Super-Resolution Ultrasound Imaging – A New Technique for Microvascular Imaging

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Introduction

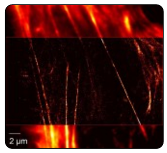
- Ultrasound (US) imaging is used in hospitals throughout the world to visualize a patient's internal tissues in real time
  - Safe, noninvasive, and relatively inexpensive
- Over the last few decades, US image quality has been steadily improving owing to advances in both system hardware and software algorithms
- Like other wave-based imaging techniques, the achievable spatial resolution of US is limited due to the way the acoustic waves spread out (diffract) as they propagate in tissue
  - Two objects are distinguishable from one another only if they are more than half a wavelength apart

Introduction

- While using a shorter wavelength to improve US imaging is feasible to some extent, attenuation of US waves increases strongly as the wavelength decreases
  - Limits the depth that tissue can be imaged
- Resolution limit in clinical US imaging is on the order of a few hundred micrometers
- To obtain higher-resolution US images and at tissue depth, it is necessary to bypass the half-wavelength physical limitation

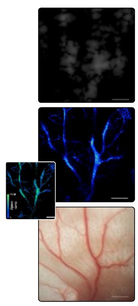
Super-Resolution Optical Imaging

- A breakthrough in light microscopy has introduced the ability to obtain spatial resolutions greater than the diffraction limit of the optical system
  - Awarded 2014 Nobel Prize in Chemistry
- Achievement of super-resolution optical imaging:
  1. Image light-activated fluorescent molecules that act as tiny, randomly distributed sparse flashes of light
  2. Determine the exact position of each point-like source by finding the center of the point spread function (PSF)
  3. Repeat the illumination and detection steps many times until a dense map of point sources has been built up
- Spatial resolution of the resultant optical image exceeds the diffraction limit because it is determined by the accuracy with which the position of each point source can be estimated



Super-Resolution US Imaging

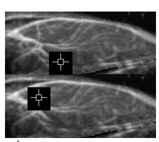
- In 2013, researchers achieved super-resolution US (SR-US) imaging by using a dilute solution of a gas-filled microbubble (MB) contrast agent [1,2]
  - MBs are strong US scatterers and act like point sources
  - *In vivo* spatial resolution of about 20 µm
- In-plane MB tracking allowed quantification of blood flow velocity at the microvascular level
- *In vivo* SR-US imaging of the microvasculature is an exciting prospect
- Potential to substantially advance the study of normal and diseased tissue microvascularity
  - Vascular dysfunction in diabetes
  - Tumor angiogenic network

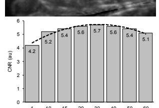


[1] *Viessmann et al., Phys Med Biol, 2013*
[2] *Christensen-Jefferies et al., IEEE Medical Imaging, 2015*

Methodology

- Contrast-enhanced US image data was acquired using a clinical scanner (Acuson Sequoia 512, Siemens Healthcare) equipped with a 15L8 linear array transducer
  - Transducer fixed throughout each imaging period to help capture microvascular patterns along the same image plane
  - Nonlinear imaging mode was used at a low acoustic output (mechanical index, MI = 0.2) to improve MB detection
  - US image data was collected before MB injection and thereafter for 10 min
- Custom Matlab software (Mathworks Inc) was used to implement our SR-US image processing strategy
  - Intravascular MB signal was differentiated from tissue signal using a singular value decomposition (SVD) algorithm which functions as a highpass spatiotemporal filter
  - Number of singular values removed was determined adaptively based on a local contrast-to-noise ratio (CNR) [3]

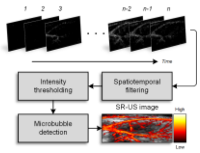




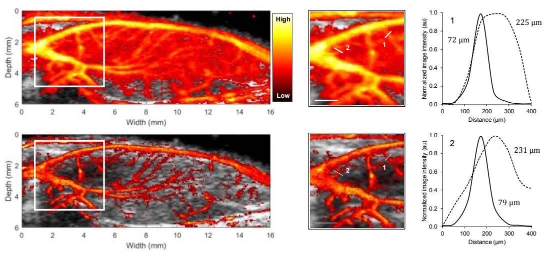
[3] *Ghosh et al, Medical Physics, 2017 (In press)*

Methodology

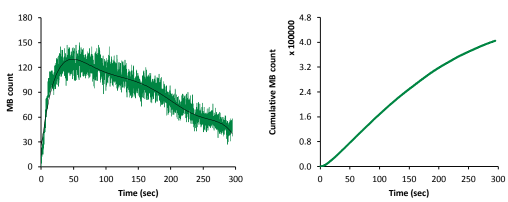
- After isolation of the spatial MB signal, individual MBs were identified before calculation of their intensity-weighted center of mass
- SR-US images produced by processing the entire image stack and mapping cumulative MB position (*i.e.*, MB density image)
  - MB count from each US image can be plotted to describe the time history of MB circulation and used to derive parametric measures of tissue perfusion and microvascular function
- A series of *in vivo* SR-US imaging studies were conducted using healthy mice and animal models of cancer or diabetes
- Histologic analysis of excised tissue samples was used to help validate SR-US findings



SR-US Images Depict Fine Microvascular Detail



Time MB Density Curves

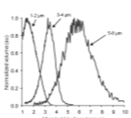


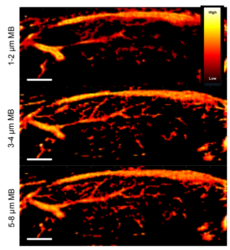
Quantitative analysis of these new time MB count curves will help minimize the variance and reproducibility issues associated with current time intensity curve analyses

Vascular Dysfunction in Diabetes

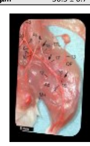
- Diabetes is a major cause of morbidity and mortality, and rising healthcare costs worldwide
- A major aspect of type 2 diabetes and obesity-induced insulin resistance is impaired insulin action in the skeletal muscle
  - 80% of whole body glucose disposal
- Several studies in human and animal models indicate that attenuations in skeletal muscle microvascular responses to insulin play a critical role in disease progression
- Greater knowledge of the processes that regulate muscle microvascular function will increase our understanding of type 2 diabetes and could lead to new therapeutic strategies

Super-Resolution US Imaging
Healthy Skeletal Muscle Microvascularity

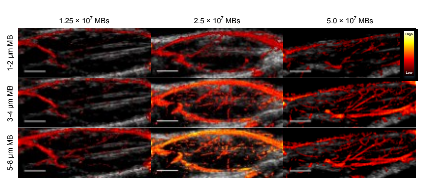




MB size	Microvascularity (% area)
1-2 μm	14.6 ± 2.8
3-4 μm	21.8 ± 2.5
5-8 μm	36.5 ± 6.7

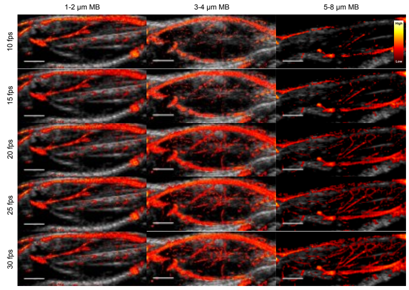


Super-Resolution US Imaging
Healthy Skeletal Muscle Microvascularity



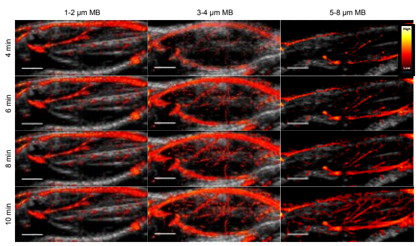
Super-Resolution US Imaging

Healthy Skeletal Muscle Microvascularity



Super-Resolution US Imaging

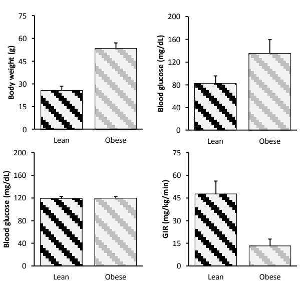
Healthy Skeletal Muscle Microvascularity



Super-Resolution US Imaging

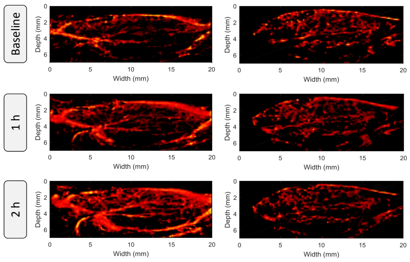
Lean versus Obese Animals

Euglycemic clamp procedure tests how sensitive tissue is to insulin:
- Fixed insulin infusion, 20 mU/kg/min
- Variable glucose infusion, 120 mg/dL



Super-Resolution US Imaging

Lean versus Obese Animals



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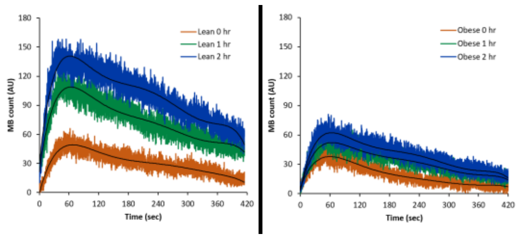
Super-Resolution US Imaging

Lean versus Obese Animals



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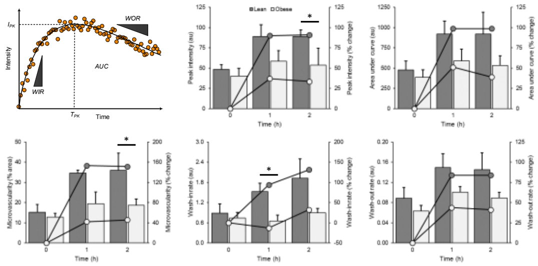
Super-Resolution US Imaging

Lean versus Obese Animals



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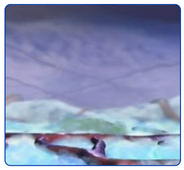
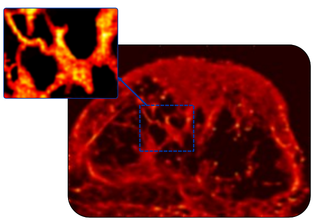
Tumor Angiogenesis

- Tumor growth beyond a few millimeters is driven by angiogenesis
- Increased microvascularity provides a key indication of tumor aggressiveness
  - Blood supply is crucial for the rapid growth of malignant tumors
  - Tumors with greatest amount of angiogenesis are most likely to recur after treatment
- Angiogenesis represents an important imaging biomarker for cancer research
  - Blood vessels form a substantial portion of tumor mass (up to 10% of total volume)



Super-Resolution US Imaging

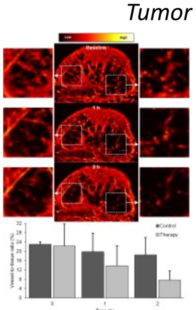
Tumor Angiogenesis

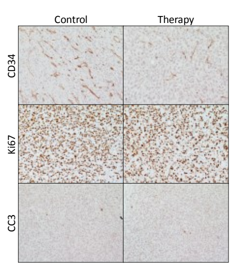


Abnormal vascularity
- Chaotic
- Tortuous
- Dilated
- AV shunting

Super-Resolution US Imaging

Tumor Angiogenesis



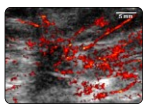


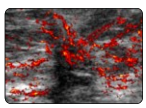
Concluding Remarks

- MB size and concentration has a tremendous impact on SR-US image quality in addition to US system level consideration such as imaging rate and data acquisition length
  - All parameters should be carefully considered when using SR-US for any *in vivo* imaging applications
- SR-US can detail microvascular structures below the diffraction limited (subwavelength) resolution of the US imaging system used for data acquisition
- SR-US is a powerful new imaging modality for quantifying early microvascular changes associated with type 2 diabetes and tumor response to treatment

Future Direction

- Implement 3D SR-US imaging using a programmable US system (Vantage 256, Verasonics Inc) equipped with a custom-built high-speed volumetric imaging transducer technology (4DL7, Vermon)
  - Image processing techniques for quantifying tissue perfusion and microvascular morphology 3D space
- Develop new motion correction algorithms to help eliminate any artifacts that corrupt SR-US image quality
- Clinical translation and *in vivo* SR-US imaging studies in human subjects





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