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Non-Invasive Measurement of the Temperature Rise in Tissue Surrounding a Kidney Stone Subjected to Ultrasonic Propulsion*

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Abstract

Transcutaneous focused ultrasound (US) is used to propel kidney stones using acoustic radiation force. It is important to estimate the level of heating generated at the stone/tissue interface for safety assessment. An in-vitro experiment is conducted to measure the temperature rise in a tissue-mimicking phantom with an embedded artificial stone and subjected to a focused beam from an imaging US array. A novel optical-imaging-based thermometry method is described using an optically clear tissue phantom. Measurements are compared to the output from a fine wire thermocouple placed on the stone surface. The optical method has good sensitivity, and it does not suffer from artificial viscous heating typically observed with invasive probes and thermocouples.

I. Introduction

While diagnostic ultrasound (US) has a long history of safe, widespread clinical use, its therapeutic counterpart is evolving steadily from research and development to clinical use in an increasing number of applications [1]. Emerging clinical technology require thorough safety assessment. A need arises for improved understanding of the physical phenomena underlying therapy, and for specialized measurement tools and methods. Recently, Harper *et al.* [2, 3] have described the development of a new therapeutic device that utilizes an ex-

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corporeal focused US array to propel, non-invasively, calculi formations and stone fragments within a kidney utilizing the acoustic radiation force property of the sound beam.

A source of concern when bone or calcification is present in the US propagation path is collateral damage from sound absorption and heating [4, 5, 6, 7]. Investigators have worked to estimate typical temperature increases using numerical simulation [7], magnetic resonance imaging MRI [8], and using thermocouples. The tissue bone interface was found to be critical in the heating process. It is possible that similar interfacial heating could occur at the tissue/stone interface within a kidney undergoing US propulsion procedure, which would be important to quantify. Yet, accurate, and time resolved temperature measurements under ultrasonic irradiation can be challenging. Cost and technical issues become important measurement concerns; including spatial and temporal resolutions, accuracy, and viscous heating in the case of invasive tools such as thermocouples [9]. Optical methods for thermometry [10] such as laser-induced fluorescence [11] and Raman scattering [12] hold good promise in meeting many of the technical challenges in pre-clinical laboratory testing. They provide high spatial and temporal resolutions, accuracy, and non-invasiveness, which is important in US applications. They do, however require optical clarity for proper operation.

A novel optical-imaging-based method is described here for the non-invasive measurement of temperature in tissue surrounding a kidney stone undergoing ultrasonic propulsion, *in vitro*. The method bears resemblance to laser speckle thermometry described by Kihm [13] such as the underlying principle, which is light deflection due to thermo-optic refraction. The core of the novel method is the flow measurement technique particle image velocimetry (PIV), which uses a laser light sheet to illuminate passive particles seeded in a medium [11] as tracers. By taking image pairs of the tracers at short time delays, and cross correlating them, their 2-D particle displacement (velocity) vector map in the medium can be obtained.

II. METHODS

A. Experimental Setup

An artificial kidney stone (BEGO USA, Lincoln, RI) of cylindrical shape (dia. 6 mm x length 10 mm) was placed in the center of a plastic box (2.5 cm cube). PDMS (Sylgard 184, DowCorning, USA) was poured, after vacuum degassing, to fill the cube and allowed to cure for two days into an optically clear vulcanized RTV tissue phantom. The stone was allowed to soak in ethanol/PDMS mixture to expel air bubbles prior to casting. The liquid PDMS had 100 nm TiO₂ particles (Sigma-Aldrich, MO, USA) added to it. The particles acted as fixed spatial markers randomly distributed in the tissue phantom. Their negligible amount and sub-micron size rendered them acoustically passive. The tissue phantom was placed in a water tank to provide acoustic coupling with the US head as depicted in fig. 1. The acoustic propulsion system consisted of a Verasonics based US engine (Bellevue, WA) and C5-2 US probe (Philips Healthcare, Bothell, WA). The same probe was used for imaging and pushing. The system was controlled using a Matlab[®] algorithm. Beam focusing on the stone was assured with the machine's US imaging mode. A focused US beam push was fired one at a time, for a duration of 50 ms, and voltage levels of 10 V to 90 V. The operating frequency was 2.3 MHz. Two beam forming modes were used (I) and (II).

The green beam from a 200 mW diode laser (Thorlabs, NJ, USA), was formed using a lens arrangement into a light sheet less than 1 mm thick and about 2 cm wide and was directed to illuminate a cross section of the tissue phantom perpendicular to the stone axis near mid length. A fine wire thermocouple junction was placed at the face of the stone near its mid length prior to casting to provide simultaneous temperature measurement (75 μ m type T bare wire, Omega Engineering, Stamford, CT). The purpose of the laser sheet was to illuminate the embedded spatial marker particles in the sheet plane. A 25 fps, 1292 $\times$ 964 pixel, gray scale CCD camera (Stingray F-125, Allied Vision Technologies Inc., Exton, PA) aligned orthogonal to the light sheet recorded images of the particle positions.

B. Optical Temperature Measurements and Calibration

A sample particle image as recorded by the CCD camera is shown in fig. 2. The particles provided a randomly distributed set of fixed spatial markers within the tissue. When illuminated, each particle acted as a point source of reflected laser rays, which travelled through the tissue phantom to the camera. The geometric intersection of these rays at the CCD imager plane resulted in the formation of the particle image. As the phantom was heated under ultrasonic irradiation, the temperature variations resulted in spatial variation in the optical index of refraction, which caused the ray paths (from the same original particle) to curve and deflect, causing the particle image to shift in relation to the original image taken prior to US exposure. As depicted in the qualitative representation of fig. 3, heating in the tissue phantom would cause the rays to propagate towards the camera in curved paths making them appear to originate from a different location. The PDMS phantom has a relatively strong refractive index dependence on temperature as measured by its thermo-optic coefficient $dn/dT \sim 4.5E-4 \text{ K}^{-1}$, which means good temperature sensitivity. The Matlab[®]-based cross correlation algorithm PIVLAB2000 used in PIV flow studies [11, 14] was employed without modification to detect these apparent planar shifts in the particle positions between the US-exposed image and the pre-exposure (unheated) image. Sub-pixel displacements were accurately identified. Out-of-plane image shift could also occur, leading to out-of-focus particle images, or blurred images, and potentially could result in reduced quality of the correlation peaks. The in-plane (and out-of-plane) particle image shifts were directly dependent on the tissue temperature distribution. Heating had no effect on the particles themselves or their distribution in the tissue mimicking gel.

A particle image displacement resulted from the integral of continuous refractive shifts along the whole ray path from the particle to the CCD. With the current method, a localized heated spot would be more accurately measured than a wider, spatially distributed heated region. In principle, the magnitude and direction of the particle image displacement vector depend on the local temperature (refractive index) gradient and its direction. By knowledge of the temperature far away at the boundary of the tissue phantom domain, it may be possible to integrate the temperature gradient along various paths to the stone surface, resulting in a 2D temperature map. As a first step in the technique of retrieving the temperature information from the particle displacements, a direct calibration approach of the optical imaging signal (particle image shifts) against the thermocouple wire reading was used. A reference ('cold' or isothermal) image of the particles was obtained when the tissue was at uniform temperature prior to the initiation of the ultrasound push. A 'hot' image (or a

time sequence of images) was acquired right after the ultrasound push when an increase in the temperature of the tissue was expected. The cold/hot image pair was cross-correlated using 32×32 pixel interrogation windows. This produced a two dimensional, two-component displacement map $(u, v) = (\bar{u}, \bar{v}) + (u', v')$ as shown in fig. 4, which resulted from cross correlating two sequential particle images similar to the one shown in fig. 2. The displacement map was decomposed into a pure translation component $(\bar{u}, \bar{v})$ from the mechanical push on the whole of the phantom block assembly, plus a distortion component (u', v') from the refractive thermo-optic effect. The rubber-like tissue phantom block had a modulus of elasticity reported by the manufacturer to be around 2 MPa, so the ultrasonic push force (order of <1 gram) was too low to produce any detectable mechanical distortion within the tissue phantom (strain estimated to be of the order $1E-6$), or roughly less than $1E-3$ pixel for a 32 pixel correlation window size, which is on the order of the baseline noise level. The measured image distortions $((u', v')$ order of 0.5 pixel) were thus only due to the thermo-optic effect. The RMS value of the whole (u', v') distortion field over a 2D region adjacent to the stone was computed resulting in a single, spatially averaged distortion value;

$$RMS = \sqrt{\sum (u'^2 + v'^2)}$$

Figure 5 shows the time trace RMS for the total displacement field (u, v) and for the distortion field (u', v') . Filtering out the mean translational component eliminates the effect of background vibrations and phantom oscillations from the US push.

Computing the $RMS = \sqrt{\sum (u'^2 + v'^2)}$ from a 2D area next to the stone amounted to integrating (and averaging) the spatial temperature gradient but disregarding the direction of the gradient. This simple process was deemed adequate as a proof-of-concept preliminary analysis. The time sequence of the distortion RMS was plotted on the same figure as the temperature time trace from the thermocouple as shown in fig. 6. An ad-hoc calibration constant ($^{\circ}C/pixel$) was multiplied with the distortion $RMS = \sqrt{\sum (u'^2 + v'^2)}$ such that it would give optimal agreement between the thermocouple time trace and the distortion RMS time trace during the cooling phase (beyond the thermocouple viscous heating phase; 2~5 sec after the US push).

III. RESULTS

Fig. 6 shows the temperature time trace signals from the stone face thermocouple and from the thermo-optic particle image displacements for two US push cases. The same calibration constant was used for all experiments to convert particle displacement into temperature. The two methods show the immediate heating after the US pulse. Though, the thermocouple signal exhibits an initial viscous heating effect. The optical signal is not biased by viscous heating, and it reads a lower temperature than the thermocouple at the instant of the push. In mode (I) push, it takes about 5 seconds from the US pulse for the two curves to agree. The cooling curves after this point match well. The optical signal is used to yield the peak temperature at the moment of the US pulse, ($\sim 0.4^{\circ}C$). For mode (II) push, the match between the two curves is reasonably acceptable in the initial phase after the push as well as in the cooling tail-off part. The first two optical data points after the push are questionable, and they may be contaminated by the mean phantom translation, or the possible image blurring effect discussed earlier.

IV. CONCLUSION

A novel optical imaging tool for thermometry has been described and demonstrated in the case of temperature rise around a kidney stone being pushed by an ultrasound beam. The method is attractive since it is non-invasive, relatively simple, and can be quite sensitive to temperature rises below 1 °C. The measurements do not suffer from the viscous heating effect encountered in thermocouple data. Sensitivity can be increased with higher optical magnification to better estimate particle displacements. Our current effort is directed towards a more elaborate analysis of the particle displacement field to yield the 2D temperature distribution in the tissue instead of a single point measurement.

The measured particle image displacements resulted from the thermo-refractive distortion of the ray paths. Mechanical displacement of the embedded particles (strain of the tissue phantom) from the US push was deemed negligible due to the relatively rigid tissue phantom. Theoretically, if the tissue is strained from the US push, it will recoil back once the effector disappears. The elastic recoil time scale (based on Young's modulus, density, and length scale) is estimated to be 0.4 ms. If mechanical tissue deformation is present it may not be possible to detect with the current frame rate of the CCD. Hence, it would not affect the temperature measurements. Lastly, due to the optical nature of this technique, it would be quite challenging to extend it for use *in vivo*. However, it can be an invaluable laboratory tool.

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Figure 1.

A picture of a section of the experimental setup showing the artificial, cylindrical kidney stone inside the tissue-mimicking phantom block with embedded marker particles around it. The whole system was placed in a water tank for acoustic coupling. The curved ultrasound head appears on the right. The thermocouple wire can be seen wrapped around the center of the stone. During experimentation, the US head position was adjusted to focus the beam at the side of the stone with the thermocouple junction.

Figure 2.

A sample gray scale image of the spatial marker particles in the tissue phantom illuminated by the laser light sheet. The circular object to the top left is the kidney stone.

Figure 3.

A schematic description of the thermo-optic particle image displacement effect. Particle (A) is illuminated by the laser sheet propagating into the page, while the camera records from the left. In an isothermal tissue medium, the particle will reflect rays in straight path marked as (1) and their intersection in the CCD plane forms the image of the particle. When a thermo-refractive index gradient is generated with the US pulse, the rays originating from particle (A) will travel in a curvilinear path denoted as (2). These rays will appear in the CCD imaging plane to originate from the location marked as (B). The shift (d) within the plane of the light sheet can be measured from cross correlating an image pair taken before and after the US pulse. An out of plane image shift can result too, which would manifest as out of focus effect.

Figure 4.

Distortion map (u' , v') from a 50 ms, 30 V ultrasound push (mode I), taken within 0.04 sec after the push (first frame). Stone on top left.

Figure 5.

Time trace of the spatially averaged particle image displacement; *above*: total particle displacement field (u, v) ; *below*: distortion particle displacement field (u', v') . The US push was fired at time zero, with 40 V in mode (I).

Figure 6.

Temperature rise time trace plots from the stone surface thermocouple (small gray dots) and from the thermo-optic particle image displacement (black circles) when a single US push pulse is discharged at time zero seconds for mode (I) push at 30 V (top); and mode (II) push at 90 V (bottom).