A LOW FREQUENCY (220 kHz) ULTRASOUND SYSTEM FOR ENHANCEMENT OF GALLSTONE DISSOLUTION

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ABSTRACT

A clinical system using 220 kHz broad-beam ultrasound has evolved for the dissolution of gallstones. Ultrasound is applied in the transcutaneous mode and a gallstone solvent is introduced directly into the gallbladder using a uniquely designed catheter which is inserted through the skin surface to the gallbladder. Experiments using surgically implanted human gallstones in the pig gallbladder have shown acceleration of gallstone dissolution with solvent combined with ultrasound. This gallstone dissolution system has been designed and constructed (mechanical components fabricated by LABECO, Mooresville, IN) by our development team and has recently been applied in the clinical arena.

Our animal studies have shown, in addition, the ability to produce gallbladder ablation by a change in the acoustic intensity parameter. This exciting possibility has yet to be considered for clinical implementation. Based on our studies it remains to be seen what other organ and tissue systems might be clinically treated with this type of system.

INTRODUCTION

The system presented in this report evolved from a study initiated to explore ways in which ultrasound might be used in the clinical treatment of gallstones. Our objectives were to completely eradicate gallstones in a manner as non-invasive as possible with minimal patient trauma while aiming for reduced costs compared to surgery or other methods. The study was initiated in 1983 and predated the clinical use of shock waves in this field. Because of the clinical necessity to reduce gallstones to small particle sizes (less than 1 to .5 mm) for clearing through the cystic duct leading from the gallbladder to the common bile duct, any method we considered required either the production of an extremely fine powder or must greatly accelerate the chemical dissolution of the stones.

Our first experiments used continuous wave focused ultrasound at 1 MHz frequency (3 dB radial beam width 4 mm, 3 dB axial beam length of 30 mm). Focal spatial and temporal peak intensities (SPTP) were in the range of 1000 w cm^{-2}. The beam was directed at a tethered human gallstone (1 cm diameter primarily cholesterol stone) submerged in a water bath at 37°C. A rapid boring (few seconds) of the stone was achieved with a very fine stone mist (particle size less than 0.1 mm). By moving the focus over the gallstone volume much of the stone was reduced to a fine mist. Although this experiment demonstrated a correct response the untethered nature of stones in the human gallbladder posed problems deemed too serious for implementation of this type of approach which would be applied transcutaneously. It was judged that a total clinical treatment time could meet acceptable limits of a two- to three-hour procedure but to accomplish this would require spatially fixed stones. Further pursuit of this method was terminated and the next approach involved gallstone dissolution with clinically applicable solvents using unfocused broad-beam ultrasound which could be applied transcutaneously.

Initial *in vitro* studies were conducted in a latex gallbladder simulation envelope containing human gallstones in appropriate solvents with the entire system immersed in 37°C degassed water and illuminated with a broad-beam ultrasound configuration. Great acceleration was demonstrated in gallstone dissolution over that unaided by ultrasound irradiation.

In order to quantify and optimize gallstone dissolution while fulfilling the clinical requirements of safety and efficacy we established an optimal ultrasound frequency and ultrasound intensity ranges and time on/time off periods which would yield clinically acceptable total treatment times. In the frequency range studied from 100 kHz to 1 MHz the optimal frequency was around 220 kHz. Using 18 w cm^{-2} SPTP intensity as the upper intensity which would be clinically acceptable, a series of *in vitro* experiments was conducted using monooctanoin (MO) and methyl tertiary butyl

1051-0117/90/0000-1635 $1.00 © 1990 IEEE

ether (MtBE) which are clinically acceptable solvents for use in the gallbladder.

SYSTEM DESIGN

Based on the experimental data and analysis a set of design parameters was established for a clinical system which could be used for the preclinical studies on an experimental animal model using good laboratory practice (GLP) leading to an IDE issued by the FDA for a precisely described limited human clinical series.

DESIGN SPECIFICATIONS

Operating frequency—220 kHz.

Coupling to be provided from the ultrasonic irradiating unit in a direct skin contact with appropriate coupling medium with the transducer exit port to be no larger than 9 cm diameter. This size is dictated by human anatomical constraints.

The irradiating beam emerging from the transducer housing to be as uniform as possible over a radial diameter of 6 cm in order to illuminate as much of the human gallbladder as possible in a fixed housing arrangement with respect to the patient.

Alignment of the irradiating transducer to be accomplished by collinear ultrasound visualization of the gallbladder (3.5 MHz operating frequency).

SPTP intensity to have an upper limit of 18 w cm^{-2}. This was judged to be proper from the point of no gross cavitation in the body tissues while staying below bioeffects levels in general particularly those relating to temperature rise in delivery regimes meeting the criteria related to total treatment time in the clinic.

The device had to meet r.f. radiation standards.

It had to be mechanically strong and movement flexible to adjust to the individual body placement.

It had to be user friendly from the clinical operative standpoint. All the essential technical and clinical data had to be both on-line visualizable as well as being stored for a permanent record for each individual patient.

It had to be acoustically stable over long time periods (months to years) and be readily calibrated and its acoustic output intensity and beam configuration checkable on an essentially immediate basis in the clinical setting.

IMPLEMENTATION

In order to achieve a maximum skin contact diameter of 9 cm with an axially and radially uniform intensity beam capable of covering most of a human

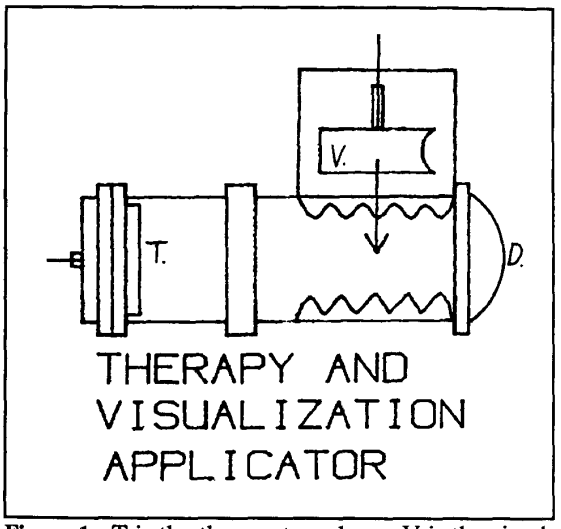

Figure 1. T is the therapy transducer, V is the visualization transducer which is moved in and out of the therapy field and D is the diaphram which couples to the patient.

gallbladder it was necessary to derive a wave guide system in which the transducer was placed. The 7.5 cm diameter transducer selected operating at 220 kHz frequency projecting into a large water bath has a Frenel transition distance of 23.43 cm, and beyond this region the field has a substantially Gaussian radial distribution with a spherical wave propagating axially. The human gallbladder is some 5 to 6 cm on average below the skin surface so a Gaussian distribution does not give a good radial fit to the gallbladder region which is of the average radius (in the acoustic field) extent of some 6 cm. To more nearly match these tissue geometric constraints while providing for a more uniform beam intensity in 3 dimensions at the gallbladder site, a number of wave guide configurations were investigated. The most satisfactory arrangement involved the configuration shown in Figure 1. The axial field plot is shown in Figure 2 with the human and experimental animal gallbladder position indicated. The radial half intensity beam plot in water at the gallbladder depth from the diaphragm surface is shown in Figure 3. Smooth wall wave guide configurations invariably sharpened the radially and axially dimensions, whereas the corrugated configuration provided the

appropriate wave interference patterns at the wall to project a more uniform beam into the tissue. This beam configuration has been used in all experimental animal studies, preliminary clinical trials and *in vitro* studies generally.

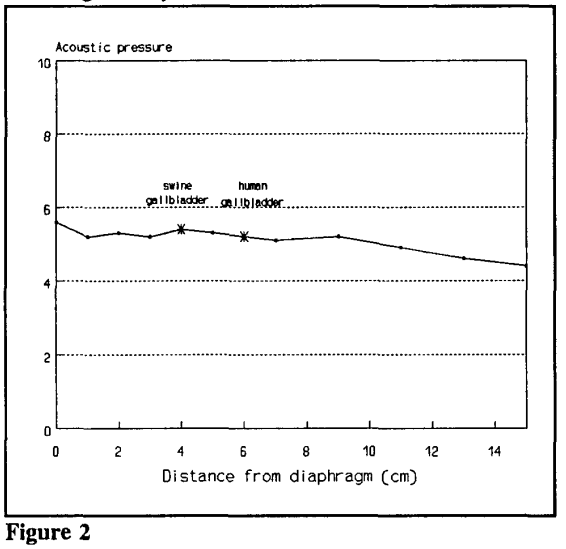

Figure 2

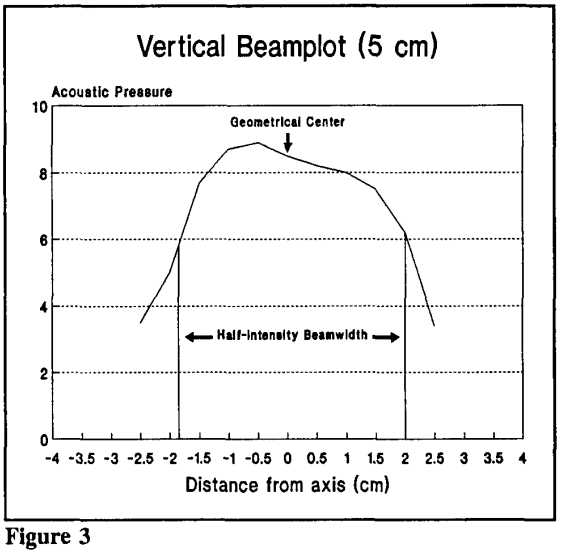

Figure 3

Once the acoustic beam configuration and frequency were known, it was now possible to do all the specific designs, namely, mechanical, acoustic, electrical, electronic and software. The system block diagram is shown in Figure 4. A picture of the entire system is shown in Figure 5. The system software was designed on a menu-driven basis. Each patient procedure would be stored on a separate floppy disc for subsequent analysis and archival purposes. All the pertinent patient data are keyboard input at the start of each procedure.

The acoustic beam configuration and intensity was determined by use of a calibrated hydrophone (U.S. Navy E27) and a steel ball radiation force method. The SPTP acoustic intensity in degassed 37°C water was obtained starting at the diaphragm face of the irradiation wave guide and extending to a 25 cm distance away from this face. Radial beam plots were made at 1 cm spacing intervals throughout this axial range.

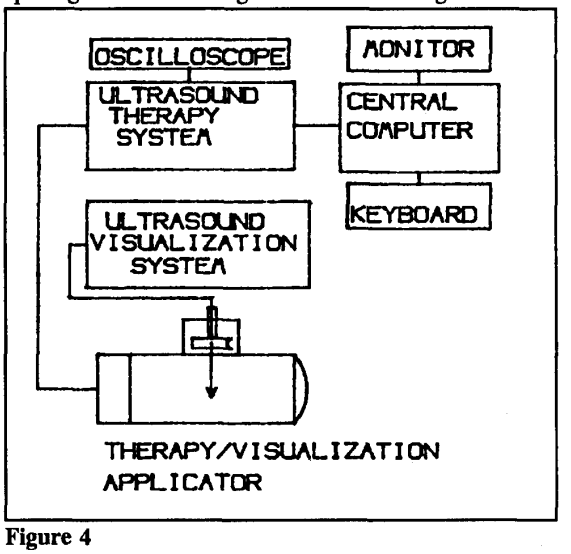

Figure 4

Comparison studies were conducted with human cholesterol gallstones and manufactured cholesterol pellets. These elements were in the latex envelope placed in degassed 37°C water at a distance from the irradiating diaphragm encountered in the human clinical situation (skin surface to gallbladder). A very large body of data has been accumulated in this study relating ultrasound intensity and time sequence delivery formats as they relate to chemical species and gallstone dissolution rates *in vitro*. For this report we have abstracted data having relevance to dissolution mechanisms. The ultrasound irradiation produces a rapid movement of gallstones or pellets in the liquid embedding media and at some level of intensity it is apparent that cavitation occurs. In an attempt to separate cavitation from the mechanical motion in evidence a series of tests were run at both atmospheric pressure

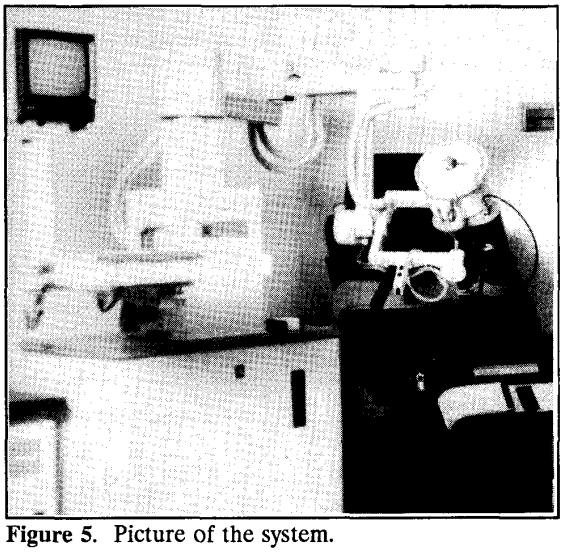

Figure 5. Picture of the system.

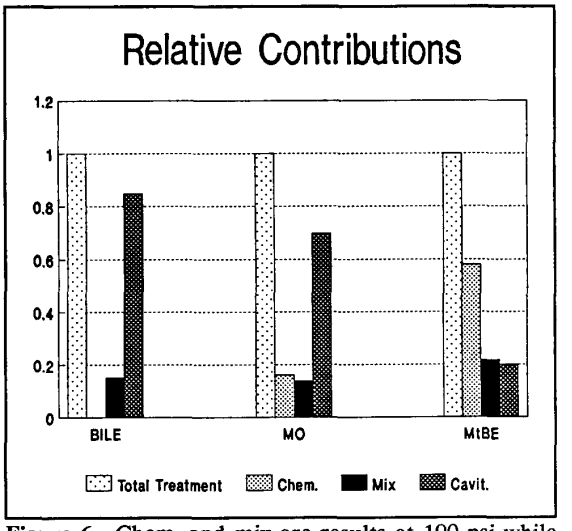

Figure 6. Chem. and mix are results at 190 psi while Cavit. represents the suppressed amount at 190 psi. Total treatment represents the amount at atmospheric pressure.

and at 190 psi under exactly similar ultrasound circumstances. The relative contributions of chemical dissolution with no ultrasound, ultrasound providing movement and mixing at both atmospheric pressure and 190 psi have been determined and graphed in Figure 6. A fixed SPTP intensity of 6 w cm^{-2} with 4 sec. on and 20 sec. off was used. The total elapsed time is 240 minutes for the human bile group, 35 minutes for the MtBE group and 60 minutes for the monooctanoin (MO) group. For bile the effect is heavily dependent on the presence of cavitation (atmospheric pressure vs 190 psi mode). MO treatment is still 70% dependent on cavitation whereas MtBE relies only 20% on cavitation. Bile produces no measurable dissolution on cholesterol stones without motion or cavitation.

Implementation of *in vivo* work involved the development of a swine model in our laboratories[1] as well as a specific designed catheter (Mallinckrodt, Inc.) for introducing chemical species in a transcutaneous approach to the gallbladder. The specially designed catheter is inserted into the patient gallbladder under real-time ultrasound guidance. The therapy system is then brought into contact with the patient lying on the special patient couch which accepts and absorbs ultrasound passing through the patient. A collinear real-time ultrasound transducer in the therapy unit is used to center the therapy unit over the gallbladder. Once the alignment is complete, the irradiation sequence is implemented. Typical results of *in vivo* studies using the fast-acting MtBE is shown in Figure 7.

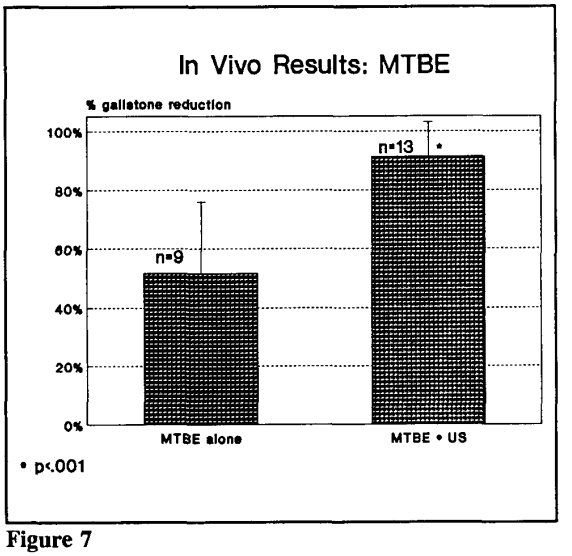

Figure 7

At 220 kHz the gallbladder site intensity compared to the free field value in water is

$$I_{GB}=I_{FF}e^{-\mu z} \qquad I_{GB}=\frac{I_{FF}}{1.16}$$

I_{GB}= intensity at gallbladder
I_{FF} = intensity in FF at gallbladder position
μ = taken as .025
z = distance from skin to gallbladder

As can be seen this insertion loss is comparatively quite small.

Results of this type with substantial instrumentation documentation allowed the FDA (Food and Drug Administration) to issue an IDE (Investigational Device Exemption) permitting a limited clinical trial series under a prescribed protocol using MtBE. The protocol as written and applied permitted little opportunity for ultrasound use since the MtBE in this first 10-patient series was effective in eliminating the gallstones encountered in a shorter time period than had been anticipated. In addition the permitted ultrasound intensity could not be used since the patient pain threshold using an ultrasonic gel coupling was inadequate. This coupling was resolved but the series was completed before the adequate coupling method could be implemented.

During the course of the animal studies using MtBE it became apparent that above a sound intensity level of 6 w cm^{-2} a large percentage (70%) of the animals in addition to having essentially no gallstones also had an extremely high occurrence of a fibrotic mass replacing the normal gallbladder. A very small animal series (2 animals) having 1 year survival time showed no gallbladder in one animal and a very small gallbladder-type remnant in the second animal. This poses the possibility that the approach used might not only eliminate the gallstones but the gallbladder as well in a non-surgical procedure (i.e., transhepatic cholecystectomy).

The potential generic aspects of this method related to other organ systems or possible ductile systems has yet to be explored.

REFERENCES

1. Griffith SL, Burney BT, Fry FJ and Franklin TD Jr.: A Large Animal Model (Swine) to Study the Diagnosis and Treatment of Cholelithiasis. *Investigative Radiology*, February 1989, 24(2):110–11.