Review of Ultrasound as Neurological Treatment

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Abstract—**In addition to its imaging applications, ultrasound is increasingly being used as treatment for a number of medical conditions. We are exploring the state of the art of neurostimulation and neuroablation using ultrasound on human tissue and simulation phantoms. Ultrasound focal measurement papers are reviewed in terms of amplitude measurements and deposited ultrasound focused energy. World experience in the matter was represented by 12 reports. The range of deposited energy is 0.002 to 159 W.s, across 12 reports. Focused ultrasound radiation looks promising as a technique for the treatment of neurological diseases, either inhibiting neural activity or performing specific ablations. This is so because the acoustic power required to produce thermal bioeffects is of the order of 1 W.cm-2 at any given time.**

Keywords— **ultrasound, neurology, ablation, neuromodulation, neurophysiology.**

I. Introduction

Ultrasound (US) is a technique that is being studied to be used as a treatment in various diseases, in addition to its clear use in diagnostic imaging. Within neurology, US is promising in terms of living tissue treatment, to perform neurostimulation or neuroablation at different intensity levels according to the needs of every patient. In our research, the final objective is to obtain ideal parameters to achieve a non-invasive treatment on neurological diseases, within the ranges of neurostimulation or neuroablation depending on the needs of each disease. The present paper is a preliminary review study towards the goal of a new consensus for US in neurology.

To explore the feasibility of a non-invasive device capable of precision neuromodulation or neuroablation, we have reviewed the literature. The main result of the present paper is to provide a set of parameters that could be of use for further research and to design a device to deliver controlled amounts of US energy in a specified intracranial volume.

Since US is a non ionizing form of energy, US beams could modulate neuronal activity or perform thermal ablations at specific points in the brain [1] provided they are focused appropriately. Neuromodulation consists of altering neuronal excitability in such a way that the electrical activity of these cells is modified with no need for invasive procedures. Since US is a technique which can focus stimulation energy in controlled beams [2] its use can be envisaged specifically for the treatment of focal refractory epilepsies. Neuroablation uses the heat created by US to destroy nerves or specific biological tissue, such as brain tumors or areas of brain hypertrophy.

This energy of US radiation may be associated with possible effects such as thermal ablation or neuromodulation according to recent publications [3,4]. US applied to the brain can increasingly be considered an option as a treatment modality. Neuromodulation with US might provide clinicians with a future potential instrument to noninvasively address and solve refractory epilepsy, eventually discarding surgical ablation [5].

A. Ultrasound Treatment as Reviewed

US as a treatment can be applied by producing lesions (ablation) by increasing the temperature or less invasively by modulating neuronal activity. Both modalities are described as follows:

Thermal ablation was demonstrated [1]) by localized thermal lesions (3 - 4 cm deep) US induced. This is a well-known, non-ionizing treatment for brain tumors and different neurological disorders, provided it is applied with selective targeting. High temperatures (> 56 °C) generated by sonication can induce cell damage as a result of protein denaturation and heat-induced coagulation necrosis. The volume of the damaged tissue depends on the power, duration of sonication and the type of tissue [6,7] The acoustic power required to produce thermal bioeffects according to the American Institute of Ultrasound in Medicine (AIUM) is 1 W.cm-2 [8] at a given time.

Neuromodulation is achieved with the application of focused US with low intensity, usually referred to as “Low Intensity Focused Ultrasound” (LIFUS). LIFUS initiates mechanical waves in the neuronal membrane producing depolarization and activating voltage-gated ion channels, which trigger an action potential [9]. In this way, the excitability of the neuronal tissue is temporarily modified by a regulation of ion channels without any increase in temperature [10]. The predominant physical mechanism in

US neuromodulation is the acoustic radiation force (ARF) [11].

Treatment with US has shown by electroencephalogram recordings is capable of attenuating chemically-induced epileptic activity in cats and rats [9, 10] It is an advantageous neuromodulatory technique because it is less invasive than other types of stimulation such as deep brain stimulation and optogenetic methods. It also has higher spatial resolution and deeper penetration than transcranial magnetic stimulation [12] and modulates brain activity using intensities that do not cause substantial heating or irreversible effects [8]

II. Methods

A bibliographic research was carried out through the Timbó Foco platform. Those works that had clinical studies in people, animals or phantoms, with the main objective of reaching a therapeutic goal through US, were taken into account. From a first search, 15 works were taken. Finally, those that specified any of the following parameters of our interest (intensity, frequency, power, duty cycle and/or transmission mode) were selected.

III. Results

Inspired by the work of [9], Table 1 shows the parameters used in US stimulation by different authors applied to living tissue and phantoms. Within the articles reviewed, we were able to calculate the deposited power and deposited energy in the target area only in a subset of the articles, while most of them omit such numerical details (Table 1).

Of the 10 studies reviewed, 8 had a therapeutic objective addressed with neuromodulation, while the remaining 2 carried out the investigation with thermal ablation. All authors used in vivo models to demonstrate their research, except for one that was carried out in a phantom [13] Many of them followed the inhibition of epileptic seizures as their objective, while others investigated tumor and non-specific ablation, behavioral disorders, states of consciousness, stimulation of the visual cortex for blindness and neurodegenerative disorders.

The frequencies used, taking into account all the authors, were in the range of 0.2 to 3.8 MHz. Specified intensities of 0.03 to 115.8 W.cm-2 were used. The energy deposited was calculated in 2 of the studies that specify the parameters used, being 25 to 59 W.s for ablation [13] and 0.002 to 0.003 W.s for neuromodulation [4]

Table 1 US Energy Measurements in Tissue and Phantoms

Author	Frequency (MHz)	Intensity ($W.cm^{-2}$)	Deposited energy (W.s)	Clinical application	Model
[9] +	<1	0.03 – 0.3	-	inhibit electrographic seizure activity	in vivo
[2] +	0.2	-	-	inhibit seizures	in vivo
[3] +	0.2	Low intensity	-	inhibit seizures	in vivo
[10] +	0.5	Low intensity	-	inhibit seizures	in vivo
[11] +	0.5	115.8	-	blindness	in vivo
[14] +	0.5 - 0.68	0.07 - 0.235	-	neurodegenerative disorders	in vitro / in vivo
[4] +	0.65	0.719 - 14.39	0.002 - 0.003	consciousness state	in vivo
[15] *	1	-	-	tumor ablation	in vivo
[13] *	1 - 10	-	25 - 59	ablation level	phantom
[12] +	3.8	0.14 - 0.70	-	behavior disorders	in vivo

CW Continuous wave. PW Pulsed wave, CPP Cycles per pulse. PRF Pulse Repetition Frequency. np number of pulses, Af Acoustic frequency, + Neuromodulation, * Thermal ablation. Deposited power (W) =Á.I.Deposited energy (W.s)= (duty cycle . seconds. deposited power)/2. Where Á is the target area by the emitter and I is the intensity

IV. Discussion

The range of values of the experiments published by the authors in Table I, must be evaluated in order to formulate provisional conclusions on the feasibility of delivering controlled amounts of energy to neural tissue. The description of the experiments, including elaborated sequences of US pulses and silences, makes it extremely difficult if not impossible to estimate amounts of energy actually deposited in the tissue of either animal models or phantoms.

As can be seen in Table I, [12] the area was 0.25 mm2 with 0.14 - 0.70 W.cm-2 intensity pulsed wave (PW), therefore the deposited power was 0.035 - 0.175 W.cm-2, we are unable to calculate the deposited energy because there is no information about duty cycle, used for behavior disorders treatment, claiming success. [14] specifies an area of 1.65 cm2, with 0.07 - 0.235 W cm-2 intensity, PW 40 minutes, therefore 0.11 - 0.38 W deposited power, without information of duty cycle, used for neurodegenerative disorders treatment. [4] had an area of 0.19 cm2, 0.719 - 14.39 W.cm-2 intensity, therefore 0.14 - 2.7 W deposited power, 5% duty cycle, 0.5ms PW, therefore 0.002 to 0.003 W.s deposited energy, used for consciousness state enhancement in intensive care patients [11] had an area of 1.22 cm2, 115.8 W cm2 intensity, and they tried both modes: CW (2 ms - 15 ms), and PW (0.5 – 5 ms) with 25 - 50% duty cycle. The deposited power is 141 W and deposited energy CW 0.141 - 1.06 W.s, PW 0.008 - 0.170 W.s, used for revert blindness, as demonstrated by enhancement of visual evoked potentials. All in all, instantaneous power as described by PW in Table I, with different duty cycles, has a range of 0.035 - 141 W across the authors. The energy levels involved range from 0.002 - 0.170 W.s. to alter nervous system obtaining as a result alteration of consciousness levels [4] and to enhanced visual evoked potentials of retinal pigment epithelium (RPE) dysfunction [11] who also used CW with similar results [2] and [9] obtain promising seizure inhibitions using CW US albeit their publications do not allow to infer the amount of energy delivered. [13] using CW reach an ablation level energy of 25 - 159 W.s and temperature increase of 6.6 - 30.6 ºC for thermal ablation in phantoms as simulator as soft tissue. In our work we reach an energy delivered of 0.32 - 1.98 W.s which is in the range of neuromodulation according to the review.

Variety in the parameters of the studies reviewed suggests that it is mandatory to continue investigating the use of US for neurological treatment in order to have a global consensus for its clinical use. There is not yet a large number of works that focus on epilepsy from the point of view of US as a treatment, so many of the variations seen in the parameters of Table I are different due to the problems addressed, in addition to epilepsy. The results range from neuromodulation of the visual cortex for the treatment of blindness [11], activation of autophagy for the improvement of neurodegenerative diseases [14], changes in the state of consciousness [4], tumor ablation [15] to behavioral disorders [12]. The case of epilepsy as being addressed by [9, 3, 2, 10] with unclear results with respect to the interaction of US with epileptic foci. The published parameter radius does not allow us to calculate the deposited energy in view of comparing it with an estimation of the energy needed to either destroy or modulate neural tissue. The direct measurements of US deposited energy is object of a companion paper [16]

Calculating the energy deposited in phantoms or in vivo tissue is of crucial importance since it integrates the factor of time with the intensity of the transmitter. Time is a double effect variable since the longer the time, the greater the energy deposited, but the longer the time, the absorption coefficient will have more interference since much of that energy will be dissipated by the tissues in the form of heat [13] or blood flow heat transfer. Precisely, one of the terms that most influences ultrasonic ablation in the biothermal model is blood perfusion, which acts as an energy sink.

V. Conclusions

There is not yet a device that assures neurological patients a non-invasive way for the treatment of their disease, with limited adverse effects and reasonable efficacy. US as a technique is under development and has demonstrated that it is capable of inhibiting specific neural activity as well as specific ablations. The variety of physical parameters on which to base US ablation and neuromodulation makes it necessary to reach a consensus on hard facts including frequency, intensity and energy deposition rate.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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