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General Review

Therapeutic Ultrasound for the Heart: State of the Art

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Abstract

This work describes the use of therapeutic ultrasound as a treatment of cardiovascular disease including recent, state of the art approaches. Therapeutic ultrasound researchers have made recent advances in the highly dynamic and changing world of interventional cardiology where they are confronted with several challenges, such as of the complexity of ultrasound propagation in the highly heterogeneous environment of the thorax or the complexity of the heart (in term of motion and physiology). It is believed that with these recent innovations, therapeutic ultrasound for cardiac applications will soon have a place in the toolkit of cardiologists.

Keywords: Ultrasound therapy; Cardiovascular disease treatments; HIFU; Ultrasound ablation

1. Introduction

Cardiovascular disease (CVD) is a major concern for current global health. According to the American Heart Association (AHA) [1] and the European Society of Cardiology [2], CVD is the number one cause of death in Western countries.

CVD affects the heart and surrounding blood vessels and can be divided into two classes:

- **Structural disorders.** These affect the anatomical function of the heart such as malfunctioning valves, coronary artery blockage or congenital heart defects.
- **Electrical disorders.** These concern all mechanisms involved in an abnormal production or propagation of electrical waves through the heart. Electrical disorders could be the consequence of isolated cells malfunctioning, scar tissues and/or other perturbations in tissue electrophysiological structures.

A wide range of techniques combining the use of medication, surgery and other interventional means (e.g. stents) are used to cure CVD. Cardiology research is under a constant state of rapid evolution leading to improved outcomes for CVD patients [3].

Direct, real-time and inexpensive, ultrasound imaging is already utilized as a routine clinical procedure for cardiology, often coupled with contrast agents [4]. Advances in ultrasonic imaging systems have improved diagnostic abilities by incorporating new imaging enhancement technologies such as ultrafast imaging (allowing for elastography and electromechanical imaging) [5] and 3D/4D imaging [6] allowing for a better understanding and monitoring of tissue properties.

Therapeutic ultrasound (TU), using ultrasound as a treatment as opposed to a diagnostic, is seen as an emerging technology in the cardiovascular field as well. Over the last decades, many researches have highlighted that TU could provide alternatives to the existing radiofrequency or cryotherapy-based catheters thanks to its versatility. As an extremely versatile tool, TU can be used for a large variety of applications [7]. These applications include thermal ablation, distant scalpel, and even drug delivery.

In the following, after a quick summary of the bio-effects capable of being induced using TU, we review the different

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techniques applied to the treatment of CVD and their current status. We also consider their challenges and limitations to find a way to their clinical viability.

2. Therapeutic ultrasound: principle

A summary of the bio-effects associated with TU is provided to help the reader. Compared with other imaging modalities such as CT-scanning, ultrasound imaging has lower risks of side-effects due to the relatively low acoustic intensities used (e.g. 430 mW/cm^2 spatial-peak, time-averaged intensity for cardiac diagnostic ultrasound device [8]). However, if the energy level is increased, ultrasound does have the potential to induce cellular and tissue level changes in the body. A large part of ultrasound research has been and continues to be done to evaluate and regulate the induced biological effects [8,9]. In the case of TU, these effects are especially important as the energy levels that are used can modify the tissue structure. Ultrasound bio-effects can be divided into two broad categories, thermal and mechanical, which are described in greater detail below.

2.1. Thermal effects

The thermal effects of the US are due to the acoustic absorption of the waves which is converted into heat [10]. It is directly related to the exposure time and intensity of the ultrasound field. One common way to quantify thermal exposimetry is the thermal dose, which is described by the following equation defined as the cumulative equivalent minutes at 43 °C [11,12]:

$$CEM_{43\,^\circ\mathrm{C}} = \int_0^t R^{T-43} dt \tag{1}$$

where T is the temperature and R is 0.5 above 43 °C and 0.25 below 43 °C.

$CEM_{43\,^\circ\mathrm{C}}$ quantifies the biologically equivalent heating time at 43 °C that the tissue undergoes. This thermal dose variable expresses only the equivalence between specific time–temperature exposure configurations. It does not describe the mechanisms of the tissue and cellular level changes induced by the heat. The hyperthermia effect on the cellular behavior under long exposure and mild temperature (e.g. alteration on the cancerous cells proliferation under ∼45° for 1 h [13]) and the thermal lesion caused by high temperature for a short time (e.g. protein coagulation, tissue inflammation and cell necrosis).

Thermal effects are commonly produced by continuous (or quasi-continuous) sonication with relatively low intensities (∼10^2 W/cm^2 spatial-peak, temporal-average intensity). High intensity ultrasound (HIFU) transducers concentrate the US beam energy in a small focal region (focal lengths range from ∼2 to 135 mm [10]). The lesions created are often small (on the order of 1–2 wavelengths [10]), precise and placed without damaging the surrounding tissue.

2.2. Non-thermal effects

Non-thermal effects are attributed to mechanically induced effects of the ultrasonic pressure wave, mainly due to cavitation phenomenon in TU and secondly to radiation force. Non-thermal effects can be produced by short exposure (<0.05 ms) with relatively high pressure (>20 MPa) [14] or with longer exposure and relatively low pressure (∼55 kPa – [15]) to not induce heating. Transducers used are either focalized as HIFU or non-focused.

Cavitation phenomenon is the expansion and contraction of the natural gas voids [16]. This phenomenon is triggered when there are gas voids in the tissue in the presence of an acoustic field. Gas bubbles can dissolve in physiological tissue, but when the tissue is under an ultrasound field, the compression and especially rarefaction waves can cause the bubbles to grow, a phenomenon known as rectified diffusion [17].

Cavitation divides into two forms [17]:

- Stable cavitation describes a sustainable, periodic and non-linear expansion and contraction of a gas bubble.
- Inertial cavitation refers to the violent collapse of bubbles. During this collapse, local pressure and temperature are instantly increased, producing micro-jets and light emission which can cause tissue fragmentation, free radical production and shock-waves.

The second main non-thermal mechanism is the radiation force. The radiation force is a period-averaged force exerted on the medium by a sound wave. It induces the generation of fluid streaming [18] and tissue displacements [19].

2.3. Combinatory effects

Still, it must be noted that all of the aforementioned phenomena interact with each other, creating combinatory effects [20]. For example, a temperature increase induces bubble formation which forms an acoustic mirror due to the impedance mismatch between tissues (∼1.5 Mrayls) and air (415 rayls), increasing cavitation effect (boiling histotripsy [14]).

3. Thermal ablation and arrhythmias

3.1. Anatomy and physiology of the arrhythmias

A complex electrical network runs through the heart causing its contractions: from the sinoatrial node in the right atrium, electrical impulses travel through the heart, first in the atria then descending to the ventricles through the atrioventricular node. Alteration of the "normal" pattern of electricity causes arrhythmias often due to unwanted tissues which create abnormal electrical pathways. These lead to shortcuts, re-entrant circuits, or ectopic pulsing nodes [21] which encompass several diseases including atrial fibrillation, the most prevalent one [22].

Arrhythmias treatments include medication, heart resynchronization (pacemaker), catheter intervention and/or surgery. In lieu of conventional surgery cardiologists more commonly prefer the use of catheter ablation [23]. As with surgery, thermal ablation attempts to treat arrhythmias through the destruction of the abnormal electrical zone.

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