. A commercial polyacrylamide gel (ONDA Corporation, Sunnyvale, CA, USA) was used. This expensive commercial gel, is the only that can reveal the appearance of thermal lesions. The gel was placed in a tank with degassed water. The transducer was placed on top of the gel phantom, thus providing good acoustical coupling between the gel and transducer.

2.3. Agar/silica/milk phantom for temperature measurements

In order to obtain MR thermometry maps of the transducer's heating, an agar/silica/milk phantom was used which was produced in the laboratory at a very low cost. One of the ingredients of the phantom was agar powder of bacteriological grade type (Himedia Laboratories, Mumbai, India). In order to control the acoustic properties of the phantom, Crystalline silica dioxide powder (Merck Millipore, Darmstadt, Germany) was added which is insoluble in water and possesses a high melting temperature (1750 °C). Following a recipe described by Madsen et al. [19], evaporated milk was added in the gel. Being a low scatterer and rich in proteins and fats, evaporated milk served to control attenuation of the gel primarily through the process of acoustic absorption. The recipe of the tissue mimicking agar gel was 2% w/v agar, 1.2% w/v silica dioxide, and 25% v/v evaporated milk. The details of the recipe and the steps for the preparation of the silica-agar-evaporation milk phantom are described in Menikou et al. [20] and Menikou et al. [21].

2.4. In vitro clot preparation

Blood clots were obtained by natural coagulation of fresh porcine blood. Firstly, porcine blood collected from healthy slaughter pigs, was transferred into a pre-weighed custom made plastic container. The lower part of the container (where the blood was placed), included a $20 \times 30\ mm^2$ window, closed with a thin cellophane membrane. The container was incubated in a 37 °C water bath for 3 h before refrigerated at 5 °C for 72 h, to ensure maximal clot retraction [23].

After clot formation, serum was aspirated out from the container with great caution and was weighed again to determine the net mass clot weight (C_{NW}):

$$C_{NW} = W_c - W_T \quad (1)$$

where W_C is the weight of the container plus the clot and W_T is the weight of the container alone.

After the experiment, the residual clot was carefully removed from the container and was left to dry for 60 min before weighted again to obtain the mass clot removed due to thrombolysis. In the mass measurement, a digital balance device (Scaletec, SM001, Heiligenstadt, Germany) was used.

2.5. Preparation of tenecteplase tissue plasminogen activator (TNK-tPA)

TNK-tPA (Boehringer, Ingelheim, Germany), is a 3rd generation modified tissue plasminogen activator that is more fibrin-specific and more resistant to plasminogen activator inhibitor. Due to higher thrombolytic potency and longer half-life than rt-PA, TNK-tPA can be administered as an intravenous bolus [24,25]. Although this thrombolytic agent is an approved safe drug for acute myocardial infarction, due to its safe administration and ease of use, can be a new choice for acute ischemic stroke treatment [26]. TNK-tPA was obtained as powder mixed with sterile water as per manufacturer's instructions.

2.6. Ultrasound bubbles

Prior to the experiment with clot, a bolus of an ultrasound contrast agent (SonoVue; Bracco SpA, Milan, Italy) was injected at a dose of 0.02 mL/kg in a small container containing degassed water.