An experimental investigation into the all-optical acousto-optic interaction within a tellurium dioxide crystal is presented. The all-optical acousto-optic effect describes the combination of laser generated ultrasound with acousto-optic interaction. Laser generated ultrasound spectra are analyzed for tellurium dioxide using a 266 nm and a 1064 nm pulsed source, and used to characterize the acousto-optic interaction. The interaction is shown to be dominated by longitudinal acoustic waves. Results are given for a simple device structure which obtains nearly a thirty percent diffraction efficiency. Future trends are also discussed. The authors would like to thank GE Global Research for their support of this work.

TUESDAY, OCTOBER 7, 2003

* Author presenting Paper

Session: 1G

CONTRAST AGENTS IV
Chair: H. Routh
Philips Research

1G-1  4:30 p.m.
(Invited)
ULTRASOUND-INDUCED BIOEFFECTS:
MICROBUBBLES AND PATHOPHYSIOLOGIC
RESPONSES TO INJURY
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Although the benefits of ultrasound contrast agents (CA) are widely accepted, researchers are assessing their cardiovascular risks. CA-induced cardiovascular bioeffect risks can be categorized as: intravascular, transvascular, and extravascular. Intravascular bioeffects are characterized by hemolysis of erythrocytes in microbubble-containing insonified blood. Results of in vivo studies, supported by in vitro studies, document this phenomenon. Cavitation is the suggested mechanism. Transvascular bioeffects are characterized by injury to capillaries, arterioles, or venules. Results of in vivo studies have documented: 1) vascular leakage; 2) hemorrhage; and 3) leukocyte adhesion following insonification of microbubbles in blood. Based on vascular structure, the mechanism of injury is likely limited to capillaries. Results of in vivo studies suggest that leakage could result from alterations in endothelial permeability and alterations of occluding (tight) and anchoring junctions of continuous and fenestrated endothelia (skin, muscle, intestine). Mechanisms leading to hemorrhage require endothelial injury of sufficient severity to allow erythrocytes to escape. It has been hypothesized that leakage and hemorrhage result from cavitation. Injury to endothelia could also result in alterations of membrane: 1) selectins, ICAMs, and integrins that mediate leukocyte/platelet-endothelial cell adhesion, and 2) proteins that
regulate thrombosis and platelet adherence by maintaining a nonthrombogenic boundary between coagulation cascade molecules and luminal surfaces of endothelia. Extravascular bioeffects are characterized by the absence of structural injury to endothelia or cardiac muscle and the transient occurrence of functional lesions resulting in cardiac arrhythmias that occur only when ultrasound interacts with CA. In all three risk categories, inertial cavitation is the most likely mechanism for structural or functional endothelial injury. Based on the proximity of ultrasound-induced bubble dynamics to endothelia in capillaries, pathogenetic experiments should be designed to study the role of microstreaming, exuberant sonoporation, hyperthermia, and free radical activity and their effects on cell-cell junctions, cell membranes, and electrical impulse generation.

We acknowledge the contributions of Drs. Leon A. Frizzell, Douglas G. Simpson, and Rita Miller and Mr. Jim Blue. This work is supported, in part, by NIH grant EB02641 (formerly HL58218) awarded to WDO and JFZ.

1G-2 5:00 p.m.

**OBSERVATION OF TRANSIENT PERFUSION DEFECTS IN A MOUSE HEART USING CONTRAST ULTRASOUND**


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There is a significant interest in noninvasive approaches for tracking anatomical and physiological changes resulting from myocardial infarction in the mouse heart. This is because the mouse provides a convenient model for human cardiovascular disease and is also amenable to genetic manipulation that enables research into genetic influences on the pathophysiology of cardiovascular disease. We assessed perfusion before, during and after an induced closed chest coronary ischemia. Lipid shelled ultrasound contrast agent, in a saline suspension, was injected via jugular cannulation in a bolus. This gave rise to contrast agent related echogenic enhancement in the RV, LV and finally the myocardium in acquired short axis views. In our studies we used a Siemens Sequoia 512 scanner and a 15L8 small parts transducer operating in harmonic imaging mode. Image sequences were transferred from the scanner to a computer for analysis. Regions of interest were manually defined in septal and anterior segments of the myocardium. During the ischemic event, which degraded perfusion in the anterior segment, mean video intensity in the affected segment was reduced by approximately one half. However, following the removal of ischemia, hyperemia (enhanced blood flow) was observed. Specifically, the mean video intensity in the affected segment was increased by approximately 50% over the original baseline level prior to ischemia. Following the approach described by Kaul [1], gamma variate curves were fitted to the time varying level of mean video intensity. In this way it is possible to quantify myocardial blood flow in perfusion deficient regions of a mouse heart using computer automated analysis of contrast image sequences.
ESTIMATION OF VASCULAR DENSITY AND BLOOD VELOCITY IN TUMORS

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Our goal is to evaluate the use of ultrasound to detect small regions of increased vascular density and altered blood flow and to quantify small changes in these parameters due to effects of new anti-angiogenic drugs. Regions containing intravascular contrast agents are identified using a strategy that combines subharmonic and phase inversion imaging. As predicted by a Rayleigh Plesset analysis, this strategy can successfully detect flow over a range of transmission frequencies from 4-6 MHz, and can therefore be used to interrogate tissues as deep as 8 cm. In a study of 25 tumors, we demonstrate that regions of viable tumor as small as 1 mm, as verified by histology, can be detected and show similar morphology to images acquired with computed tomography (CT). The spatial mapping of vessels with ultrasound is superior to contrast enhanced CT due to the intravascular distribution of ultrasound contrast agents. Estimation of the time to 80% replenishment was conducted on kidney and tumor data and is a robust parameter not altered by attenuation. Mean times to 80% replenishment of 1-5 seconds were estimated for the kidney cortex and mean times of 6-14 seconds were observed for viable tumor tissue. This broad range of replenishment times is indicative of abnormal tumor vascular density and tortuosity. Changes in flow parameters with anti-angiogenic therapy are significant beginning at 48 hours post-treatment. We will demonstrate the ability to quantify flow with a variance on the order of 3% for untreated tumors, and have observed that this flow variance increases with treatment. We hypothesize that there is a correlation between the variance parameter and the likelihood of successful anti-angiogenic therapy. For the first time, we also correlate positron emission tomography (PET) images of tumor metabolism (F18-FDG) with those obtained with ultrasound. We show that these maps of increased metabolic activity as estimated by PET correlate with contrast-assisted ultrasound maps of increased blood flow. In conclusion, ultrasound can provide a functional assessment of tumors with a spatial resolution that exceeds other modalities.

We acknowledge the support of Liexiang Fan, Pat Von Behren, and Pat Sutcliffe of Siemens Medical Systems and NIH CA 76062.
Ultrasound contrast agent applications have expanded in recent years to the assessment of perfusion and microvascularity. Myocardial perfusion studies take advantage of fast microbubble disappearance due to exposure to an ultrasound field. Thus triggering the ultrasound exposure at different time intervals allows the imaging of different amounts of fresh contrast agent that enters the field of view. The amount of contrast is then used to calculate myocardial blood volume. A polymer shelled agent, BiSphere\textsuperscript{r} (Point Biomedical, San Carlos, CA, USA), is manufactured to suit this application. The present paper investigates the ultrasound scattering properties of single BiSphere\textsuperscript{r} microbubbles in vitro. A very diluted hydrodynamically focused flow of microbubbles was exposed to ultrasound beams from 1 to 4 MHz transmit frequency and 0.2 to 1 MPa peak negative pressure. The duration of pulses was fixed to 6 periods. RF data were captured using an ultrasound scanner (Sonos5500, Philips, Andover, MA, USA). In a separate experiment data from solid copper spheres of approximately 50mm radius was used to calibrate the transducer receive and subsequently calculate microbubble scattering cross-section (SCS). Furthermore, the microbubbles were subjected to 14 consecutive triggered pulses and their survival rate was assessed. At acoustic pressures above 0.3 MPa microbubble echoes were registered at all transmit frequencies. At 0.5 MPa fundamental SCS was maximum below 1.5 MHz, while the second harmonic SCS was constant up to 2.3 MHz and greater than the fundamental between 2 and 2.4 MHz. A strong ultraharmonic was present at the majority of the scattered echoes above 0.8 MPa. At 0.5 MPa the microbubble echoes disappeared after the first insonation, suggestive of rapid dissolution. A significant proportion of these microbubbles provided echoes shorter in duration than the incident pulse, which is also probably linked with microbubble dissolution during their insonation. The largest release of ultrasound energy occurred for these shorter echoes. In conclusion BiSphere\textsuperscript{r} displayed compatibility with myocardial perfusion requirements, but most importantly the investigated scattered pulses provided spectral and temporal characteristics that could be used to optimise ultrasound examinations.

*Engineering and Physical Sciences Research Council, UK.*
INFLUENCE OF TISSUE ELASTICITY ON GAS BUBBLE DYNAMICS

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Microbubbles are playing an increasingly important role in biomedical and clinical ultrasound. In diagnostic applications, microbubbles are used for image contrast enhancement and targeted/molecular imaging. In therapy, bubbles are actively studied in connection with drug delivery, cavitation bioeffects, tissue erosion, and laser-based microsurgery of tissue. Since bubbles can be introduced in both biological liquid and soft tissue, a theoretical model describing gas bubble dynamics in elastic media was recently developed [J. Acoust. Soc. Am., in review]. In the present paper we interpret this model within the context of biomedical applications by discussing the relative importance of elasticity in the medium surrounding the bubble, and by comparison with experiments performed with gel phantoms. The theoretical model is in the form of a Rayleigh-Plesset equation with a term that accounts for shear stress in the elastic medium. The equation takes into account the fact that the equilibrium gas pressure inside the bubble can differ significantly from the atmospheric pressure some distance away from the bubble. This pressure differential can induce substantial static deformation of the surrounding elastic medium. To evaluate the influence of the elastic medium on gas bubble dynamics, both theoretical and experimental studies were performed. The tissue was modeled using Mooney’s constitutive relation for incompressible media. It was demonstrated that for equilibrium gas pressures close to atmospheric pressure, shear stress in the surrounding medium has a significant influence on bubble dynamics when the shear modulus is on the order of 50 kPa or more. As the equilibrium gas pressure is increased above atmospheric pressure, the relative influence of shear stress on bubble dynamics is reduced. Following the theoretical analysis, experimental studies were performed using gel phantoms with embedded gas bubbles of varying sizes. The gel concentration was varied to change the elastic properties of the surrounding medium. Comparison of measured bubble radii with predictions based on the theoretical model will be discussed. Augmentation of the theoretical model to account for radiation loss, viscosity, and elastic inhomogeneity of the surrounding medium are discussed.

This work was supported by the Office of Naval Research, the Internal Research and Development program at Applied Research Laboratories, The University of Texas at Austin, and U.S. Army Medical Research and Material Command.