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Extracorporeal acute cardiac pacing by High Intensity Focused Ultrasound

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ABSTRACT

Ultrasound has been shown to produce Premature Ventricular Contractions (PVC's). Two clinical applications in which acute cardiac pacing by ultrasound may be valuable are: (1) preoperative patient screening in cardiac resynchronization therapy surgery; (2) Emergency life support, following an event of sudden death, caused by cardiac arrest. Yet, previously the demonstrated mean success rate of extrasystole induction by High Intensity Focused Ultrasound (HIFU) in rats is below 4.5% (Miller et al., 2011). This stands in contrast to previous work in rats using ultrasound (US) and ultrasound contrast agents (UCAs), where success rates of close to 100% were reported (Rota et al., 2006). Herein, bi-stage temporal sequences of accentuated negative pressure (rarefaction) and positive pressure HIFU transmission (insonation) patterns were applied to anaesthetized rats under real-time vital-signs monitoring and US imaging. This pattern of insonation first produces a gradual growth of dissolved gas cavities in tissue (cavitation) and then an ultrasonic impact. Results demonstrate sequences of successive successful HIFU pacing. Triggering insonation at different delays from the preceding ECG R-wave demonstrated successful HIFU pacing induction from mid ECG T-wave till the next ECG complex's PR interval. Spatially focusing the beam at different locations allows cumulative coverage of the whole left ventricle. Analysis of the acoustic wave patterns and temporal characteristics of paced PVCs is suggested to provide new insight into the mechanisms of HIFU cardiac pacing. Specifically, the observed HIFU pacing temporal success rate distribution suggests against sarcomere length modulation current being the dominant cellular level mechanism of HIFU cardiac pacing and may allow postulating that membrane deformation currents are dominant at the applied insonation conditions.

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1. Introduction

1.1. Cardiac pacing by ultrasound

Harvey first described the ability of ultrasound energy to cause premature ventricular contractions in 1929 (Harvey, 1929). Over the past several decades, the effect of ultrasound on cardiac tissue has been described in various species and with varying effects, depending on the exposure conditions (Dalecki, 2004; Dalecki et al., 1991; Delius et al., 1994; Miller et al., 2011; Tran et al., 2009). Some of the clinical interest in this phenomenon concerns observations of arrhythmia induction during diagnostic ultrasound examinations or lithotripsy (Dalecki et al., 1991). Yet, if acoustic energy can produce a pacing focus without significant myocardial injury, it would be clinically useful and would be considered a disruptive technology in the fields of clinical cardiology and electrophysiology. The ultrasound device would not require surgery or any intravascular catheter-based procedures, avoiding all the complications and high costs associated with implanted devices. In contrast to the current standard of temporary transvenous pacemakers, the envisioned technology would be completely extracorporeal: an external, wearable ultrasound pacemaker. Such a pacing system could be utilized for temporary pacing in various clinical settings such as in the evaluation of V–V optimization prior to biventricular lead placement, after cardiac device extraction in the setting of bacteremia, in the setting of acute bradyarrhythmia, acute myocardial infarction or drug toxicity/overdose, during emergency transportation and postoperatively, following cardiothoracic surgery. Currently, the three techniques used for temporary cardiac pacing are suboptimal and problematic: (1) intravascular catheters require invasive procedure, posing the risks of bleeding, infection, stroke, heart attack and death; (2) transcutaneous electrical stimulation can be painful and impractical for prolonged utility, as discomfort from skeletal muscle contraction is often the limiting

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factor in non-invasive pacing use (Syverud, 1988); and (3) epicardial leads placed during cardiothoracic surgery, though rare, major postoperative complications have been reported in patients on anticoagulation or with bleeding diathesis (Nido and Goldman, 1989; Reade, 2007).

Therapeutic applications of ultrasound are based on a variety of thermal or non-thermal biophysical effects (Baker et al., 2001; Dalecki, 2004; O'Brien, 2007). Results obtained by Dalecki et al. (1993) suggest that PVC induction by US is predominantly a non-thermal process. The underlying mechanisms could be cavitation (Rota et al., 2006) and radiation force (Dalecki et al., 1997). A generalized description for acoustic cavitation would include all US induced bubble activity in a medium containing gas bodies (O'Brien, 2007). Acoustic cavitation is characterized by oscillatory motion of gas body envelopes due to acoustic pressure changes. Acoustic cavitation is categorized into two subclasses: stable and inertial cavitation. Inertial cavitation occurs when gas bodies collapse due to inertial forces of the surrounding medium; inertial cavitation is also referred to as transient or unstable cavitation, as opposed to stable cavitation, where bubbles do not collapse due the surrounding medium inertial forces. Acoustic cavitation increases acoustic energy absorption in a medium, and therefore may enhance thermal mechanisms. Non thermal bio-effects of acoustic cavitation may result from acoustic radiation force, strain, micro-streaming shock waves, jetting and free radicals production (O'Brien, 2007). In 1930, Hyman (Hyman, 1930) demonstrated that mechanical stimulation, by needle insertion into the myocardium, is capable of restarting hearts in asystole. This suggests that a PVC could arise from generating an ectopic focus of modest dimensions. Hence, HIFU could be used for cardiac stimulation. HIFU utilization may improve the spatial resolution of stimulation local selection. Moreover, it may improve power utilization and reduce the damage to adjacent tissue.

To produce an effective ventricular contraction a cascade of processes must take place. Initially, the HIFU transmission (insonation) should be properly designed, amplified, directed and timed to reach the myocardium. When ultrasound reaches the target tissue, it produces a mechanical force. Through this bioeffect, ultrasound interacts with the cardiomyocytes via mechano-sensitive pathways activating the mechano-electric feedback circuit, which in turn initiates cellular depolarization. This cellular depolarization produces an action potential that propagates through the entire ventricular myocardium. The process cascade is illustrated in Fig. 1. Effective ultrasonic cardiac pacing requires that this cascade of events be repeated successfully at least 60-80 times per minute.

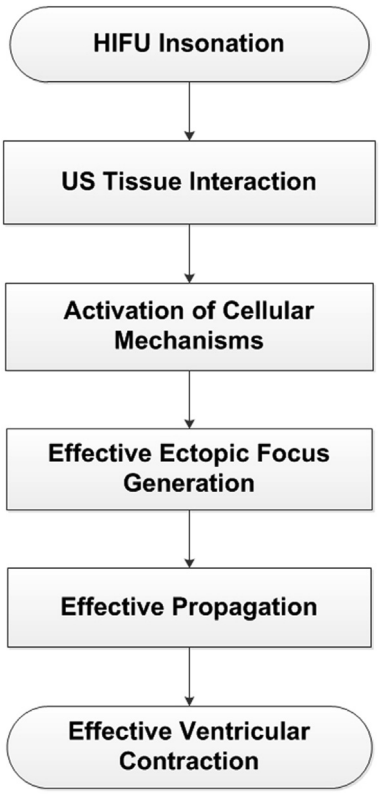

Fig. 1. The cascade of processes that must take place, to achieve an effective ventricular contraction, by HIFU insonation.

1.2. Ultrasound tissue interaction mechanisms

As mentioned above, it is suggested that the relevant US tissue interaction mechanisms are non-thermal (Dalecki et al., 1993), and include combined contributions of acoustic radiation force (Dalecki et al., 1997) and cavitation (Rota et al., 2006). HIFU insonation may induce both stable and inertial cavitation in blood and tissue (Church and Yang, 2006; Church, 2002; Yang and Church, 2005a, 2005b). Moreover, recent work by Krasovitski et al. (2011) presents a cellular level model for intra-membrane cavitation induction under insonation. The model is instrumental in describing US tissue interaction and the resulting bio-effects at levels ranging from the subcellular to the whole organism, and at insonation intensities below and above the cavitational threshold.

1.2.1. Ultrasound safety

Ultrasound is a non-ionizing form of energy, yet its application may damage tissue via thermal and non-thermal mechanisms. In therapeutic US (TUS) applications (Ter Haar, 2007), where high intensity is applied, collateral damage may result due to cavitation and temperature rise. Thus, clinical application of US requires attention to safety and proper dosage. US dosage determination and damage mechanisms were reviewed in (O'Brien, 2007).

1.3. Cardiac mechano-electric coupling

In cardiac tissue, local mechanical stimuli cause myocardial depolarization (Avitall et al., 1982; Pellis and Kohl, 2009; Pellis et al., 2012, 2009a; Taggart and Sutton, 1999). The response of the cardiac tissue is dependent on the magnitude, location and timing of the external mechanical stimulus (Avitall et al., 1982; Quinn, 2013). Mechano-sensitive responses can manifest as either purely electrically events, (early or delayed after depolarizations), or as electro-mechanical events, (premature extrasystolic contractions) (Franz, 1996; Franz et al., 1992; Hansen et al., 1990). In addition, important anecdotal evidence can be found during routine procedures in the cardiac catheterization laboratory, as pressure from a catheter on the cardiac endocardium frequently induces premature beats (Taggart and Sutton, 1999).

Ultrasound can interact with cardiac tissue by imposing mechanical force (radiation force and/or cavitation) on cardiomyocytes and can modulate mechano-electric feedback. Electrical and mechanical activity in the heart is linked through a regulatory loop, involving both excitation contraction coupling and mechano-electric feedback (Bers, 2002; Kohl et al., 2011; Lab, 1982). Mechano-sensitive channels have been described in a wide variety of cell types, not limited to cardiac muscle, skeletal muscle, neurons, epithelium, or oocytes (Morris and Horn, 1991; Morris and Juranka, 2007a,b). Mechano-sensitivity in cardiac tissue has been well documented, involving both cell membrane electrophyisiology and Ca^{2+} handing (Quinn and Kohl, 2012). There is significant evidence supporting the idea that many types of voltage-gated

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