STUDY ON THE EFFECT OF THE SONICATION POWER AND INTERSONICATION COOLING TIME ON THE NEAR FIELD TEMPERATURE IN MAGNETIC RESONANCE HIGH INTENSITY FOCUSED ULTRASOUND

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TABLE OF CONTENT

PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

HIFU	High intensity focused ultrasound
MR	Magnetic resonance
MR-HIFU	Magnetic Resonance High Intensity Focused Ultrasound
POI	Pixel of interest
PRF	Proton resonance frequency
QA	Quality assurance
SAR	Specific Absorption Ratio
WAFT-MRI	fat-water thermal MRI

ABSTRAK

Objektif: MR-HIFU ialah teknologi terkini untuk merawat ketumbuhan dengan secara tanpa pembedahan. Ia adalah selamat dan mempunyai banyak kebaikan, namun komplikasi boleh terjadi samada pada sasaran atau pada kawasan medan dekat. Persediaan ultrabunyi khusus pada MR-HIFU sistem mestilah dibuat sebelum prosedur dimulakan yang boleh mempengaruhi suhu pada kawasan medan dekat ini. Oleh itu, objektif kajian ini ialah untuk menyelidik bagaimana masa penyejukan antara sonikasi dan kuasa sonikasi mempengaruhi suhu pada kawasan medan dekat.

Metodologi: Jaminan qualiti fantom Philips telah digunakan. Jumlah semua pembakaran adalah 100 dengan menggunakan berlainan masa penyejukan antara sonikasi iaitu 30 saat, 60 saat, 90 saat dan 120 saat, dan berlainan kuasa sonikasi iaitu 40 W, 80 W, 120 W, 160 W dan 200 W. Kawasan berjarak dekat diambil pada 2sm dari dasar fantom. Data dikaji dengan menggunakan analisis statistik. Tahap kepentingan ditentukan ($p < 0.05$).

Keputusan: Tiada hubungkait antara masa penyejukan antara sonikasi dan suhu pada kawasan medan dekat, dengan $p = 0.089$. Namun, ada hubungkait signifikan antara kuasa sonikasi dan suhu pada kawasan berjarak dekat, dengan $p = 0.001$. Analisis regresi menyatakan bahawa kuasa sonikasi menyangka perubahan suhu [$R2 = .416$, $F(1,18) = 14.533$, $p = .001$].

Kesimpulan: Tiada perkaitan antara masa penyejukan antara sonikasi dan suhu pada kawasan medan dekat. Namun, ada perkaitan antara kuasa sonikasi dan suhu pada kawasan medan dekat.

Kata kunci: masa penyejukan antara sonikasi, kuasa sonikasi, kawasan berjarak dekat, MR-HIFU.

ABSTRACT

Background: MR-HIFU is a technological breakthrough for non-surgical approach for treating tumour. MR-HIFU is safe with many advantages however complications may occur, at target and the near-field region. Specific ultrasound setup at MR-HIFU console must be made prior to ablation process, which can affect the near-field temperature. The purpose of this study was to investigate how intersonication cooling time and sonication power influence the near-field temperature.

Methodology: Philips QA phantom was used for ablation. A total of 100 ablations were made with different intersonication cooling time, which are 30 s, 60 s, 90 s and 120 s and different sonication power, which are 40 W, 80 W, 120 W, 160 W and 200 W. The near-field region was taken at 2cm from the base of phantom. The data were evaluated using statistical analysis. Level of significance was determined ($p < 0.05$).

Results: There was no significant correlation between intersonication cooling time and the near-field temperature, with $p = 0.089$. However, there is a significant correlation between sonication power and the near-field temperature with $p = 0.001$. Regression analysis indicates that the sonication power significantly predicted the temperature changes [R2 = .416, F(1,18) = 14.533, p = .001]

Conclusion: There is no relationship between intersonication cooling time with near-field temperature. However, there is relationship between sonication power and near-field temperature.

Keywords: intersonication cooling time, sonication power, near-field temperature, MR-HIFU.

CHAPTER 1: BACKGROUND

1.1 INTRODUCTION

Magnetic Resonance High Intensity Focused Ultrasound (MR-HIFU) is a breakthrough technological development which is non-surgical approach for treating tumour. It mainly uses focused ultrasound beam to destroy targeted tissues, leaving surrounding tissue safe. It was approved for therapeutic purposes in October 2004 by Food & Drug Administration (Ringold, 2004). MR-HIFU was used in therapeutic procedure to ablate multiple target organ such as fibroids (Bohlmann *et al.*, 2014; Ji *et al.*, 2017; Zhang *et al.*, 2017a; Zhou, 2011), prostate (Ahmed *et al.*, 2012; Alkhorayef *et al.*, 2015; Mearini and Porena, 2010), breasts (Kovatcheva *et al.*, 2017; Okita *et al.*, 2018; Peek and Wu, 2018), kidneys (Nabi *et al.*, 2010; Ritchie *et al.*, 2010), liver (Holbrook *et al.*, 2010; Wijlemans *et al.*, 2012) and brain (Coluccia *et al.*, 2014; Jagannathan *et al.*, 2009).

The high intensity ultrasound beam is focused into a specific target. The target accumulates energy in a form of kinetic energy and heat which in turn will raise temperature of the target. With prolonged accumulation of the energy and a raised temperature, the ablation can takes place after target temperature for tissue necrosis. All these occur within the target organ without skin incision (Bohlmann *et al.*, 2014; Ji *et al.*, 2017; Zhang *et al.*, 2017a; Zhou, 2011).

MR-HIFU has been widely used throughout the world, and Hospital Universiti Sains Malaysia (HUSM) is also a frequent users. In HUSM, therapeutic procedures are only for uterine fibroids. In MR-HIFU, a specific MR bed has ultrasound transducer which is fixed underneath the bed is used. Patients need to lie in a sustained prone position in the MR tabletop (Figure 1). Then, the bed will be moved into the gantry for scanning and treatment procedure.

The treatment procedure is started by performing routine T2-weighted scan to identify the target. Afterward, the images from MR console transferred to the MR-HIFU console for tumour ablation planning. In MR-HIFU console, a specific settings must be setup before ablation can take place which are target location, near-field and far-field, specific ultrasound settings and repetitions of ablations. The specific ultrasound settings are the sonication power and sonication target cell size. During the ablation, “MR temperature mapping” phase sequence is used. This sequence is a real time temperature monitoring, which is displayed in colour bar and temperature graph. Specific temperature point can also be obtained using this sequence.

Target temperature must be above 60 ^{0}C based on suggestion by Zhou (2011) as this temperature will promote tissue necrosis (Zhou, 2011). This ablation procedure then repeated multiple times, based on the size of the target lesion. The whole process can take up 2 to 4 hours depending on size of the target. Afterward, T1-weighted fat suppression post contrast study is performed in MR console, to check remaining tissue.

Although this procedure has many advantages, complications cannot be neglected. The complications involve the target tissue (Bohlmann *et al.*, 2014; Kim *et al.*, 2015a) and also the surrounding tissues (Jian-Jun *et al.*, 2007; Jian-Jun *et al.*, 2009). Surrounding tissues which are affected include the near-field and far-field. Near-field is defined as the area from the ultrasound transducer toward the target. And for uterine fibroid, it consists of skin, subcutaneous tissue, fat and muscle (Mougenot *et al.*, 2010).

The most documented complication for near-field region is skin burn (Copelan *et al.*, 2015; Leon-Villapalos *et al.*, 2006; Leung *et al.*, 2014; Li *et al.*, 2009; Zhang *et al.*, 2009). Skin burn is particularly common due to the difference between soft tissue and fat in skin structure (Mougenot *et al.*, 2010). For uterine fibroids, few reasons of heat accumulations within the near field region which can be air bubbles (Hacker *et al.*, 2006) or skin defect such as scar (Furusawa *et al.*, 2007).

Numerous researches have been done to study target temperature (Zhou, 2011) and various target cell types (Jeong *et al.*, 2016; Kim *et al.*, 2015b). Only one study investigated about near-field region which was done by Mougenot *et al.* (2010). However, Mougenot *et al.* (2010) only focused the relationship of near-field temperature with different sonication distance and sonication cell sizes. To the best of our knowledge, no study published to investigate the relationship of sonication power and intersonication cooling time with near-field temperature.

Mougenot *et al.* (2010) and Hipp *et al.* (2014) have studied the MR-HIFU using different types of phantoms. Hipp *et al.* (2014) has used phantom for ablation by using tissue-mimicking phantom and porcine tissue. However Hipp *et al.* (2014) study is focuses on distal distance of the phantom which involves air, rubber or acyclic. Mougenot *et al.* (2010) in other hand studies the near-field temperature with the ablation of the generalised anaesthesia of 11 pigs, which found there is linear relationship of the sonication distance and cell sizes with near-field temperature.

However in this study, the property of the phantom is not an issue, as the main focuses of this study is to determine the ultrasound parameters which can affect the near-field heat temperature changes. The property of the phantom is act as a constant variables, thus property of the phantom is not studied.

Due to the fact that there is significant complication at near-field region such as skin burn during MR-HIFU procedure and lack of studies about near-field region especially in regards to sonication power and intersonication cooling time, therefore, the purpose of this study is to investigate the relationship between ultrasound parameters, specifically the sonication power and intersonication cooling time with near-field temperature.

1.2 OBJECTIVES

1.2.1 General Objective

To investigate how intersonication cooling time and sonication power influence the near field temperature.

1.2.2 Specific objectives

1. To determine the correlation between intersonication cooling time with near field temperature
2. To determine the correlation between sonication power with near field temperature

CHAPTER 2: LITERATURE REVIEW

MR HIFU system: components

MR-HIFU system consist of MR ultrasonic transducer, MR scanner and steering board (Filipowska and Lozinski, 2014). The MR-HIFU scanner tabletop has high power transducer embedded within it, together with 3-channel radiofrequency coil, with 1 build into tabletop and 2 channel placed behind patient to ensure optimal coverage and providing high resolution imaging (Filipowska and Lozinski, 2014). The MR system generates 3D images for treatment planning with temperature-sensitive phase images during the procedure. The steering board is to place the target based on the pre-planning procedure. MR temperature mapping phase sequence then is used which converted to temperature mapping.

MR temperature mapping

Based on Rieke and Butts Pauly (2008), there are two ways to measure temperature using MR temperature mapping. Absolute temperature is measured using MR spectroscopy (Kuroda, 2005; Thrippleton *et al.*, 2014) while other are based on relative temperature change based on reference temperature. For relative temperature measurement, measurements are based on proton density, T1 and T2 relaxation time of water proton, the diffusion coefficent, magnetization transfer, and proton resonance frequency (PRF) (Rieke and Butts Pauly, 2008).

Kuroda (2005) has investigated MR temperature mapping using MR spectroscopy which utilised temperature induced water proton chemical shift for absolute temperature measurement. However, it has limited application in realtime MR thermometry due to low temporal and spatial resolution (Rieke and Butts Pauly, 2008).

For the relative temperature measurement, proton density temperature has advantage of measuring fat temperature, however the acquisition is long with relatively high uncertain temperature of 3 ^{0}C (Chen *et al.*, 2006). Other measurement is based on T1 and T2 relaxation time of water proton. T1 relaxation of water proton has been described by Parker (1984), however it time consuming and not suitable for monitoring thermal therapy. T2 relaxation time also was investigated which relies on water composition in tissues. However it has disadvantage of non-linear but sigmoidal increment (Graham *et al.*, 1998).

Other MR temperature mapping has been investigates is Diffusion - Brownian Molecular Motion, which was investigated by Le Bihan *et al.* (1989). However Rieke and Butts Pauly (2008) mentioned that it has difficulty due to fat containing tissue due to low diffusion coefficient in fat. Graham *et al.* (1999) and Young *et al.* (1994) have investigated the effect of magnetization transfer to measure temperature. However Rieke and Butts Pauly (2008) stated the sensitivity is limited and is strongly tissue dependent.

As from Wlodarczyk *et al.* (1998) and Yuan *et al.* (2012), the proton resonance frequency (PRF) methods is the most sensitive way to measure temperature changes, with less than 1^{0}C sensitivity. Fat will cause abnormal signal to the PRF signal (Yuan *et al.*, 2012), due to no hydrogen bonding and causes susceptibility artifact (Poorter *et al.*, 1995). However, based on Yuan *et al.* (2012), PRF is independant of tissue type, but only limited to aqueous tissues. As fat cause abnormal signal to PRF, T2-weighted fat suppression is used during image acquisition. PRF signal is poor for moving organs, on the other hand, stationary lesions such as fibroids is not an issue (Yuan *et al.*, 2012).

In another study by Poorter *et al.* (1995), PRF temperature mapping has been showing good correlation, which based on experiments done for measuring muscle temperature. Poorter mentioned that PRF thermometry has accuracy of 0.2 ^{0}C in phantoms. The study also concluded that PRF has limitation in measuring temperature of tissue containing fat.

As for Philips MR-HIFU machine, the Sonalleve MR-HIFU system uses proton resonance frequency (PRF) to measure temperature and produce mapping maps (Philips, 2010).

Soher *et al.* (2010) has suggested WAFT-MRI technique to overcome the limitation of MR temperature mapping in fat tissue. Soher *et al.* (2010) suggested MR sequence which separates the water and fat during scanning. However it has limitation if the voxel has 0% or 100% fat or water content.

Ultrasound component and near-field

Ultrasound is propagated by displacement of molecules of a medium into regions of compression and rarefaction (Kim *et al.*, 2008). Therefore the energy of ultrasound beam is gradually reduced as it passes through the medium as heat. As molecules of medium attain maximum displacement from initially equilibrium position, their motion stops and this energy transformed from kinetic energy into potential energy associated with position in the compressed zone. As the energy is laterally transmitted, the conversion process of kinetic energy and potential energy repeats itself in cycles. And the some heat will always be loss in the conversion process. Thus production of heat in the near-field occurs (Allisy-Roberts *et* *al.*, 2008). Allisy-Roberts *et al.* (2008) and Mougenot *et al.* (2010) defines as near-field is the region from ultrasound transducer toward the target ultrasound.

In diagnostic ultrasound, energy of propagating ultrasound waves are low, thus energy transfer is low. Nevertheless, the energy transfer is still measured as Specific Absorption Ratio (SAR) as a safety measure for a safe diagnostic ultrasound. However in HIFU, due to the use of high intensity focused ultrasound, energy of the transmitting ultrasound is higher than diagnostic ultrasound. Thus an in depth understanding of near-field heating is required. Time-average intensities for diagnostic ultrasound has maximum of 720 mW/cm^2, however with HIFU system, it can reach up to 100-10000 W/cm^2, with compression pressure of 70 MPa and rarefaction pressure to 20 MPa (Zhou, 2011).

In MR-HIFU, ultrasound transducer is in curvilinear in shape thus ultrasound beam can be focused in a point. The ultrasound beam passes from transducer through water, gel pad, skin, subcutaneous tissue, muscles and lastly to the target. Heat can be accumulates along these layers, but the main focus in this study is the near-field, which is epidermal fat layer. Epidermal fat layer is taken as it is the most occurred complication during this procedure (Mougenot *et al.*, 2010).

The ultrasound transducer emits pulses of ultrasound wave during the ablation of the target lesion then allowed to cool down with intermittent cooling time. The temperature of the target region is measured using MR temperature mapping as a real-time temperature monitoring. Temperature of target region slice 4 and 5 (in Figure 2) is particularly important to the study as it represents the near field i.e. patient's skin and fat. The difference in the tissue component (skin, fat and muscle) causes heat accumulation at this region as ultrasound beam refract and reflect between soft tissue component differences (Mougenot *et al.*, 2010). As Mougenot *et al.* (2010) points out, the complications occur at subcutaneous fat layer rather than skin layer.

Ablation Target - Phantom

In radiology departments, quality control of the machines which include radiograph, fluoroscopy, computed tomography scan and MRI uses phantoms. As thus, the purpose of the phantom is to estimate the dose and evaluate quality of the images of the machine, without reducing the diagnostic value of the images produced. Based on Watanabe and Constantinou (2006), phantoms must closely mimic the human tissue. And based on King *et al.* (2011), the phantom should and have the ultrasonic properties to soft tissue, such as attenuation coefficient, speed of sound, acoustic impedance, thermal conductivity and diffusivity especially in HIFU phantom. Thus Philips phantom should have the acoustic properties as a soft tissue before quality assurance can be used.

Hipp *et al.* (2014) has investigated the safety of phantom in MR-HIFU by using different phantoms. Phantoms investigated were tissue mimicking phantom and ex-vivo porcine tissue. Hipp *et al.* (2014) study focuses on the difference in distal interfaces, by using air, acrylic and rubber. Hipp *et al.* (2014) mentioned that tissue interfaces could cause a shift in HIFU focal spot location.

Mougenot *et al.* (2010) has investigated the relationship of near-field heat with ablation of 11 pigs under general anaesthesia. Mougenot *et al.* (2010) focuses on cell sizes and distance of sonication from the transducer. It shows linear behaviour increment of near field temperature with different cell sizes and sonication distance. King *et al.* (2011) has studied multiple phantom properties to create tissue mimicking phantoms. Many factors have been investigated by King *et al.* (2011) such as acoustic impedance, backscatter coefficient, thermal properties and thermal response under HIFU exposure. King *et al.* (2011) suggested tissue mimicking phantom using a gellan gum hydrogel as the substrate, with aluminium oxide particles, calcium chloride and potassium sorbate.

<u>Applications of MR-HIFU</u>

MR-HIFU has many uses since approved by Food Drug Administrator in 2004 (Huisman and van den Bosch, 2011; Ringold, 2004). Most well published usage of the MR-HIFU is to ablate uterine fibroids. Numerous studies has been published (Bohlmann *et al.*, 2014; Chang *et al.*, 2016; Zhang *et al.*, 2017a) are the few example saying that the MR-HIFU clearly give benefits to patients in post-procedural size of fibroid and the clinical symptoms. And most importantly it is safe to use as alternative to surgical procedure.

Few studies has mentioned about the use of MR-HIFU in adenomyosis. Zhang *et al.* (2017b) reported that adenomyosis is more challenging compared to uterine fibroids due to vascularity. However from Cheung (2017), MR-HIFU for adenomyosis has a good outcome.

Huber *et al.* (2001) firstly described the usage of MR-HIFU for breast cancer treatment on 2001. Merckel *et al.* (2016) also described that MR-HIFU for breast cancer gives very good success rate, with very few complications. Another study by Li and Wu (2013) and Peek and Wu (2018) also mentioned the difference between MR guided HIFU and ultrasound guided HIFU with both benefits from HIFU in tumour ablation of breast cancer.

Catane *et al.* (2007) has described the first application of HIFU for treating bone metastases on 2007. Huisman (2014) has described in detail about HIFU application for pain management for bone metastases. Huisman (2014) mentioned very good success rate in curing the pain from bone metastases. The lesions include either osteolytic, osteoblastic or mixed, which arrives from multiple primary cancer such as kidney, colorectal, breast, sarcoma, prostate, lungs and mesothelioma.

Several applications also noted for ablation of liver tumours (Holbrook *et al.*, 2010). Study by Leslie *et al.* (2012) stated that the ablation of liver tumour has been successive in comparison with intraoperative findings. However MR-HIFU for liver has few difficulties compared to ablation of uterine fibroids. Difficulties include breathing artefacts even with quiet inspiration which will affect the target location and MR temperature mapping (Holbrook *et al.*, 2010). Wijlemans *et al.* (2012) mentioned other difficulty in liver ablation as liver has more perfusion with the presence of hepatic vessels which can distribute heat quickly. Presence of ribs also can limit the ultrasound beam (Leslie *et al.*, 2012).

Ahmed *et al.* (2012) and Alkhorayef *et al.* (2015) have studied the effectiveness of MR-HIFU in prostate tumour. Ahmed *et al.* (2012) mentioned that MR-HIFU is superior in treating prostate cancer with very low genitourinary side effects with early absence of clinically significant prostate cancer. For MR-HIFU prostate specific transrectal HIFU probe must be used (Ghai *et al.*, 2015; Rouviere *et al.*, 2011).

MR-HIFU also has been used to treat brain lesions. Coluccia *et al.* (2014) mentioned that MR-HIFU has been used to treat multiple functional brain disorder such as chronic neuropathic pain, essential tremor, tremor dominant Parkinson's disease. Coluccia *et al.* (2014) has published the effectiveness of MR-HIFU in treating gliblastoma multiforme. Limitations include presence of skull which absorb and deflect acoustic energy (Quadri *et al.*, 2018). However Quadri *et al.* (2018) has stated this limitation has been overcome by a computerized multichannel hemispheric phased-array transducer. Quadri *et al.* (2018) also mentioned for brain application, MR-HIFU still lacking and further research must be conducted.

Despite MR-HIFU is used for treating tumour, it also has roles in cosmetics. Gadsden *et al.* (2011) has studied the effectiveness of HIFU in removing unwanted deposits of subcutaneous adipose tissue in abdominal region. Gadsden *et al.* (2011) mentioned that HIFU is safe for removing and remodelling abdominal subcutaneous tissue for aesthetic reason.

<u>Complication of MR-HIFU</u>

MR HIFU has many advantageous for nonsurgical procedure; however this procedure has many complications. Most common complications are pain and skin burns (Bohlmann *et al.*, 2014; Gadsden *et al.*, 2011; Kim *et al.*, 2015a; Leon-Villapalos *et al.*, 2006; Li *et al.*, 2009; Li and Wu, 2013; Zhang *et al.*, 2009).

According to Jawad and Jawad (2015), there are 3 types of skin burn which are first, second and third degree burn. First degree burn involves epidermis with red appearance and pain. It appear dry and without blister. Second degree burn can be classified as partial or full thickness. Partial second degree burn involves entire epidermis and upper layer of dermis. Blister can appear. Full thickness second degree burn involves entire epidermis and most of dermis. It can appear dry with present or diminished skin sensation. Third degree burn involves all layer of skin with extension into subcutaneous tissue and no pain sensation was felt. Li *et al.* (2009) mentioned that there are few cases of skin burns which involve first, second and third degree burns for MR-HIFU in hepatocellular patient, with the highest of second degree burn with 48 cases, out of 59 patients (67%). Also Jian-Jun *et al.* (2007) mentioned that there are cases of skin burn which involve first, second and third degree burns for MR-HIFU in patient with abdominal tumour, with highest of first and second degree burn with 8 cases each. Leon-Villapalos *et al.* (2006) in the other hand reported only 1 case of full thickness skin burn that requiring surgery. Gadsden *et al.* (2011) also mentioned that 8 patients out of 703 patients (5%) for ablating abdominal subcutaneous tissue have skin burn.

There are few causes identified for skin burn which include skin scar (Zhu *et al.*, 2016), air bubbles within the ultrasound gel (Hacker *et al.*, 2006) or abdominal wall defect such as skin scar or skin dimple (Furusawa *et al.*, 2007). Zhu *et al.* (2016) suggested for scar patch for abdominal scar to reduce risk of skin burn. Ikink *et al.* (2015) suggested MR-HIFU with direct skin cooling which can significantly reduce skin burn in ablation of uterine fibroid.

CHAPTER 3: METHODOLOGY

3.1 STUDY DESIGN

This work is an experimental study (Phantom study), which was conducted in the Department of Radiology, Hospital Universiti Sains Malaysia (HUSM).

3.2 POPULATION AND SAMPLE

3.2.1 Study population (Phantom)

MR Philips Quality Assurance phantom (Philips Medical System, Ayrintie 4, Vantaa, Finland) with serial number: E-1929-4 was used (Figure 3). Dimension is 19 cm diameter and 19 cm height with volume 5388 cm^3. Acoustic property of the phantom is 1536 m/sec and attenuation is 0.417 dB/cm Mhz, density is 1.03 g/cm^3 and acoustic impedance is 1.54 × 106 kg/ (m^2s).

The quality assurance phantom is made by polymethyl metacrylate (PMMA) container filled with a polymer mixture containing mainly gel. After filling, the polymeric mixture inside phantom solidifies and cannot be removed from container.

3.2.2 Sample size

This is a pilot study. Standard deviation of difference was calculated.

3.3 MATERIALS AND METHOD

3.3.1 Research Tools

1. MRI machine – Philips 3 Tesla Achieva MR Scanner, Best, The Netherlands.
2. HIFU tabletop assembly which contained:
    a. Ultrasound transducer
    b. Positioning mechanics
    c. Tabletop connector panel
    d. HIFU pelvic coil
3. MR-HIFU QA phantom (Figure 3).
4. Stopwatch
5. HIFU console (Sonalleve MR HIFU) system (Figure 4)

Integrated clinical MR-HIFU system (Sonalleve, Philips Medical Systems, Vantaa, Finland and Philips Achieva TX 3 Tesla, Philips Healthcare, Best, the Netherlands) was used. It has a phased arrayed 256 channel ultrasound which has an aperture of 12.8 cm, radius of curvature of 12 cm and a focal length of 12 cm, with emitted ultrasound wave of 1.2 MHz. The transducer has mechanical displacement device with 5 degrees of freedom (3 translational and 2 rotational). The system has 5 different sized ellipsoidal treatments which are 2 mm, 4 mm, 8 mm, 12 mm and 16 mm in axial and 10 mm, 20 mm, 30 mm and 40 mm longitudinal dimension.

3.3.2 Imaging protocols

MR images for treatment planning were using 3D T2-weighted turbo spin echo (TSE) pulse sequence [TR/TE = 1000 / 130 ms, echo train length = 62, field of view (FOV) = 250 × 250 × 122 mm, acquisition matrix = 160 × 111 × 90, reconstructed in plane voxel size = 0.49 mm, number of averages = 2] (Table 1). Dynamic temperature monitoring based on proton resonance frequency (PRF) was using 2D fast field echo (FFE) segmented echo-planar imaging (EPI) [TR/TE = 38/20 ms, flip angle = 19.5^0, EPI factor = 11, FOV = 200 × 200 mm, acquisition matrix = 100 × 100, slice thickness = 7 mm, number of slices = 6, in plane pixel size = 1.25 mm] (Table 2).

MR thermometry was used for HIFU ablation by using proton resonance frequency (PRF) with time resolution of 2.9 seconds. 6 planes (3 coronal target region planes perpendicular to the beam axis, and 2 coronal planes positioned of the near-field and far-field. Temperature were calculated online and overlaid on to the magnitude images. Temperature maps (Figure 4c) and heating curve (Figure 4a) were automatically calculated.

3.3.3 Operational definition

1. Intersonication cooling time - Time interval in between each successive sonication (in seconds)
2. Sonication power - Power of therapeutic ultrasound delivered to the phantom in order to cause ablation (in Watt)

3.3.4 Methods

Phantom was placed on top of MR-HIFU tabletop, with degassed water placed in between to avoid air bubbles that can interfere the treatment procedure. Routine quality assurance was performed as a initial phase before MR-HIFU sonication takes place. Pretreatment planning scan was performed using MRI scanner (Philips Achieva 3 Tesla, Philips Healthcare, Best, Netherlands) which consist of fat suppressed T2-weighted, in sagittal and 3 coronal views. Then, these images were transferred to MR-HIFU console (Sonalleve) for treatment planning procedure.

Images were stacked automatically in MR-HIFU console as Monitor Stack A (coronal) and Monitor Stack B (sagittal). Monitor Stack C is the postulated far-field and Monitor Stack D is the near-field (Figure 4b). Based on these stacked images, operator will assign target for the ablation. Specific settings of the ultrasound transducer will then be assigned (as stated below).

3.3.4.1 Measurement of near-field distance

In this study, near-field target is taken at 2 cm and in the middle from the base of the phantom (Figure 4c).

3.3.4.2 Reference temperature

Prior to the ablation procedure, 37 ^{0}C was keyed in to the operating system. Therefore, all ablation were started using a reference temperature of 37 ^{0}C. Thus, the temperature measured from this study does not represent the actual temperature of the cell (phantom) in the near-field region, but a relative temperature to 37 ^{0}C. 37 ^{0}C was selected because it is rounded number for human body temperature.

3.3.4.3 Fixed Parameters

During the procedure, the sonication target distance was fixed at 4cm, which is the midpoint location from the minimum target (0 cm), and maximum target (8 cm) from the transducer, allowed by the system. The target cell size, was also fixed to 8 mm, the MR-HIFU allows for four ablations cell sizes, which are 4 mm, 8 mm, 12 mm and 16 mm. Thus the medium size that is 8 mm was chosen to achieve the objective of assessing the parameters.

3.3.4.4 Variation of sonication power and intersonication cooling time

The sonication power was varied for 40, 80, 120, 160 and 200 Watt. For each sonication power assessed, the intersonication cooling time was varied at 30, 60, 90 and 120 seconds. The time was measured using stopwatch, which starts after the initial sonication has stopped andMR-HIFU cooldown period console has elapsed (Figure 4a, which give example of 118.7 seconds).

The MR-HIFU cooldown period became fixed by the system subject to the sonication power used and the shape temperature curves as a function of time. After the cooldown period has elapsed, the next sonication was performed. The briefest cooling time was set at 30 seconds, which is the shortest possible intersonication cooling time during clinical setting.

Each sonication procedure were repeated 5 times. The whole study consisted of 100 sonication procedures (5 sonication power × 4 intersonication cooling time × 5 repeatition).

3.3.5 Image analysis

Data analysis was performed at MR-HIFU Sonalleve console (Figure 4). During the ablation process, there is variation of colour of the target which indicates by the colour bar. These colour bars represent temperature legends at the treatment panel (Figure 4b). Temperature curve is also generated during ablation process, which completed after the ablation ends (Figure 4a).

Pixel of interest (POI) then was placed at the near-field region which is 2 cm midline from the base of the phantom (based on measurement of near-field). Temperature value was collected at this POI, as post processing (Figure 4c).

3.3.6 Data Collection

Data collection includes intersonication cooling time, sonication power to temperature changes (Appendix B). Table was created for 40, 80, 120, 160 and 200 W with cooling time of 30, 60, 90 and 120 seconds.

3.4 STATISTICAL ANALYSIS

Pearson correlation was applied to identify correlation between intersonication cooling time and temperature variation. Pearson correlation was also applied to identify correlation between sonication power and temperature variation. Then linear regression was applied between intersonication cooling time and temperature variation; and sonication power and temperature variation. Significant value was set as $\alpha = 0.05$. All statistical analyses were performed using IBM SPSS Statistics (version 22).