Advances in Experimental Medicine and Biology 880

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Therapeutic Ultrasound

Springer

Advances in Experimental Medicine and Biology

Volume 880

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2014 Impact Factor: 1.958

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ISSN 0065-2598 ISSN 2214-8019 (electronic)
Advances in Experimental Medicine and Biology
ISBN 978-3-319-22535-7 ISBN 978-3-319-22536-4 (eBook)
DOI 10.1007/978-3-319-22536-4

Library of Congress Control Number: 2015953337

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface

Besides the well-known and wide use of ultrasound in diagnostics, the therapeutic use of ultrasound has recently emerged. The understanding of the action of ultrasound waves at the cellular level has prompted an increased use of these waves alone or in combination with local activators in several domains. A book on therapeutic ultrasound needs to cover a broad spectrum of techniques and indications, which is quite a challenge. In addition, it should provide an up-to-date review and evidence of treatment efficacy.

All this is presented in three different parts within this book. The first part describes the use of high intensity ultrasound (HIFU) waves to perform tissue ablation: Following a thorough review of the underlying concepts, seven chapters provide detailed reports on different organs of interest. In addition, this part also mentions the synergy between ultrasound and other techniques, such as MRI, for certain indications while others might be achieved with ultrasound techniques exclusively. This underlines the high adaptability of ultrasound to different constraints with respect to the desired objectives. Last but not least, while bone typically represents a barrier for the propagation of ultrasound waves, results obtained in brain applications are absolutely amazing and pave the way for a new method of treating brain diseases.

The second part is based on the existing synergy between ultrasound waves, microbubbles and nanodroplets to exhibit a new therapeutic approach. Here again, after a detailed explanation of underlying mechanisms, even those that are not totally clarified, the following chapters report on the use of this synergy in several domains with a demonstration of efficacy. Conversely to the first part, where clinical trials have clearly demonstrated the high potential of HIFU in several indications, there is less clinical evidence for "sonoporation" to be an invaluable therapeutic improvement, with the exception of sonothrombolysis. However, more and more evidence is now emerging, and no doubt this will be the main challenge for the years to come and might eventually result in a second edition of this book.

The last part of the book deals with further therapeutic applications of ultrasound which do not rely on high intensity focused ultrasound or synergy with microbubbles and nanodroplets. This part illustrates the flexibility of ultrasound which can be used for bone repair or as a new approach for cancer treatment named "sonodynamic therapy".

Altogether, the three parts provide a near-complete overview of the therapeutic potential of ultrasound and offer researchers and clinicians an extensive review on the topic. There is clear evidence of the value of therapeutic ultrasound in several domains but, this will surely be further substantiated in the coming years based on the clinical evidence of sonoporation and the increased number of clinical results demonstrating a highly positive therapeutic index.

Many thanks to the Editors Jean-Michel Escoffre and Ayache Bouakaz for accepting the challenge of putting together a reference book on this subject, to Jacqueline Butterworth for the English proofreading of the book and to all the authors for their voluntary contribution.

Plan-Les-Ouates, Switzerland François Tranquart, PhD, MD

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Part I

High Intensity Focused Ultrasound Ablation of Pathological Tissue

HIFU Tissue Ablation: Concept and Devices

1

Gail ter Haar

Abstract

High intensity focused ultrasound (HIFU) is rapidly gaining clinical acceptance as a technique capable of providing non-invasive heating and ablation for a wide range of applications. Usually requiring only a single session, treatments are often conducted as day case procedures, with the patient either fully conscious, lightly sedated or under light general anesthesia. HIFU scores over other thermal ablation techniques because of the lack of necessity for the transcutaneous insertion of probes into the target tissue. Sources placed either outside the body (for treatment of tumors or abnormalities of the liver, kidney, breast, uterus, pancreas brain and bone), or in the rectum (for treatment of the prostate), provide rapid heating of a target tissue volume, the highly focused nature of the field leaving tissue in the ultrasound propagation path relatively unaffected. Numerous extra-corporeal, transrectal and interstitial devices have been designed to optimize application-specific treatment delivery for the wide-ranging areas of application that are now being explored with HIFU. Their principle of operation is described here, and an overview of their design principles is given.

Keywords

Ultrasound therapy • Thermal ablation • Cancer • Heating • High Intensity Focused Ultrasound (HIFU) • Ultrasound transducers

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J.-M. Escoffre, A. Bouakaz (eds.), *Therapeutic Ultrasound*, Advances in Experimental Medicine and Biology, Vol. 880, DOI 10.1007/978-3-319-22536-4_1

1.1 Introduction

As the name suggests, High Intensity Focused Ultrasound, HIFU, is the term used to describe the application of focused beams of high power ultrasound for therapeutic benefit. The technique is also sometimes referred to as focused ultrasound surgery, FUS. The common feature of the now many, and varied, HIFU treatments is the need to provide a beam in which the energy is sufficient to produce biological change solely within the focal volume. With few exceptions, the aim is to induce irreversible damage, although in some applications, such as drug delivery, the goal is to produce more transient effects.

1.2 Principles of HIFU

In the frequency range 0.8–5 MHz, the wavelength of ultrasound in tissue is ~2–0.3 mm. This means that small regions of high pressure (intensity) can be created at a distance from the source, in the focal plane. In principle, therefore, if there is sufficient energy in the ultrasound beam travelling through an absorbing medium, it is possible to obtain a biologically significant temperature rise solely in this region, with negligible rises elsewhere.

A common analogy here is that of a magnifying glass used to concentrate the sun's rays, with the purpose of igniting dry kindling. This is only successful when the fuel is placed where the bright spot is at its most intense, that is, in the focal plane of the lens. When the spot is more diffuse, it is not possible to set fire to the kindling, as the fuel is no longer in the focal region. Similarly, when a HIFU focus is placed at depth inside soft tissue, it is possible to raise the temperature at the focus to levels at which thermal necrosis occurs (>56 °C) while leaving the temperatures elsewhere close to their original levels, including those of tissues lying in the beam path overlying the focal volume. Figure 1.1a shows the principle of this technique. The gross appearance of a HIFU lesion (the term used to describe the region of damage induced) can be seen in Fig. 1.1b, while Fig. 1.1c shows a histological section taken at the lesion's edge. The very sharp drop off in temperature is reflected in the sharp demarcation between live and dead cells.

1.3 History of HIFU

Since this use of high intensity focused beams was first proposed in ~1942 (Lynn et al. 1942), it has been explored for a number of different potential medical applications. The aim in the 1940 and 1950s was to destroy regions of the brain selectively, in the quest for a better understanding of neurobehavior (Fry et al. 1954, 1958; Fry 1953; Fry and Fry 1960). These early efforts were hampered not only by the poor quality of the ultrasound images used for targeting, but also by the necessity of removing a portion of the skull to provide an acoustic window for the focused beam into the brain. Despite these limitations, it was possible to destroy pre-determined regions of the brains of experimental animals with good selectivity, and some human treatments of Parkinson's disease were also carried out (Ballantine et al. 1960). The early work achieved 'focusing' by using several plane transducers whose beams all crossed in the same plane. The development of HIFU coincided with the introduction of the drug L-dopa. From a patient's perspective, L-dopa proved to be a more acceptable treatment for Parkinsonism, and from a clinical viewpoint, was easier to administer.

HIFU did not really gain significant clinical acceptance until the 1990s, despite successful ophthalmological treatments before this date. The first proposal to use focused ultrasound in ophthalmology came from Lavine et al. (1952) who demonstrated cataract formation when the lens of the eye was targeted with a focused beam. Other studies demonstrated that HIFU can decrease intra-ocular pressure (Rosenberg and Purnell 1967) and produce lesions in the vitreous, lens, retina and choroid (Coleman et al. 1980, 1985a, b; Lizzi et al. 1978). The first human treatments of glaucoma, undertaken in 1982, gave encouraging results. 79 % of the patient cohort treated had a sustained lowered intra-ocular

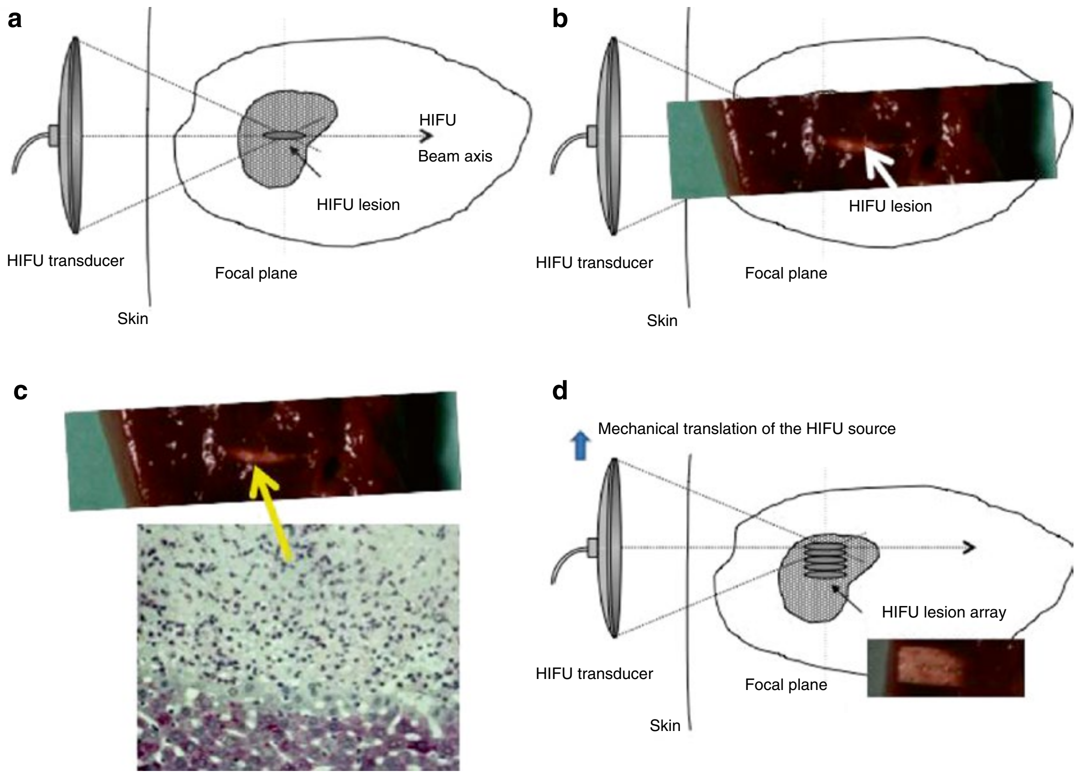

Fig. 1.1 (**a**) Schematic diagram showing the principle of high intensity focused ultrasound (*HIFU*). (**b**) Slice of *ex-vivo* bovine showing a HIFU lesion. (**c**) Histological section showing the sharp demarcation between ablated and unablated cells (Hematoxylin and Eosine staining). (**d**) Schematic diagram showing the formation of confluent regions of ablation

pressure after 1 year (Silverman et al. 1991). Although HIFU showed considerable promise in these, and other, ophthalmological applications, laser surgery has enjoyed wider success and application, presumably because of its apparently simpler technology and application. It is only now that the use of HIFU in the treatment of glaucoma is being revisited, with considerable success (Aptel et al. 2014).

Overview of clinical usage The realization of the full potential of HIFU treatments is only possible now that precise targeting and good treatment follow-up techniques, (with anatomical and functional imaging), are available with modern diagnostic ultrasound scanning and magnetic resonance imaging (MRI) methodologies. The provision of real-time images with excellent spatial resolution and contrast has opened a window of opportunity for HIFU which can only be used to full advantage when the tissue volume to be destroyed can be precisely targeted. Both ultrasound and MRI have been used to guide and monitor HIFU treatments. Each method comes with its advantages and disadvantages. MRI gives anatomical images, and can provide thermometry sequences that allow the tissue temperature to be mapped, thus providing information not only about the success of ablation in the target, but also about the safety of critical regions outside this volume. While ultrasound thermometry has not yet found clinical implementation, this modality offers superior spatial and temporal resolution for imaging. Confirmation of successful ablation under ultrasound guidance relies on the appearance of bright echoes on an ultrasound scan, The ability of HIFU to ablate subcutaneous tissue volumes non-invasively has made it an attractive potential therapy for deep-seated soft tissue tumors. Malignant tumors of the liver, kidney, breast and pancreas have been successfully targeted (Al-Bataineh et al. 2012; Orsi et al. 2010; Wu et al. 2004, 2005a, b). While ultrasound does not significantly penetrate bone, many osteosarcomas break through the bone cortex, and thus are also good candidates for HIFU treatment (Li et al. 2010; Chen and Zhou 2005). The successful palliation of pain resulting from bone tumors has also been reported, with the treatment here being aimed at destroying the nerves lying on the peri-osteum (Liberman et al. 2009; Hurwitz et al. 2014). Care must be exercised to avoid bowel gas that lies in the propagation path. In some treatment orientations this gas may be successfully displaced by applying pressure from a water balloon placed against the abdomen. HIFU has proved to be an attractive technique for the treatment of uterine fibroids. These may be clearly visualized on either MR or Ultrasound images (Froeling et al. 2013; Hesley et al. 2013; Quinn et al. 2015).

Trans-rectal HIFU treatment of prostate tumors has also been widely investigated. Both benign prostate hyperplasia (BPH) and prostate cancer have been targeted (Crouzet et al. 2015; Thüroff and Chaussy 2015). Initial results from clinical trials for treatment of BPH (Gelet et al. 1993; Sullivan et al. 1997) were encouraging, with increase in flow rate and decreases in post-void residual volume. However, the long-term results of Madersbacher et al. (2000) were disappointing, with 44 % of patients requiring a salvage trans-urethral resection of the prostate (TURP) within 4 years. HIFU has thus not proved to be significantly better than the "gold standard" treatment (TURP). Treatment of cancer in the prostate presents different problems from those associated with the treatment of BPH (Crouzet et al. 2015; Thüroff and Chaussy 2015). Prostate cancer is a multi-focal disease, the foci of which are difficult to detect with diagnostic ultrasound. It is important for its control that all foci are destroyed. Initially HIFU treatments were aimed at ablation of the whole gland (Chaussy et al. 2001; Dickinson et al. 2013). More recently, there has been a move towards partial ablation, with either hemi-ablation, or focal ablations (Crouzet et al. 2014; Baco et al. 2014; Valerio et al. 2014). There is little in the way of conventional therapy to offer patients whose prostate cancer recurs after radiation therapy. High intensity focused ultrasound may be able to fulfill this role as it offers selective tissue destruction without side effect. Early trials for this application have shown encouraging results (Ahmed et al. 2012; Gelet et al. 2004).

1.4 Exposure Dosimetry

In imaging and therapies that use ionizing radiation, a distinction is clearly made between "exposure" and "dose", with exposure for these energy forms being the amount of ionization produced in air by X- or γ-rays. The unit of exposure is the Roentgen, R. Exposure describes the amount of radiation that reaches the body, but does not describe the fraction of that incident energy that is absorbed within tissue. A second parameter is used for this, the "absorbed dose" (commonly referred to as "dose"). Dose characterizes the amount of energy deposited per kilogram and has units of the gray (Gy) and the rad, where 1 rad = 100 Gy. A weighting factor (relative biological effect, RBE) is used in an attempt to compare the biological effects of different forms of ionizing radiation. This leads to a "dose equivalent" parameter, whose units are the rem or Sievert, Sv, (1 rem = 100 Sv). These parameters are related by the equation: Dose equivalent (Sv) = dose (Gy)x RBE. X-rays, γ-rays and ß particles have an RBE of 1.0, whereas α particles have an RBE of 20.

The terms "exposure" and "dose" are used interchangeably in medical ultrasound, although a convincing case for drawing the distinction can be made. Different biological effects result from different modes of ultrasonic energy delivery. For example, two exposures that use the same total acoustic energy over an identical time span, where one is delivered in continuous mode, and the other in short pulses at low repetition rate and high amplitude may result in very different effects in tissue. The first is more likely to induce thermal effects, while the second may stimulate cavitation activity and its associated characteristic cell damage (ter Haar 2010).

Ultrasound exposures are most usually characterized in terms of the acoustic field determined under "free field conditions" in water. Here, "free field" is taken to describe the conditions in which the ultrasound beam propagates freely, without influence from boundaries or other obstacles. A full description of HIFU exposures requires knowledge of frequency, exposure time, transducer characteristics, total power, acoustic pressure and/or intensity (energy flux in Watts.cm^{-2}) and mode of energy delivery (single shots, scanned exposures, *etc.*) (ter Haar et al. 2011).

In order to make the transition from exposure to dose in an ultrasound field, it is necessary to know the acoustic characteristics of the propagation medium. The parameters of most importance are the attenuation and absorption coefficients, the speed of sound and the nonlinearity parameter B/A. There are large gaps in knowledge about these parameters for both normal and malignant human tissues, although many have been tabulated (Goss et al. 1980; Duck 2013). Generally HIFU exposures are described in terms of free field water measurements, but in some cases, an attempt is made to calculate an *in-situ* intensity by estimating the total attenuation in the beam path. Spatial peak (focal peak) intensities and spatially averaged intensities are also sometimes quoted.

Two dose parameters related solely to thermal effects have been proposed. Sapareto and Dewey (1984) proposed a thermal dose parameter. This has been used extensively to describe hyperthermic cancer treatments. The temperature-time history for a particular tissue volume is integrated and reduced to a biologically equivalent exposure time at 43 °C, t_{43}. This equivalent time is given by the equation:

$$t_{43} = R^{(T-43)}\Delta t \tag{1.1}$$

where R is 0.5 above 43 °C and 0.25 below 42 °C, and T is the average temperature over a time Δt.

This has been shown to be valid up to about 50 °C, but is difficult to validate experimentally for the short times required above this temperature, since very fast heating and cooling rates are required. An alternative parameter related to the heating potential of the HIFU beam is the product of intensity and time (a measure of the total energy), but this concept has not gained widespread acceptance in the therapy ultrasound literature. Clinically, a t_{43} of 240 min is used as the threshold for successful thermal ablation (MacDannold et al. 2006). It is now well accepted that cavitation can enhance the heating in a HIFU field (Holt and Roy 2001; Khokhlova et al. 2006). However, there is, as yet, no validated method of quantifying cavitation activity, nor accepted method for defining "cavitation dose" (Chen et al. 2003; Hwang et al. 2006).

1.5 HIFU Treatment Delivery

The devices used to deliver HIFU clinically are broadly divided into two classes, extra-corporeal and interstitial. The basic components however, do not differ much, comprising as they do, the transducer, a signal generator, amplifier, matching circuitry to maximize the electro-acoustic efficiency, a power meter, and in some cases a method of cooling the transducer. These are connected to an operator console that allows movement and positioning of the source, and also provides a means of monitoring the treatment.

The focusing required for HIFU treatments can be achieved in a number of ways. The simplest is to use a single element transducer: most commonly, either in the form of a planar disc fronted by a lens, or shaped as a spherical bowl. Such transducers are limited in that they can only provide a fixed focus, and if clinically relevant volumes are to be treated, the whole transducer assembly must be physically moved in order to place lesions side by side (Fig. 1.1d). The more common alternative is to use multi-element transducer arrays. Electronic phasing of the signal to individual elements allows both flexibility in shaping the focal volume, and some dynamic control of its position, both axially and transaxially (Gavrilov et al. 2000; Gavrilov and Hand 2000; Daum and Hynynen 1999). The geometry