Program Digest, 2019 IEEE International Ultrasonics Symposium (IUS)
Glasgow, Scotland, October 6-9, 2019

Non-invasive fast, large and selective *in vivo* HIFU ablation of the liver with a toroidal transducer.

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Abstract— **Treatments using high intensity focused ultrasound (HIFU) are routinely used to treat many kinds of diseases. Common HIFU systems use spherical transducers to create deep but small lesions. As an alternative, we have been developing intra-operative toroidal HIFU transducers allowing ablation rates 30 times faster than spherical transducers. This technology is currently under clinical validation for treating liver metastases. In the present study, we are extending our previous work to provide a completely non-invasive treatment of the liver with toroidal HIFU transducers. After numerical simulations and *in vitro* studies, *in vivo* experiments were conducted in pigs. The HIFU transducer has a toroidal shape with a diameter of 73 mm, a radius of curvature of 70 mm focusing on a circle of 30 mm in diameter. The transducer was divided into 32 concentric rings of equal surface. The working frequency was 2.5 MHz. An ultrasound imaging probe operating at 7.5 MHz was placed in the center of the HIFU transducer. Thirty-two power amplifiers were used to drive the 32 individual HIFU transducers for dynamic focalization. Inside each amplifier, a directional coupler allowed to measure the direct and reflected electrical power. A peristaltic pump drove coupling water at 8°C around a closed circuit to cool the transducer during treatment.**

***In vivo* trials were conducted in 4 pigs under general anesthesia. Animals were positioned as to have an anatomical access to approximately 50% of the liver whilst avoiding the rib cage. The exposure parameters were defined based on numerical simulations and preliminary *in vitro* experiments. In particular, three sets of exposure parameters were defined according to the: (i) the angle between the probe and the skin, (ii) the thickness of intermediate tissues (less than 10 mm, between 10 and 15 mm or between 15 and 20 mm) and (iii) the acoustic attenuation of intermediate tissues. The probe was held by hand and placed on the skin under ultrasound imaging guidance to target the liver. HIFU ablations were created using an acoustic energy between 3870 J and 6450 J corresponding to an exposure time between 30 and 50 seconds. Four lesions were created in the liver under *in vivo* conditions without skin burns and without damaging the intermediate tissues. The toroidal probe allowed for fast, large and precise ablations. Lesions were reproducible with an average diameter of 11.6±1.7 mm, an average length of 16.8±4.5 mm and a safety margin of 4.2±3.3 mm. Treatment parameters are sensitive to thickness variations of intermediate tissues within a 5 millimeter precision. This *in vivo* work provides a first demonstration of the feasibility and the safety of treating the liver non-invasively with a toroidal transducer. Ablations were large and obtained in less than one minute of treatment without resorting to mechanical scanning.**

Keywords—HIFU, liver, non-invasive, toroidal transducer

I. INTRODUCTION

High intensity Focused Ultrasound (HIFU) is a worldwide therapeutic reality, which already treated more than 215,000 patients around the world in many medical fields, including oncology [1 - 9]. Regarding the treatment of liver tumors, several minimally invasive techniques have been developed, such as Radiofrequency Ablation (RFA) [10]. However, HIFU is the only therapeutic modality which can be completely non-invasive [11 - 13]. Despite the methods' clinical potential, the liver is a particularly challenging organ for HIFU treatment due to the combined effect of respiratory-induced liver motion, partial blocking by the rib cage, and high perfusion/flow [14, 15]. Moreover, before reaching the organ, HIFU beams will have to cross harmlessly through skin, fat and muscle layers. It is known that different tissues have characteristic speeds of sound, attenuation, and density - all of which can alter the pressure field as it propagates into the body. Finally, bones that protect the liver are known as very strong ultrasound absorbers and reflectors. The variation in material property values between differing tissue types can result in aberration of the acoustic field, which can significantly affect focusing and can lead to skin burns or other complications [16]. Several technical and clinical solutions have been investigated during the past 20 years but to date without providing effective solutions. Most of the HIFU devices that are used for treating liver tumors are based on a spherical transducer. The volume of ablation ('lesion') following a single HIFU exposure is small and will vary according to transducer characteristics, but is typically cigar shaped with dimensions in the order of 1–3 mm (transverse) × 8–15 mm (along beam axis). To ablate clinically relevant volumes of tissue for the treatment of solid cancers, hundreds of these lesions must be placed side by side systematically to cover the target tumor using sophisticated robotized arm, generally associated with complex electronics to drive hundreds of transducers. It has already been reported that treatment times are longer than is desirable for hepatic tumors [17, 18].

Despite all the advantages of the HIFU technology, these long treatment times and the difficulty to treat some difficult organs are the main limitations to widespread the use of HIFU, mainly for liver tumors. We have previously studied a form of treatment by HIFU using a toroidal-shaped transducer that has been used intra-operatively and which could represent a promising alternative for treating colorectal liver metastases [19, 20]. The principal interest lies in the possibility of treating hepatic parenchyma in a short period of time (ablation of 7 cm3 in 40 s) without organ penetration. This correspond to an ablation rate 30 times higher when comparing with spherical transducer [21, 22]; and importantly, without resorting to mechanical scanning. In addition, ablations created with a trodoidal transducer in

the liver were shown to be independent from perfusion [23]. Here, we report the *in vivo* results obtained completely non-invasively using this HIFU device in a pig model.

II. Material and Methods

A. Toiroidal Transducer

The transducer is composed of 32 ring-shaped emitters with identical surface areas (78 mm^2) that operate at a frequency of 2.5 MHz. The ultrasound emitters were distributed according to a toroidal geometry. The radius of curvature of the transducer is 70 mm and its active diameter is 67 mm. Because of this toroidal geometry, the focal zone observed in the focal plane is a ring of 30 mm in diameter. In addition, the ultrasound beams coming from each of the 32 emitters intersect between the principal focal ring and the transducer to form a secondary focal zone, which contributes to increase the volume of the lesion and to reinforce its homogeneity. Spatial distribution and intensity of the pressure field produced by one ultrasound emitter can be controlled electronically by modulating the amplitude and the phase applied to each of the 32 individual transducers. An ultrasound-imaging probe (Vermon, Tours, France) working at a frequency of 7.5 MHz is placed in the center of the HIFU transducer and is connected to a BK HAWK 2012 EXL scanner (B-K Medical, Herlev, Denmark). The ultrasound-imaging plane is aligned with the HIFU acoustic axis to precisely guide the treatment. The US emitting transducers (for therapy and imagery) were placed into acoustic contact with the placenta with US coupling fluid (Ablasonic®, EDAP, Vaulx-en-Velin, France). The fluid was contained in a sterile polyurethane envelope (CIV-Flex Transducer cover, CIVCO, Kalona, IA, USA) that also covered the device, which made it possible to use the HIFU system under sterile conditions. This envelope attenuated the ultrasound pressure by approximately 2% at 2.5 MHz. A continuous flow (0.4 L/min) maintained the degassed coupling water at 8°C and allowed for the cooling of the HIFU transducer during treatment. A peristaltic Masterflex pump (L/S model 7518–60, Cole-Parmer Instruments Co., Chicago, IL, USA) drove the water around a closed cooling circuit. All of the procedures were guided and controlled by a computer [24]. The user interface displayed the position of the HIFU-treated region superimposed on the sonogram, which was obtained by the integrated ultrasound-imaging probe. In this manner, it was possible to locate the ablation and visualize the treated zone that was created during ultrasound exposures in real time.

B. In vivo experiments - Animals

In vivo trials were conducted in four pigs under general anesthesia. Animals were 10- to 14-weeks-old Landrace pigs weighing between 30 and 35 kg were used. The porcine model was chosen because of its similarities with human anatomy. The pigs were housed on site 7 days before surgery and fasted for 24 hours before the operation. A mixture of ketamine 15 mg/kg, azaperone 2.2 mg/kg, and atropine 0.5 mg was used as intramuscular premedication. A 20-gauge catheter was then placed in an auricular vein. Anesthesia was induced by slow intravenous injection of propofol, followed by intubation and assisted ventilation. Intravenous prophylactic amoxicilline 400 to 800 mg was administered. Anesthesia was maintained with a continuous intravenous perfusion of 1% propofol 10 to 20 mL/h. Postoperative analgesia was administered by a fentanyl patch 100 µg/h. Animals were placed in an inclined supine position in order to have an anatomical access to approximately 50% of the liver whilst avoiding the rib cage. The exposure parameters were defined based on numerical simulations and preliminary *in vitro* experiments. In particular, three sets of exposure parameters were defined in order to compensate the acoustic attenuation of intermediate tissues by adjusting the acoustic power accordingly. The probe was hand-held and placed on the skin under ultrasound imaging guidance to target the liver. Each HIFU exposure was performed during apnea to avoid liver movement. Apnea periods always began 5 s before sonication and lasted 45 s. The purpose of this maneuver was to limit the movements of the liver, which could have been deleterious to the quality of the treatment. The animals were monitored continuously by evaluating hemodynamic status and blood oxygen saturation. A maximum of 50 s of apnea was fixed to preserve a minimal blood saturation of oxygen at 85%.

All procedures described in this paper were carried out in the laboratory for experimental surgery (DSV 693880501) of the Centre Léon Bérard in Lyon (F-69008, France). Animal experiments were performed under an institutionally research protocol approved by the local ethical committee of animal experimentation. These experiments were in accordance with the legal conditions of the French National Commission on Animal Experimentation. [24].

III. Results

The pigs remained hemodynamically stable during the procedure. Four lesions were successfully created in the liver (Fig. 1). In all cases, HIFU exposures lasted 40 seconds, while animal apnea, at an acoustic power of 130 W which was set according to the attenuation of intervening tissues. The thickness of intervening tissues was between 12 and 15 mm in the 4 animals. The coagulated tissues observed on gross pathology were clearly distinguishable from untreated tissue. Ablations were slightly conical in shape and had an off-white color which was sometimes dark at the most heated points. There was no secondary lesion in intervening tissues and 10 mm of liver tissue was spared. Histological analysis confirmed homogeneous necrosis in the treated zone. The dimensions of the ablations were an average diameter of 12 mm and an average depth of 16 mm.

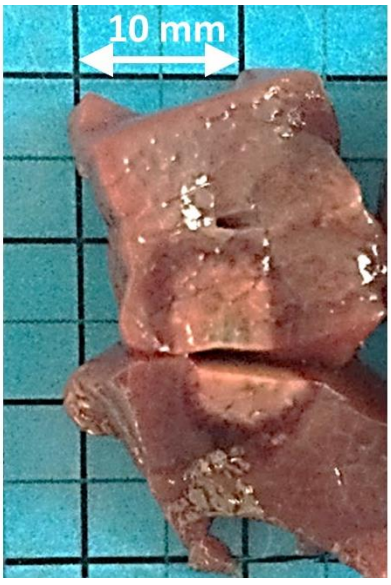

Fig. 1. Example of a HIFU ablation created in vivo in the liver in 40 seconds using a toroidal transducer.

IV. Discussion

The data from the present study demonstrated that in vivo non-invasive HIFU treatments can be performed in the liver using a toroidal HIFU device. The HIFU approach presented in this study is

characterized by the intensity of the heat deposit (around 80 ◦C in the targeted zone) and the brevity of the treatment (40 s), which makes it possible to create large zone of ablation during apnea. In all cases, ablations were created in the liver without skin burn or secondary lesions in the intermediate tissues. Lesions were created in depth in the hepatic tissue using power compensation take into account the attenuation of skin, fat and muscle. Ablations were created at 25 mm from the skin (15 mm of intervening tissues and 10 mm of liver tissue). The procedure was considered as safe and well tolerated since the pigs remained hemodynamically stable during the procedure.

These preliminary results obtained with the toroidal device are promising but an *in vivo* repeatability study will be conducted to confirm results and acquire statistics. Moreover, although our laboratory already started to address the respiration motion issue [15], work will be carry on in order to develop new treatment strategies with respect to breathing motions using gating and electronic focusing. The rib cage issue was partly addressed in this study. For many research teams, ribs remain the more challenging part. Today, many patients still can't benefit from a HIFU treatment due to their tumor localizations. Several propositions can be seen in the literature going from rib resection to shutting down elements positioned in front of the bones. These techniques induce invasiveness, surgery or loss of precision and acoustic energy during treatment; leading to an increasing of time procedures. Although our approach in this study gives access to about 52% of the hepatic volume, it ensures avoiding the ribs, non-invasiveness and fast procedure.

To conclude, through this study one see that this HIFU toroidal device seems to be a relevant and efficient tool to treat non-invasively the liver. The procedure is fast, selective and safe.

ACKNOWLEDGMENT

Authors give their special thanks to the members of ICE (Institut de Chirurgie Experimentale) who supported us for *in vivo* experiments. This project was partly funded by the FUS foundation (N° RC17129CC).

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