REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave Blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	29 January 2002	Final Technical 1 Mar 96 - 31 Oct 01

4. TITLE AND SUBTITLE
An Acoustic Hemostasis Device for Advanced Trauma Care

5. FUNDING NUMBERS
N00014-96-1-0630

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10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLIMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release

13. ABSTRACT (Maximum 200 words)
Research was conducted to develop acoustic hemostasis devices for advanced trauma care. Key accomplishments include:

1. Development of High Intensity Focused Ultrasound (HIFU) hardware. We have designed and built HIFU applicators ranging from single-element (water-, polymer- or solid material-coupled) transducers to a 32-element, 2-D annular array. We have successfully integrated imaging and therapy transducers to achieve a *real-time* ultrasound image-guided acoustic hemostasis capability. We have demonstrated successful *transcutaneous* image-guided HIFU treatment in animal models.

2. *In vitro* and *in vivo* studies. We have successfully demonstrated acoustic hemostasis *in vivo* in models for blunt and penetrating trauma, and for punctured vessels and arteries. We have conducted a variety of laboratory and *in vitro* experiments to further our understanding of the mechanisms of acoustic hemostasis. We have developed novel techniques to detect and target bleeding sites.

3. Development of simulation capabilities. Sophisticated models have been developed to predict HIFU pressure and temperature fields and study cavitation dynamics. These aid in the design of applicators and treatment protocols, as well as in improving our understanding of the physical and biological mechanisms associated with therapeutic ultrasound.

The period of performance of the grant was from 1 March 1996 to 31 October 2001.

14. SUBJECT TERMS	15. NUMBER OF PAGES
High Intensity Focused Ultrasound (HIFU), medical acoustics, acoustic therapy, therapeutic ultrasound	20
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FINAL TECHNICAL REPORT FOR ONR GRANT N00014-96-1-0630
"AN ACOUSTIC HEMOSTASIS DEVICE FOR ADVANCED TRAUMA CARE"

Lawrence A. Crum, Principal Investigator
prepared by Marilee Andrew and Lawrence Crum

I. Background

Under this grant research was conducted to develop an instrument capable of both detecting and arresting bleeding using ultrasound. The proposed use is for battlefield trauma, although the technology has clear applications in civilian emergent care. The period of performance of the grant was from 1 March 1996 to 31 October 2001.

II. Accomplishments

A. Executive Summary

This project has been an extremely successful one as demonstrated by the following:

- An entirely new medical technique for the treatment of trauma has been developed: *Acoustocautery.*

- Over 50 papers have been published, including a number of review articles in prestigious journals. Eight Ph.D. and three M.S. degrees were awarded to students supported by this grant.

- 7 Patents have already been issued and numerous invention disclosures and preliminary applications are in process.

- This Intellectual Property (IP) base has resulted in the creation of two new start-up companies (Therus, Inc. and UST, Inc., both in Seattle, WA), as well as research partnerships between the University of Washington and several other companies (Ekos, Inc., Bothell, WA; Focus Surgery, Inc., Indianapolis, IN; Diagnostic Ultrasound, Inc., Redmond, WA; Sonic Concepts, Woodinville, WA; and Sanus Medical Systems, Inc., Oxford, MS).

- This primarily 6.1/6.2 effort has been transitioned to existing 6.3 projects in both the Navy and Army. Both the Navy and Army have listed Acoustocautery as Science and Technology Objectives in their POMs; prototype devices are scheduled for human trials in the immediate future.

B. Hardware, Software and Demonstrations

B.1 HIFU systems

A variety of transducers and HIFU applicator systems were built under this project. These range from single-element transducers, with and without water or solid material couplers, to a sophisticated 32-element phased array. A few examples are shown in Figure 1.

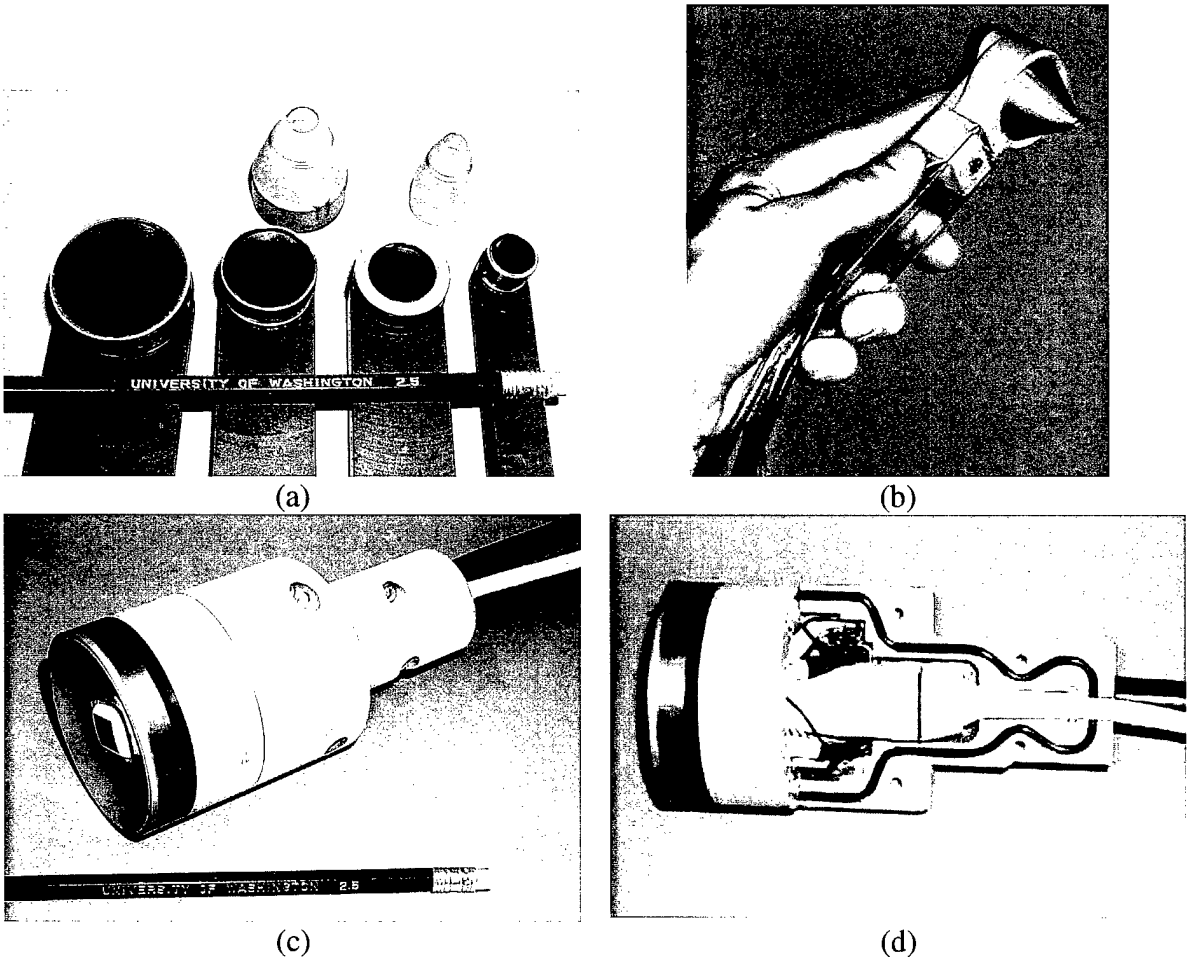

Figure 1. Hardware developed under grant N00014-96-0630. (a) Curved, single-element transducers, shown with coupling cones that can be filled with water, suitable for laboratory and animal studies. (b) Single-element transducer coupled with a solid aluminum cone, suitable for intra-operative animal studies and one of the prototypes for the intra-operative solid cone development effort. Units shown in (a) and (b) have fixed frequencies from 1-10MHz and fixed focal depths from 35-55mm. (c) and (d) Integrated imaging and therapy applicator. The larger outer region of this device consists of a 2-D, 32-element annular array that delivers the HIFU therapy. This array is optimized for 2.2MHz operation with variable focal depth of 50-80mm. Embedded within the center of the therapy array is a commercial imaging transducer (ATL P7-4).

B.2 Simulation Efforts

A 2-D full-wave, fully nonlinear acoustic model was developed as part of a Ph.D. dissertation (see Curra under the list of student theses in Section II.E). Figure 2 below illustrates how simulation can help in applicator design and treatment planning.

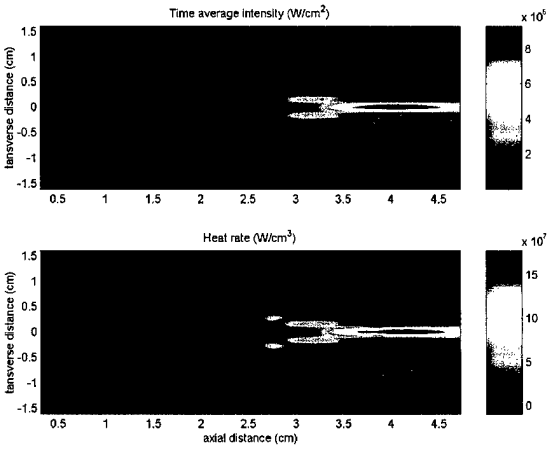

Figure 2. Continuous wave simulation that depicts the time-averaged acoustic intensity and heat rate generated by a 1 MHz line array with a 3.5 cm aperture focused at 4.3 cm. The source is at the left edge of the water layer (W) and the focal volume (red) is located in a layer of liver (L). Two intervening layers of skin (S) and muscle (M) are included in the propagation path. A thermal lesion is confined to the focal volume. This simulation illustrates that different tissue types absorb acoustic energy at different rates, and hence, a HIFU treatment protocol must select a duty-cycle that eliminates collateral damage.

B.3 Treatment Demonstrations

A variety of *in vitro* and *in vivo* tests were conducted over the course of the project in order to characterize and improve therapy applicator performance, better understand the physical and biological mechanisms of acoustic hemostasis, and assess the efficacy of HIFU treatment. A key finding is that image-guided acoustic therapy can dramatically reduce the time required to arrest hemorrhage. Extensive *in vivo* studies have demonstrated that HIFU can stop bleeding in traumatic injuries such as punctured arteries, severed capillary beds and fractured organs. Figure 3 provides a demonstration of the effectiveness of transcutaneous acoustic hemostasis in a bleeding vessel.

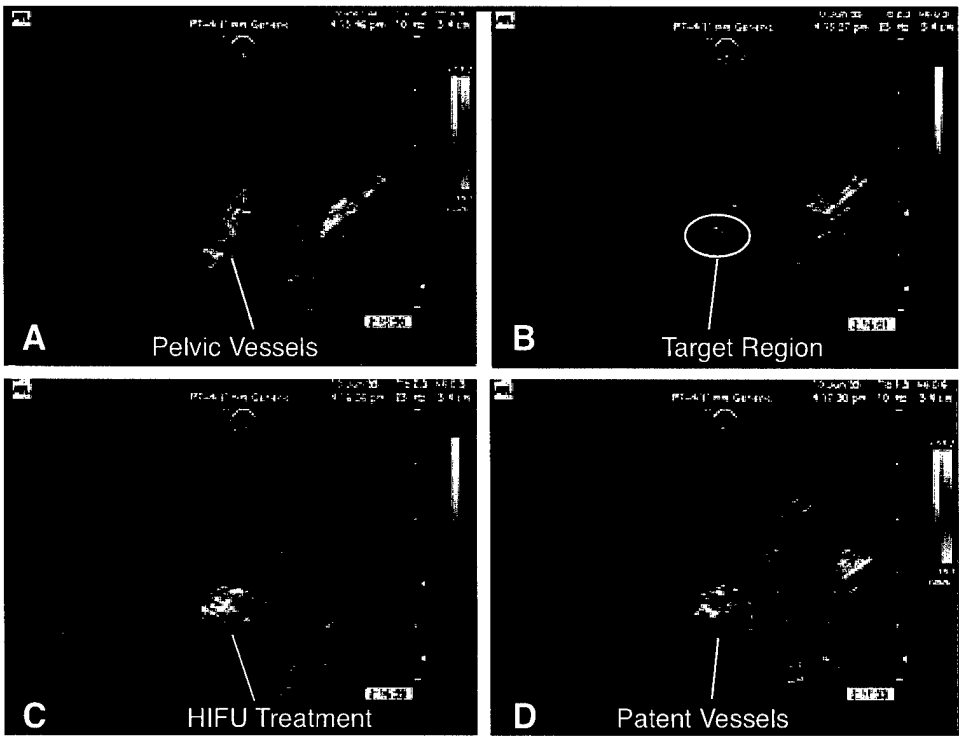

Figure 3. Targeting a bleeding pelvic vessel using an integrated imaging/therapy system. (a) The vessels were identified using color Doppler. The vessels were severed using a scalpel, and (b) gray-mode was activated. (c) HIFU treatment using ultrasound image-guidance was applied. (d) Color Doppler assessment after successful treatment and hemostasis showed patent vessels. The bleeding was arrested completely within 70 seconds.

B.4 Subcontracts

Under the Boston University Subcontract, a program focused on the application of high-intensity focused ultrasound to medical therapy was developed. The program, which was started from scratch, resulted in a fully equipped HIFU laboratory, three PhD dissertations (with a third in progress – see bibliography), and a number of spin-off projects and collaborations in biomedical ultrasound. As for technical accomplishments, Boston University collaborators have developed a first-order model for cavitation dynamics in viscoelastic media, and have taken major steps towards quantifying the role that bubbles and cavitation play in mediating and enhancing acoustic hyperthermia. Boston University has also developed a computational ability to predict the 3-D nonlinear pressure fields from focused transducers and compute the resulting 3-D temperature field, taking into account acoustic streaming, cavitation, arbitrary convective flow, boundaries, and media inhomogeneity. This model has been validated through extensive comparison with experiments performed with a flow-through phantom. Ongoing work includes an

experimental and computational study of the role that surface waves play in enhancing hyperthermia and in establishing an equilibrium bubble size distribution for sustained HIFU-induced cavitation in a tissue.

C. Intellectual Property

Note that detailed information regarding UW intellectual property resulting from this research has been reported to ONR Code 00CC1 on form DD 882 "Report of Inventions and Disclosures." Patent activity only is summarized below.

Three patents filed by THS International Inc. (on behalf of our industrial collaborator, Focus Surgery, Inc.) were relevant to this research and are listed in Table 1 below. Subsequent University of Washington Intellectual Property developed under the grant is listed in Table 2.

Table 1. Intellectual Property Filed by UW's Industrial Partner

U.S. Patent No.	Date Awarded	Title	Authors
5,882,302	16 MAR 1999	"Methods and Devices for Providing Acoustic Hemostasis"	Driscoll T, Crum L, Law W, DeMarta S
5,993,389	30 NOV 1999	"Devices for Producing Acoustic Hemostasis",	Driscoll T, Crum L, Law W, DeMarta S
6.083,159	04 JUL 2000	"Methods and Devices for Providing Acoustic Hemostasis"	Driscoll T, Crum L, Law W, DeMarta S

Table 2. Intellectual Property Filed by the University of Washington

U.S. Patent No.	Date Awarded	Title	Authors
6,217,530	17 APR 2001	"Ultrasound applicator for medical applications"	Martin RW, Brentnall, M, Proctor A
6,007,499	28 DEC 1999	"Method and Apparatus for Medical Procedures using High-Intensity Focused Ultrasound"	Martin RW, Crum LA, Veazy S, Carter SJ, Helton WS, Caps M, Kaczkowski P, Proctor A, Keilman G
6,315,741	13 NOV 2001	"Method and Apparatus for Medical Procedures using High-Intensity Focused Ultrasound"	Martin RW, Crum LA, Veazy S, Carter SJ, Helton WS, Caps M, Kaczkowski P, Proctor A, Keilman G
6,042,556	28 MAR 2000	"Method for Determining Phase Advancement of Transducer Elements in High Intensity Focused Ultrasound"	Beach KW, Brown K, Plett M, Caps M

D. Degrees and Fellowships Conferred

The following individuals earned degrees through funding provided in whole or in part by this project (see Bibliography for thesis titles):

John Allen, Ph.D., 1997.

Susannah Bloch, M.S., 1998.
Mark D. Brentnall, M.S., 1999.
Francesco Curra, Ph.D., 2001.
P. Edson, Ph.D., 2001.
J. Hwang, Ph.D., 2002.
Melanie Plett, Ph.D., 2001.
Sandra Poliachik, Ph.D., 2001.
Xuegong Shi, Ph.D. 2001.
Jonathan Yuen, M.S., 2001
Jong-Tae Yuk, Ph.D., 2000.

The following individual's Post-Doctoral Fellowship was funded in part by this project:

Dr. Cyril Lafon.

The following students are continuing research efforts that were initiated under this project:

Ajay Anand, Ph.D. candidate
George Barrett, Ph.D. candidate
Tyrone Porter, Ph.D. candidate

E. Publications

Refereed Journal Articles

Refereed Articles - 1996

Roy R. Facets of Medical Ultrasound. Echoes 1996; 6(3): 1-5.

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Plett M. Ultrasonic Arterial Vibrometry with Wavelet Based Detection and Estimation. Ph.D. Dissertation, University of Washington, 2000.

Poliachik S. An Investigation of the Mechanisms of High Intensity Focused Ultrasound Induced Platelet Activity. Ph.D. Dissertation, University of Washington, 2002.

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Yuen J. Characterization of Lesion Formation in a Tissue-mimicking Phantom for Focused Ultrasound Surgery, M.S. Thesis, University of Washington, December 2001.

Yuk J. Hemorrhage and Aortic Aneurysm Detection in the Abdomen, Using 3d Ultrasound Imaging, Ph.D. Dissertation, University of Washington, November 2000.

Technical Reports

Mourad, PD and SG. Kargl. Acoustic Properties of Fluid-Saturated Blood Clots. APL- UW TR 2003 (2000).

Abstracts, Posters & Presentations

Abstracts & Presentations - 1996

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Roy, R. "The demographics of cavitation produced by medical ultrasound," presented at the 131st Meeting of the Acoustical Society of America, Indianapolis, IN, May 1996. (Invited Paper)

Roy, R. "Cavitation and bubble detection," presented at the Allerton Park Conference for Ultrasonics in Biophysics and Bioengineering, Univ. of Illinois at Urbana-Champaign, May 1996. (Invited Paper)

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Hallaj I, Kargl S, and Roy R. "Transcranial focusing with phase conjugate arrays," presented at the 23rd International Symposium on Acoustic Imaging, Boston, MA, April 1997.

Roy R. "Some basic concepts in acoustics," presented at the NATO Advanced Study Institute on Sonochemistry, Leavenworth, WA, August 1997. (Invited Paper)

Roy R. "Fundamentals of cavitation sonophysics," presented at the NATO Advanced Study Institute on Sonochemistry, Leavenworth, WA, August 1997. (Invited Paper)

Roy R. "The detection and manipulation of transient microcavitation," seminar presented at the Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA, December 1997. (Invited Paper)

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F. Honors, Awards and Prizes

During the course of this research, the Principal Investigator was awarded the Helmholtz-Rayleigh Silver Medal by the Acoustical Society of America (2000).

The paper "Treatment of uterine fibroid tumors in a nude mouse model using High Intensity Focused Ultrasound," by S. Vaezy, V.Y. Fujimoto, C. Walker, R.W. Martin, EY Chi, and L.A. Crum, was awarded first prize at the annual meeting of the American Society of Obstetrics and Gynecology (Toronto, July, 1999).

Three graduate students supported by the project earned special honors. Francesco Curra received a Fellowship to the Physical Acoustics Summer School, Monterey, California, from National Center for Physical Acoustics (NCPA) in June, 1998. Sandra Poliachik won 2nd Prize in the Student Paper Contest for Biomedical Ultrasound/Bioresponse to Vibration presentation at 141st Meeting of the Acoustical Society of America, Chicago, June 2001. Tyrone Porter was awarded a UNCF/MERCK Pre-Doctoral Fellowship.