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Reference-less MR Thermometry on Pre-clinical Thiel Human Cadaver for Liver Surgery with MRgFUS

Abstract

Purpose: Reference-less MR Thermometry can be a promising technique for temperature mapping during liver treatment with Magnetic Resonance-guided Focused Ultrasound (MRgFUS), as it is more robust to breathing motion than Proton Resonance Frequency MR Thermometry. However, there is a lack of a pre-clinical model for repeatable testing of reference-less Thermometry. The purpose of this work was to verify the explanted Thiel embalmed human liver and whole Thiel embalmed human cadaver for application of a custom made reference-less Thermometry algorithm during MRgFUS sonication. Methods: Phase maps were generated during sonication as an input to the algorithm. A square Region-of-Interest (ROI) was designed around the heated area. The ROI was interpolated using a two-dimensional polynomial to the surrounding phase map to calculate the background phase. Results: Using the phase information from the images, the temperature rise was measured. Validation of the methodology showed accordance of temperatures with actual temperatures. Conclusion: The explanted liver and the whole cadaver constitute a promising and feasible model to study reference-less techniques for Thermometry during MRgFUS, before clinical trials.

Keywords: focused ultrasound; liver surgery; MR-guided; pre-clinical; reference-less thermometry

Introduction

Proton Resonance Frequency (PRF) MR Thermometry plays a crucial role in minimally invasive or non-invasive procedures, such as Magnetic Resonance-guided Focused Ultrasound (MRgFUS). Thermometry can provide accurate, real-time temperature measurements with high spatial and temporal resolution. Such thermal feedback facilitates the control and monitoring of the treatment, since it allows an immediate evaluation of the temperature in the targeted area and it can minimize the

risk of thermal damage in the adjacent, healthy tissues [1,2]. A challenge during treatment of abdominal organs with MRgFUS is the organ motion due to patient breathing. The motion can affect both the accuracy of the MR temperature monitoring and the quality of the temperature maps due to motion-related artefacts [2].

In baseline PRF Thermometry, where phase images (baseline) are acquired before heating of the targeted area, registration is performed between the images, and the phases are subtracted to 'read' the temperature rise [2]. Hence, this method is suitable for stationary targets only. However, in moving scenarios, the soft tissue deformation, during the respiratory motion, makes the treatment more challenging, as it induces inaccurate subtraction. For this purpose, the reference-less thermometry, a method which is more robust to motion was developed by Viola Rieke in 2004 [3]. This technique does not require phase subtraction of a baseline phase image before heating. A Region-Of-Interest (ROI) can be selected outside the heated area, but well within the treated object. The phase in the ROI is described by a polynomial (polynomial fitting) as follows:

$$\varphi(x,y) = a_0 + a_1 x + a_2 y + a_3 x^2 + \cdots \quad (1)$$

The a_i coefficients of the polynomial are extrapolated to the centre of the ROI, resulting in the extrapolated phase $\varphi_{extrapolated}$, which is equivalent to the reference phase $\varphi_{reference}$, of the baseline PRF method. Thus the temperature rise is calculated from the following equation:

$$\Delta T = \frac{\varphi - \varphi_{extrapolated}}{a\,\gamma\,TE\,B_0}, \quad (2)$$

where a is the PRF shift coefficient, γ is the gyromagnetic ratio, TE is the Echo Time and B_0 the magnetic field strength [2].

To carry on such a study involving reference-less MR thermometry during MRgFUS into a CE marked application for ablation of liver tumour in clinical practice, more evidence is required. Due to the liver motion and deformation, a model needs to be well defined for its robustness in pre-clinical studies. The model is necessary to have the precise human anatomy, with the liver surrounded by the rib cage. Early studies have successfully developed reference-less approaches for temperature mapping during liver treatment with MRgFUS [4-10]. These studies involved live animal and human testing, requiring challenging ethical approvals most of the time, which obstruct the way to research. Live animal experiments raise numerous ethical concerns, and obtaining a

license is a long and complicated procedure. Animal experimentation is strictly regulated in United Kingdom by notified bodies, i.e. the Animals (Scientific Procedures) Act 1986, and the Animal Welfare and Ethical Review Body following specific rules to minimize the pain suffering of animals.

A fresh human or animal cadaver or a fresh excised animal organ would be of no use, since it rapidly decays. The Thiel embalmed cadaver, on the other hand is more advantageous than other embalmed tissue (i.e. formalin-fixed) due to the fact that it maintains the life-like characteristics, i.e. flexibility, colour, and ease of establishment of ventilation, making the treatment similar to a real human patient [11,12]. In this work, the Thiel embalmed human liver was proposed as a reliable validation tool. Experimental work was provided as an evidence of suitability of a custom-made reference-less thermometry application. This study aims to form the basis for providing a validation tool, using a human cadaver, with the intention to use it for validation of MRgFUS applications during breathing. For the first time, a whole human cadaver is used as a pre-clinical model involving reference-less thermometry. Thus, an initially static model was completed, and based on this proof of concept this model might be utilized in motion experiments. Additionally, it would be desirable to convert the pixel size information into realistic tumour size, so regions of interest with tumour dimensions were selected.

Methods

This section gives a detailed experimental description of the methodology used in this work. Initially, it involves the preparation and the MRgFUS sonication of tissue-mimicking gel phantom, explanted Thiel embalmed liver, and whole Thiel embalmed cadaver. The reference-less algorithm was then applied, with selection of the Region-of-Interest (ROI) around the target area, interpolation, calculation of the background phase, and temperature mapping.

MRgFUS heating

A tissue-mimicking polyacrylamide gel phantom (ATS Laboratories, Bridgeport, Connecticut, USA), six explanted Thiel embalmed human livers and six

whole Thiel embalmed human cadavers were used in the present work. The phantom was cylindrical with 12 cm diameter and 20 cm height, and with 20% polyacrylamide concentration. All the human cadavers and livers were donated according to standard procedures as set out in the Human Tissue (Scotland) Anatomy Act 2006, and the Thiel Advisory Committee (University of Dundee, UK) which approved all procedures involving human cadavers. The explanted livers were excised from freshly slaughtered cows, delivered to the laboratory and left for three hours to adapt to room temperature. The cadavers were handled and moved to the operating room by trained personnel. The cadavers and livers were embalmed according to the Thiel soft-fix embalming method as currently in use at the Centre for Anatomy and Human Identification (CAHID) in Dundee [13].

The heating of the phantom and the livers was performed using the MRgFUS system, which is explained in this paragraph. Pre-sonication planning imaging was performed on the phantom and on the explanted liver, using a 1.5 T scanner (Signa HDx, GE Medical Systems, WI, USA) with a single-channel surface coil (InSightec Ltd, Tirat Carmel, Israel). The MR imaging sequence was a Fast Recovery Fast Spin Echo (FRFSE) sequence, with TE: 88.9 ms, TR: 3340 ms, echo train length: 2, bandwidth: 15.6 mm and acquisition matrix: 256 × 192. Sonications were performed using the ExAblate2100 (InSightec Ltd, Tirat Carmel, Israel) patient treatment system, which was embedded in the scanner. After several scans were applied to obtain the most suitable image quality, a three-dimensional fast imaging employing steady state acquisition (3D-FIESTA), with TE: 1.2 ms, flip angle: 75°, bandwidth: 125 kHz, field-of-view: 42 cm, slice thickness: 5 mm, and an acquisition matrix of 256 × 256 and number of excitations: 1, best imaged the abdominal area of the cadaver (Figure 1(a)). The FIESTA is a fast scanning option that can image fluid filled organs with short acquisition times. The fluids in a FIESTA scan have high signal intensity, whereas the background is suppressed [14]. The transducer was a portable, 1024-element extracorporeal planar transducer with centre frequency of 1.15 MHz and the focal point size was 2-10 mm in diameter and 10-40 mm in length. The portable transducer was placed below the right ribcage of the cadaver to allow unobstructed access of the beam path to the liver (Figure 1(b)). Pre-sonication images were checked to make sure that the focused ultrasound beam path did not pass through air. Before heating, the accurate location of the target area was verified by applying low acoustic energy sonications

(around 400 J) to detect a phase change in the thermal maps. The phantom, the organs and the cadaver were kept at room temperature (17 ^{0}C) prior to sonication. For the actual sonications, acoustic energies of 1000 J and 2000 J were delivered to the liver for 20 seconds. A total number of five sonications were conducted per organ. During each sonication, phase images were generated by the MRgFUS system software (Version 4.1, InSightec Ltd., Tirat Carmel, Israel) under a restricted field-of-view Echo Planar Imaging (rFOV-EPI) sequence with TR: 150 ms or 50 ms per slice. In 30 seconds of phase mapping, 600 phase images were acquired with bandwidth: 62.5 kHz, field-of-view: 32 cm, and an acquisition matrix of 128 × 52. With the restricted FOV-EPI, there is the advantage of simultaneous suppression of signal from fat. By restricting the FOV, only the volume of interest is isolated and there is no need for outer volume suppression pulses [15]. In addition to the phase maps, colour-overlapped PRF thermal maps and temperature graphs were generated by the FUS software.

The reference-less Thermometry algorithm

The reference-less methodology applied in this work was based on a custom made programming code, written in MATLAB software (R2014a, MathWorks, Massachusetts, USA). The phase images that were generated by the MRgFUS console were used as an input to the algorithm. The measurements were performed on the hottest phase image, i.e. the image with the maximum pixel intensity in the heated region. The algorithm gave graphs of phase (rad) plotted as a function of time (s), indicating the maximum phase at each phase image, to visually detect the hottest phase image. Each phase image had a real part, an imaginary part, and a magnitude image. Since there can be potential phase wraps at $\pm\pi$ in the MR images, the real and the imaginary parts of the phase images were fitted separately. During each measurement, the MR scanner automatically labels each phase image with an exam number and a series number. The images were extracted from the MR scanner, and were processed offline on a separate computer. The program identified the images from their exam and series number of the set of the phases labelled by the scanner. At first stage, the phase images were reconstructed to provide colour-coded phase maps that showed the heated area.

An eight-voxel rectangular frame region-of-interest (ROI) was selected by the user around the heated area for the real and the imaginary part of the hottest phase image.

The inner border was outside the heated site, and the outer border was within the object, i.e. phantom or liver. The ROI must always be selected outside the heated area, since any possible pixel change (due to temperature rise) within the ROI can confound the polynomial fit. The ROI was fitted to the outside region of the object in the phantom (Figure 2(a)) and in the liver (Figure 2(b)). The background phase or extrapolated phase, $\varphi_{extrapolated}$, was measured by applying a two-dimensional (2D) polynomial fit of the outside region in the heated region (Figure 3). The 2D polynomial can be described by Eq. (1), where the x, y are the one-dimensional vectors which contain the phase values of 2D matrices in x- and y-directions, respectively. The order of the polynomial, from second to sixth, was determined according to which polynomial best approximated the phase in the ROI, using the 'polyfit' function of the MATLAB programme. Usually, low order polynomials, i.e. first, second, cannot track the background phase and show residual phase in the ROI. Higher order polynomials enhance the phase fitting, however the polynomials with too high order (> 6) increases the variance in the phase, as they detect noise, affecting the temperature maps.

The temperature rise was calculated using the background phase, according to Eq. (2). The PRF shift coefficient of the Thiel embalmed liver i.e. 0.009 ppm/°C [16] was used in the measurements. The total time of the process was approximately four to five hours: three hours to transfer the MR images to the processing computer and one to two hours process and use them for guidance.

Validation of the accuracy of the algorithm

This section describes the validation measurements performed to assess how accurately the methodology calculates temperatures. For this purpose, the temperature rise calculated from the reference-less code was averaged and compared to the baseline PRF temperature rise measured by the FUS console (Version 4.1, InSightec Ltd., Tirat Carmel, Israel). The FUS console is an already CE marked device for the treatment of bone pain and uterine fibroids. Additional temperature validation work in Thiel embalmed tissue ablated with the FUS console has been previously conducted [8]. Thus, the measured temperatures from the code were compared to the temperatures generated by an already validated system.

Results

A series of thermal maps showing the temperature increase in the hottest image were generated for the phantom (Figure 4(a)), the explanted organ (Figure 4(b)) and the cadaveric liver (Figure 4(c)). The temperature maps and the temperature rise were calculated from the phase maps, according to Eq. (2). The average temperature rise measured by the reference-less algorithm was compared to the average temperature rise calculated by the FUS console.

The average temperature differences (with standard deviations) between the reference-less algortihm and the actual temperatures (measured by the FUS system) were 0.2 (±0.01) for the phantom, 0.14 (±0.0) for the explanted organ and 0.22 (±0.01) for the cadaver. Figure 5(a) shows the PRF maps and Figure 5(b) shows the MR magnitude images generated by the FUS system. These maps were reconstructed to show reference-less temperature maps (Figure 6). The validation results showed an average difference of 0.01 °C (±0.001) for the phantom, 0.01 °C (±0.004) for the explanted organ and 0.02 °C (±0.001) for the human cadaver.

Discussion

The purpose of this study was to provide evidence for an *ex vivo*, pre-clinical, Thiel-based human model to test an offline reference-less temperature mapping algorithm. The results of this work demonstrated that the model was suitable for reference-less Thermometry during liver treatment. Since the interest was to select a ROI around a small target area in the liver and the phantom, a restricted field-of-view, Echo Planar Imaging (rFOV-EPI) sequence was used. Other alternatives would be fly-back EPI. However these options were not robust to off-resonance effects to pixel shifts. That would lead to major artefacts in the phase maps, even in the case of the static organ [5]. The rFOV-EPI sequence enabled the generation of high signal-to-noise ratio (SNR) phase maps that indicated the heated region.

Using the real and imaginary parts of each phase map was advantageous and facilitated the reference-less processing by avoiding the complicacy of unwrapping methods. The selection of the ROI around the heated area was performed in the liver. The two dimensional polynomial fit was successful, as it enabled calculation of the background phase and extrapolation (fitting) to the heated region. Using low order polynomials (2^{nd} or 3^{rd} order) has been reported to be more favourable for reference-less calculations (for

more detailed information, please refer to [17]. This induced high-quality thermal maps which demonstrated the maximum temperature rise, via Eq. (2).

The validation tests showed that there were low differences (< 0.5 °C) between the temperatures measured by the reference-less algorithm and the actual temperatures measured by the FUS console, in the explanted organ and in the whole cadaveric liver. The liver temperatures were well in accordance with the tissue-mimicking phantom results. This suggests that the reference-less algorithm could accurately and reliably measure the temperature rise in the Thiel embalmed liver.

The Thiel embalmed liver model was found suitable to perform reference-less MR temperature mapping during MRgFUS heating. With the establishment of the reference-less MR Thermometry on Thiel organ, and with the calculation of the Proton Resonance Frequency (PRF) coefficient for Thiel embalmed human liver (0.011 pp / $^{\circ}$C) [16] this work might pave the 'way' to researchers for various applications on Thiel cadavers, such as moving organs, improvement of acoustic protocols and steering of the FUS beam. Since this reference-less algorithm measures the temperature rise precisely, it meets the basic criteria. This indicates that the model is a good base for others to test any other Thermometry algorithm on Thiel embalmed organs. Moreover, the usage of the Thiel embalmed pre-clinical model can reduce the cost-effectiveness of using living animals, as it is costly to obtain an animal license and animal facilities, and it is time consuming, requiring numerous ethical constraints by regulatory bodies. Last but not least, it can lower the risk of infection due to fresh, frozen and formalin-fixed cadavers and explanted organs.

Conclusions

This study concludes that the explanted, Thiel liver and the whole cadaver constitute a reliable and feasible model to study reference-less techniques for Thermometry during MRgFUS, before clinical trials. The accuracy of the measured temperatures and knowledge of the PRF coefficient of Thiel liver [16] suggest the Thiel model can be the basis for further research involving reference-less algorithms.

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Declaration of interest statement

The authors report no conflict of interest

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Figure legends

Figure 1. MR images of Thiel embalmed cadaver, showing (a) a coronal T1-weighted 3D-FIESTA scan, and (b) a sagittal T1-weighted 3D-FIESTA image of the liver and the transducer.

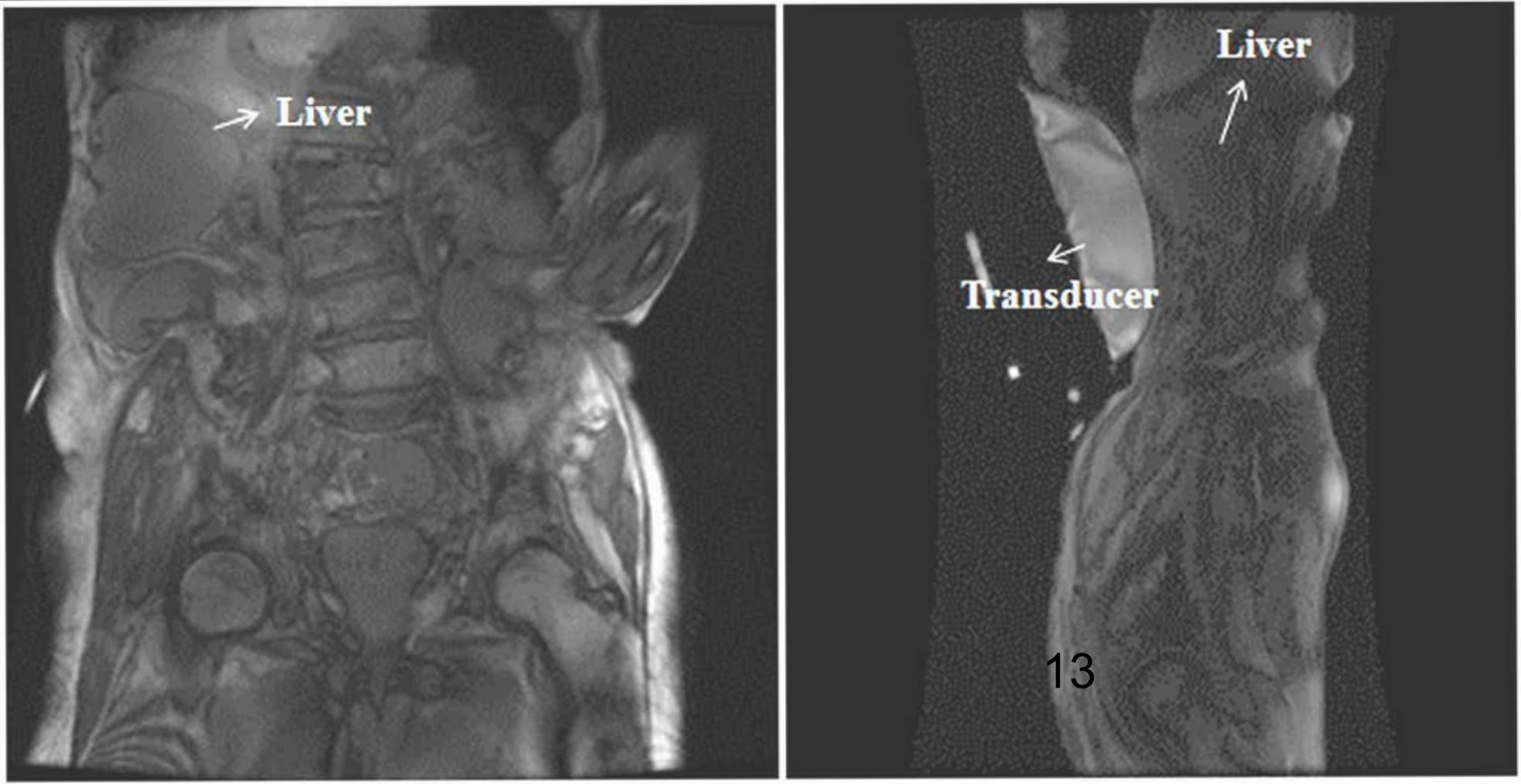
Figure 2. Reconstructed phase images showing the heated areas in (a) a coronal plane in the phantom and (b) a sagittal plane in the Thiel embalmed human cadaveric liver. X-y axes were pixel numbers, and the columns at the right the phase maps were colour bars.

Figure 3. Real and imaginary parts of the two-dimensional (2D) fit of the outside region of the hottest phase image to the heated area of the cadaveric liver.

Figure 4. Temperature maps obtained from the reference-less algorithm, for (a) tissue-mimicking phantom, (b) explanted Thiel embalmed human liver and (c) Thiel embalmed human cadaveric liver. The maps include the temperature rise in ^{0}C (labelled as 'Index').

Figure 5. Colour overlapping during FUS sonication on (a) PRF temperature maps, and (b) magnitude MR images of the Thiel embalmed human cadaveric liver.

Figure 6. Reconstructed temperature maps during FUS sonication of Thiel embalmed human liver in whole cadaver.



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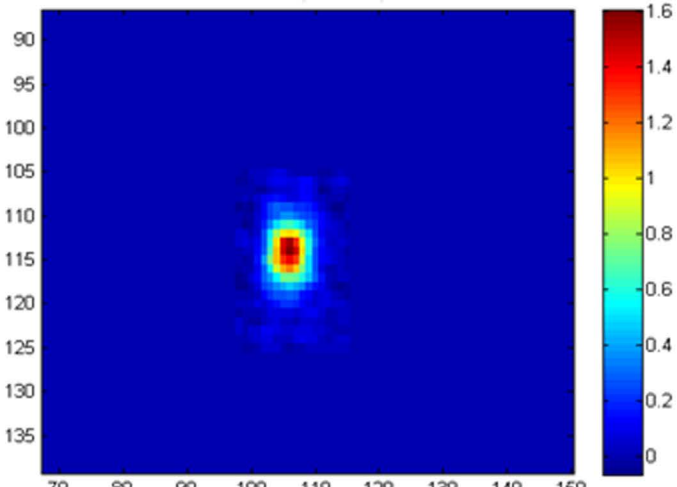
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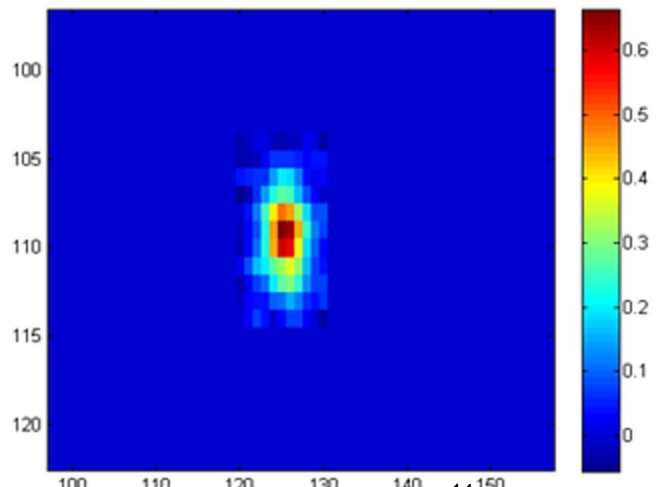
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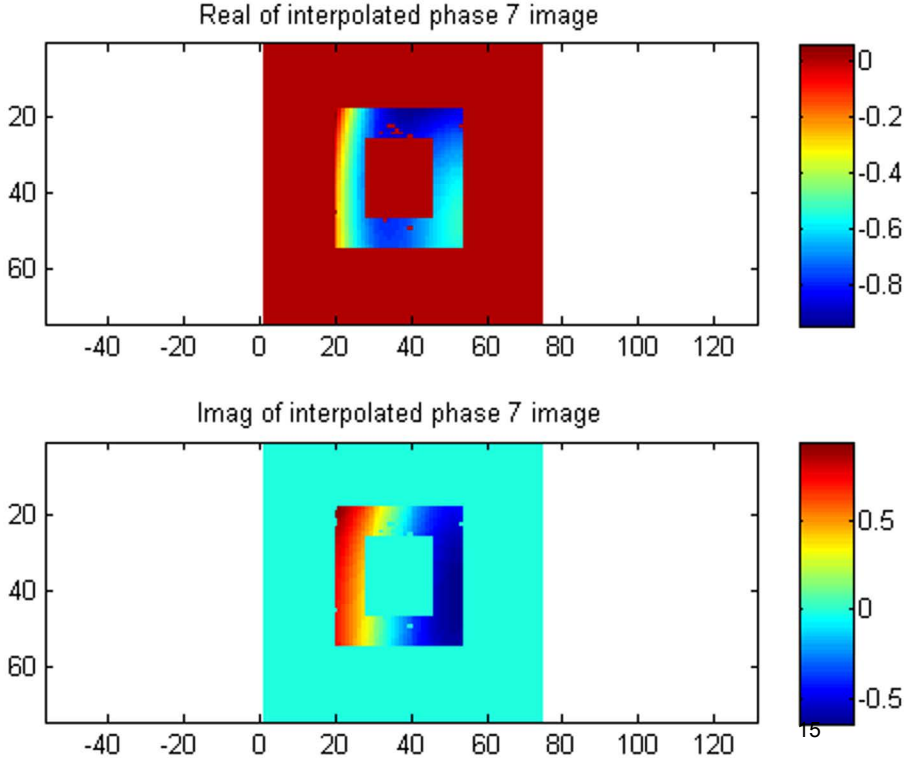
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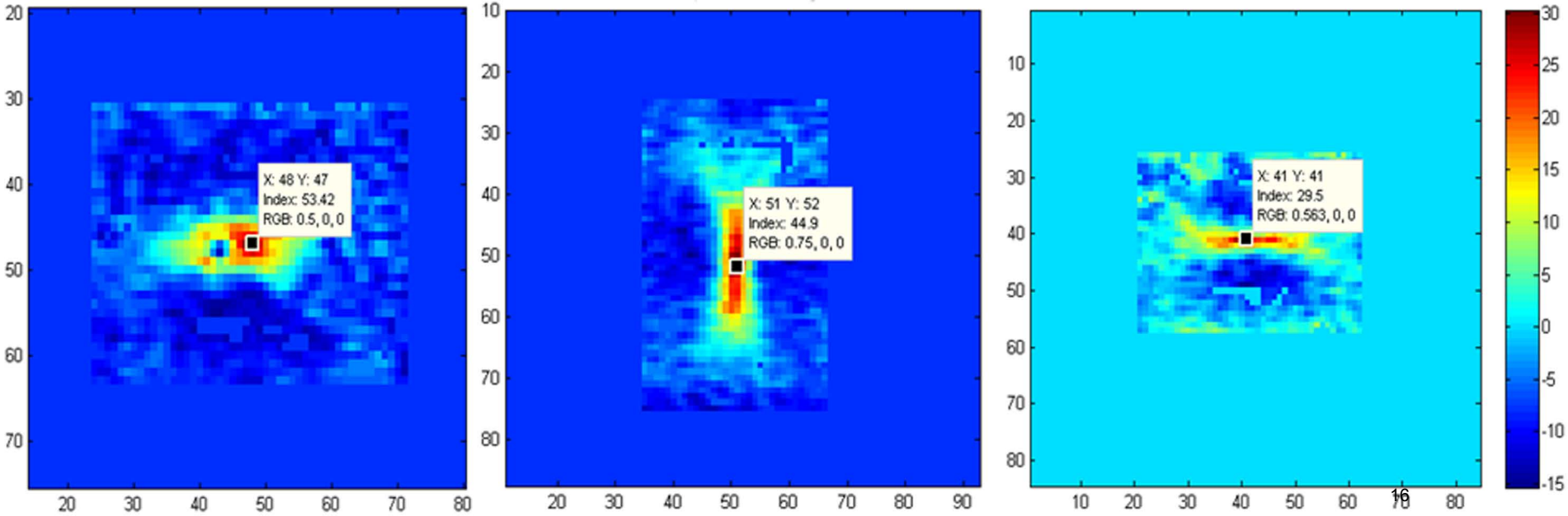
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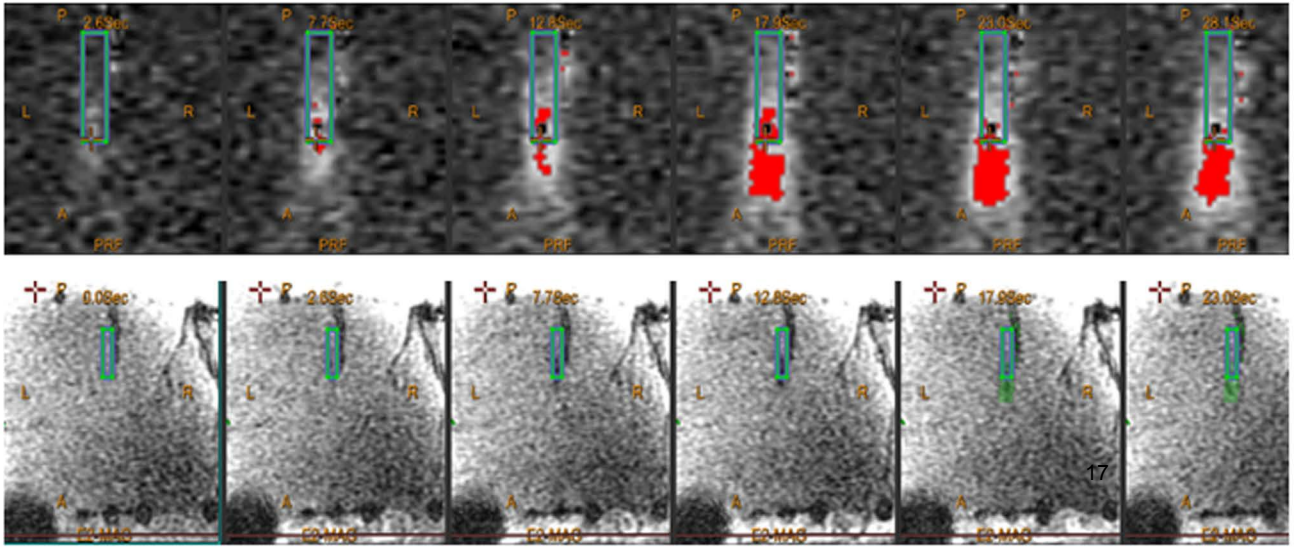
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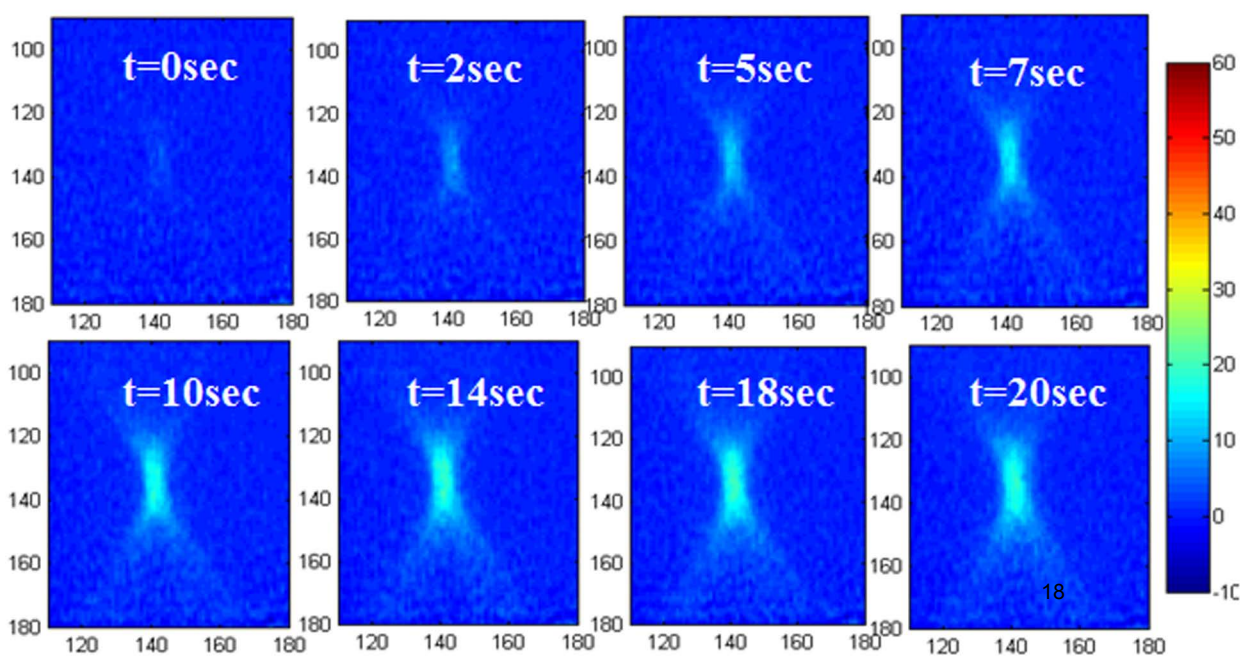
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