Ultrasound in Med. & Biol., Vol. 40, No. 12, pp. 2851–2856, 2014

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2014.07.009

● *Original Contribution*

GEL PHANTOM STUDY WITH HIGH-INTENSITY FOCUSED ULTRASOUND: INFLUENCE OF METALLIC STENT CONTAINING EITHER AIR OR FLUID

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(*Received* 9 *November* 2013; *revised* 13 *July* 2014; *in final form* 15 *July* 2014)

Abstract—We aimed to investigate whether a cylindrical structure containing either air or fluid and with or without a metallic stent affects the volume and density of cavitation produced by high-intensity focused ultrasound via a gel phantom study. Sixteen tissue-mimicking phantoms based on a polyacrylamide gel mixed with bovine serum albumin with a cylindrical hole 1 cm in diameter and 7.5 cm in length were divided into four groups of four phantoms with air in the holes (group 1), four phantoms with fluid in the holes (group 2), four phantoms with air-containing metallic stents (group 3) and four phantoms with fluid-containing metallic stents (group 4). A pulsed high-intensity focused ultrasound beam (50% duty cycle, 40-Hz pulse repetition frequency) at 75 W of acoustic power was directed perpendicularly to the longitudinal axis of the hole, with its focus at the posterior wall of the hole. The size of the cavitation on the x-, y-, and z-axes was measured, and the volumes of cavitation and coagulation were calculated using the formula for the volume of an elliptical cone. The density of cavitation was measured in the tissue phantom anterior to the hole with a 1 $\times$ 1-cm square region of interest. For statistical analysis, the Kruskal–Wallis test and Mann–Whitney *U*-test were used. The phantoms with air-containing holes (groups 1 and 3) developed larger and denser cavitations anterior to the focus, without unnecessary coagulation posterior to the focus, compared with the phantoms with fluid-containing holes (groups 2 and 4), regardless of the presence of stents. All of the axes and volumes of the anterior cavitations were significantly larger than those of the posterior cavitations in groups 1 and 3 (all *p*-values $<$0.05). The results of this study might be applied to maximize cavitation to enhance drug delivery into tumors. (E-mail: leejy4u@gmail.com or leejy@radiol.snu.ac.kr) © 2014 World Federation for Ultrasound in Medicine & Biology.

Key Words: **High-intensity focused ultrasound, Cavitation, Pancreatic neoplasms, Stent, Air, Fluid, Phantom study.**

INTRODUCTION

Unresectable pancreatic cancer is a topic of current interest in the clinical application of high-intensity focused ultrasound (HIFU). Because approximately 80% of patients have unresectable disease at the time of diagnosis and an overall 5-y survival rate of less than 1% (Ries et al. 1975–2005), the primary goals of treatment for unresectable pancreatic cancer patients are improvement of overall survival and palliation. Several previous studies have reported that HIFU is useful for palliative treatment in patients with unresectable pancreatic cancer (Wu et al. 2005; Xiong et al. 2009; Zhao et al. 2010).

High-intensity focused ultrasound can have both thermal and mechanical effects on tissue. However, tissue damage through thermal injury can increase the risk of release of autodigestive enzymes, leading to pancreatitis (Jang et al. 2010). In addition, the effectiveness of partial thermal ablation of the tumor remains questionable in patients with advanced pancreatic cancer because pancreatic cancer is regarded as a systemic disease because of its high distant recurrence rates. It seems more rational to find a way to use HIFU to aid the chemotherapy that is necessary for patients with pancreatic cancer.

Until now, many HIFU trials have focused on enhancing the cytotoxic effect of chemotherapeutic agents in diverse cancers (Daigeler et al. 2010; Iwanaga et al. 2007; Lee et al. 2011a, 2011b; Lentacker et al. 2009; Paparel et al. 2005). In terms of pancreatic cancers, a few studies have recently reported that the concurrent use of drugs and HIFU might decrease tumor growth in pancreatic cancer compared with the use of drugs or HIFU alone (Lee et al. 2011a, 2013). Ultrasound-enhanced drug delivery is known to be related mainly to sonoporation (Liang et al. 2010).

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Previous *in vitro* and *in vivo* studies have suggested that sonoporation with acoustic cavitation could enhance drug delivery by making microvessels porous and inducing the extravasation of macromolecular anti-cancer agents into the tumor (Bazan-Peregrino et al. 2012; Hancock et al. 2009; Iwanaga et al. 2007; Lee et al. 2011a, 2011b, 2013; Ohl et al. 2006).

In our institute, dozens of cases with unresectable pancreatic cancer have been treated with HIFU since 2008. During the treatments, we frequently encountered patients with metallic stents in the common bile duct (CBD) because pancreatic head cancer commonly invades the CBD. The metallic stents contained either air or fluid, as usual. Because air has high reflectivity and fluid has low reflectivity at the tissue interface on ultrasound, they are the factors most likely to affect HIFU treatment. However, to the best of our knowledge, there has been no report on the effect of metallic stents and their content on the treatment of pancreatic head cancer with HIFU.

Thus, the purpose of this study was to investigate whether a cylindrical structure containing either air or fluid and with or without a metallic stent affects HIFU treatment.

METHODS

Phantom preparation

The recipe for tissue-mimicking phantom preparation was similar to that reported by Lafon et al. (2005). This phantom was based on a polyacrylamide gel mixed with bovine serum albumin (BSA), a protein used as a temperature-sensitive indicator (Bouchard and Bronskill 2000). The following protocol for phantom fabrication was used: 64.11% (v/v) degassed, distilled water and 10% (v/v) 1 mol/L TRIS buffer at pH 8 (Biosesang, Seongnam, Bundang, Korea) were mixed to dissolve 4.05 g BSA at a concentration of 9% (by weight). A 40% (w/v) acrylamide solution (Biosesang) with a 19:1 acrylamide:bisacrylamide ratio in solution was added. The polymerization was initiated by addition of a 10% (w/v) ammonium persulfate solution (APS, Biosesang) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED, Biosesang) redox system at room temperature. The measured physical and acoustic properties of the phantom were as follows: density = 1040 kg/m^3, speed of sound = 1550 m/s, acoustic impedance = 1.61 MRayl and absorption coefficient = 0.12 dB/cm/MHz. Although no thermal properties of the phantom were measured, the BSA phantom is expected to have properties similar to those of the egg white polyacrylamide gel phantom (with egg white as an indicator protein instead of BSA) as follows: specific heat (C_p) = 4270 ± 365 J/kg/°C, thermal conductivity (k) = 0.59 ± 0.06 W/m/°C (Divkovic and Jenne 2004; Lafon et al. 2005).

The phantom measured 5 cm along the x-axis, 8.5 cm along the y-axis and 7 cm along the z-axis. A cylindrical hole 1 cm in diameter and 7.5 cm in length, simulating a common bile duct in the pancreatic head, was made in the phantom (Fig. 1). In total, 16 phantoms were prepared. The 16 phantoms were divided into four groups: group 1 = 4 phantoms with air in the holes; group 2 = 4 phantoms with fluid in the holes; group 3 = 4 phantoms with air-containing biliary stents; and group 4 = 4 phantoms with fluid-containing biliary stents. The fluid used to fill the hole was degassed tap water, automatically degassed in the water tank of the HIFU machine used. The biliary stent used was a Niti-S uncovered metallic stent (TaeWoong Medical, Seoul, Korea) 10 mm in diameter and 5 cm in length; it is made of Nitinol wire and is clinically used for palliation of malignant biliary obstruction.

HIFU equipment and parameters

The VIFU-2000 HIFU unit (Alpinion Medical Systems, Seoul, Korea) was used to deliver HIFU. The therapeutic HIFU transducer was a fixed-focus concave transducer composed of single piezo-electric element with an overall aperture of 82 mm and a focal depth of 44 mm. The HIFU transducer was driven at a frequency of 1.1 MHz. The –6-dB focal dimensions were 9.2 mm in length and 1.3 mm in diameter (Alpinion Medical Systems).

The HIFU beam was aimed at the posterior wall of the hole and moved automatically at –2 mm, 0 mm and +2 mm along the x-axis during insonation. Electrical power (100 W), exposure time (36 s), duty cycle (50%) and pulse repetition frequency (40 Hz) were determined in our pilot study. The efficiency of the HIFU transducer was 75%. The posterior wall of the hole was targeted because the intrapancreatic bile duct was anatomically posterior to the pancreatic head, so that the posterior wall of the bile duct was targeted to fully cover the pancreatic head lesion.

Measuring volume of cavitation or coagulation zone

Cavitation was defined as the formation of tiny bubbles in the phantom, and coagulation was defined as cloudy discoloration indicating tissue denaturation (Fig. 2) (Lafon et al. 2005; Lee et al. 2013; Maxwell et al. 2010). The extent of cavitation was estimated by measuring the size along the x-, y- and z-axes and the volume of the place where individual cavitation bubbles occurred. The extent of coagulation was estimated by measuring the size on the x-, y-, and z-axes and the volume of the place where cloudy discoloration occurred. The sizes on the x-, y-, and z-axes of cavitation and coagulation were measured immediately after HIFU exposure using a caliper, and the volume