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Ultrasound diffraction attenuation microscopy in human quadriceps femoris muscle blood flow imaging

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***Abstract*—In this study, by using super-resolution radial fluctuations (SRRF), we propose a non-localizing ultrasound super-resolution method termed ultrasound diffraction attenuation microscopy (UDAM). By applying spatial and temporal analysis to the contrast-enhanced ultrasound image sequence, the point spread functions (PSFs) of diffraction can be significantly attenuated. In human study illustrates the proposed approach can obtain a super-resolved skeletomuscular vessel structure using only hundreds of frames at a frame rate of 30Hz in contrast-enhanced ultrasound (CEUS) imaging mode, after a 2mL dose bolus injection of microbubbles. Compared with the conventional maximum intensity projection (MIP), the UDAM can significantly reduce the full-width-half-maximum (FWHM) of the one-dimensional microvessel signal and distinguish micro structure beyond the diffraction limitation. We conclude from our study that the UDAM provides a perspective non-invasive super-resolution imaging tool for the assessment of microvascular structure in clinical.**

Keywords—CEUS, super-resolution, radial fluctuations, human muscle

I. INTRODUCTION (*HEADING 1*)

Since proposed, the super-resolution ultrasound (SRUS) has been widely discussed, one typical super-resolution method termed ultrasound localization microscopy (ULM) [1] was based on the strategy of microbubble localization. One limitation of the ULM is that there exists a trade-off between acquisition time and microbubble localization accuracy, which results in huge time consumption and limits the clinical application. To ensure the accuracy of localization, sparse microbubble distribution is required to maintain spatial isolation of the microbubbles in each frame [2-4], which leads to a time-consuming imaging process that is not applicable in clinical practice. Localization under a higher microbubble concentration can be a means to accelerate ULM [5], the accuracy will consequently decrease. Some researchers had developed methods to reconstruct super-resolution images under relatively high microbubble concentration. Ruud. J.G. van Sloun et al. [6] proposed a new localization method to attain high microbubble localization accuracy on dense contrast-enhanced ultrasound data using a clinical dose of ultrasound contrast. Bar-Zion et al. [7, 8] introduced a PSF-suppressing SRUS method with a basic idea similar to the super-resolution optical fluctuation imaging (SOFI).

These work inspired us with two ideas. One is the super-resolution imaging can be accolated by developing effective reconstructed method under higher microbubble concentration. The other is super-resolution can be achieved using non-localizing methods. In fact, in addition to the localization, there are many other strategies in optical super-resolution, where a sequence of images acquired in a standard widefield is analyzed to reduce the size of the PSFs and directly generate a super-resolution reconstruction without fluorophore detection and localization, such as SOFI and super-resolution radial fluctuations (SRRF) [9]. As an improved optical super-resolution method of SOFI, SRRF not only includes the temporal fluctuation analysis of a sub-pixel geometrical measure applied to an image sequence but also introduces a spatial transformation, radiality transformation, to suppress the PSFs and improve spatial resolution. SRRF has several potential advantages, including faster calculating speed, smaller reconstructing image stacks, and more satisfactory adaptability

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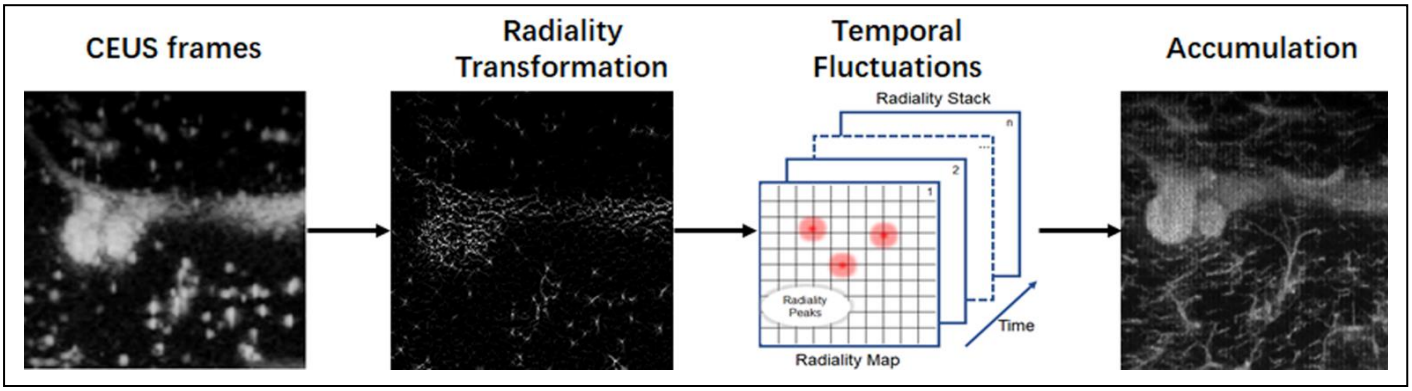

Fig. 1. The flowchart of the UDAM method.

of diversified illuminants, which we speculate that SRRF is probably a suitable method for SRUS.

In this study, we applied the SRRF to the contrast-enhanced ultrasound (CEUS) frames, and proposed a non-localizing SRUS method, which we termed as ultrasound diffraction attenuation microscopy (UDAM). Furthermore, we prove the feasibility of UDAM in human quadriceps femoris muscle blood flow imaging.

II. Methods

A. Super-resolution Radial Fluctuations

The SRRF algorithm was proposed by Gustafsson et al. [9]. Rather than detecting and localizing every single point in a given frame, SRRF estimates the degree of local gradient convergence, i.e., radiality, of the entire frame. For a given image sequence, SRRF then transforms all raw images into a radiality map stack. Thus, the characteristics of the gradient field in images, which are usually discarded by localization techniques, are maintained for further temporal analysis.

The radiality transformation can not only retain the positions of microbubble signal peaks but also a measurement of their local gradient convergence, which is temporally mutative. The radiality provides a new degree of freedom and makes the temporal featuring of microbubbles possible.

By further applying temporal fluctuation analysis (i.e. SOFI), improved performance of the contrast-to-noise ratio and contrast-to-tissue ratio can be achieved from the resulting radiality stack. Thus, a single frame with an enhanced spatial resolution can be obtained.

B. Data acquisition

Before the contrast agent injection, a portable probe holder with multiple degrees of spatial freedom was home-designed and fixed on the clinical bed to avoid probe motion caused by an operator's hand. A linear array operating around a 7-MHz center frequency (L11-3u, Mindray Ltd., Shenzhen, China) was fixed to the holder for imaging. Once the longitudinal section of the quadriceps femoris had been chosen, the whole probe holder was locked.

A vial of 59 mg Sonovue (Bracco SpA, Milan, Italy) was diluted with 5 mL 0.9% physiological saline and a dose of 2mL was injected by intravenous bolus injection into a young healthy male volunteer (26 years old, 80kg). The CEUS frames were then acquired using Mindray Resona 7 system at a mechanical index of 0.09 and a dynamic range of 60 dB. The CEUS videos were recorded at a frame rate of 30 Hz, and the duration of each video was 180 s.

C. Image Processing

The original CEUS videos were acquired from Mindray Resona 7 (video format avi.) and were pre-processed with MATLAB 2018b (The MathWorks, Natick, MA, USA) to transform the video into frames (image format tiff.).

Figure 1 shows the algorithm flow chart of SRRF based UDAM. There are two basic steps, the radiality transformation of each CEUS frame and the temporal fluctuations analysis of all the radiality maps.

The SRRF algorithm was provided in the form of the NanoJ-SRRF software package (provided by Gustafsson et al. [9]), a freely available open-source plugin for the popular ImageJ or Fiji image analysis software (Version 1.52a, National Institutes of Health). We used ImageJ with NanoJ-SRRF software package for UDAM reconstruction. All the frame stacks were reconstructed using the temporal radiality maximum method with the same parameters for all videos (ring radius 1.0, radiality magnification 1, axes in ring 2, and default values for other parameters), except for the number of frames used in the reconstruction.

Typical regions of overlapped microvessels in the maximum intensity projection (MIP) image and the UDAM image were selected and the full-width-half-maximums (FWHMs) were compared to evaluate the performance. The MIP images were reconstructed using MATLAB with the same image stacks that were used for UDAM reconstruction. The corresponding FWHMs in both MIP and UDAM images were then compared.

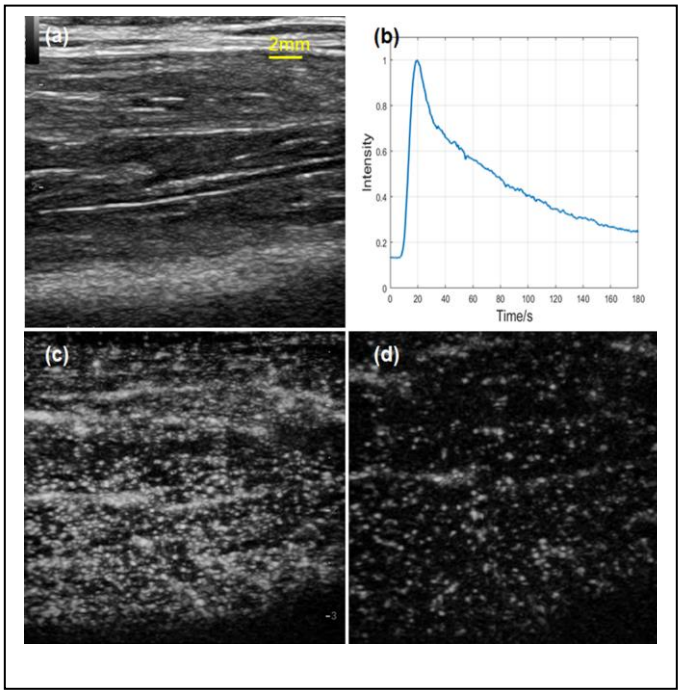

Fig. 2. Contrast-enhanced ultrasound of human quadriceps femoris muscle using a dose of 2mL Sonovue solution injected intravenously. (a) B mode, (b) time-intensity-curve (TIC), (c) a CEUS frame at 20 s after injection, (d) a CEUS frame at 120 s after injection.

III. Results and Discussion

The CEUS results in human quadriceps femoris muscle are shown in Fig. 2, including B mode (Fig. 2a), time-intensity-curve (Fig. 2b) and two typical CEUS frames at different time point. Fig. 2c represents a frame at 20 seconds and Fig. 2d represents a frame at 120 seconds. The microbubble concentration in Fig. 2d has better sparsity compared with that in Fig. 2c, and therefore, is more suitable for super-resolution reconstruction.

One fundamental difference between bolus injection and infusion is the microbubble concentration distribution related to the time. Bolus injection is widely used in clinical to observe and quantify the perfusion of tissue or organs. Many parameters can be calculated from the TIC shown in Fig. 2b, such as wash-in time, blood volume parameters [10]. However, in bolus injection, the beginning of microbubble perfusion process may be not suitable for super-resolution reconstruction. On one hand, the high microbubble concentration makes it different to estimate the real microbubble positions. On the other hand, the microbubbles need several or dozens of seconds to reach the microvessels.

Therefore, we chose a stable and representative time period with relatively sparse microbubble distribution (120-140s after microbubble injection, totally 600 CEUS frames) to exhibit the performance of UDAM. The reconstructed results with MIP and UDAM were shown in Fig. 3. Both MIP and UDAM results illustrate a type of hierarchical and continuous vascular structure,

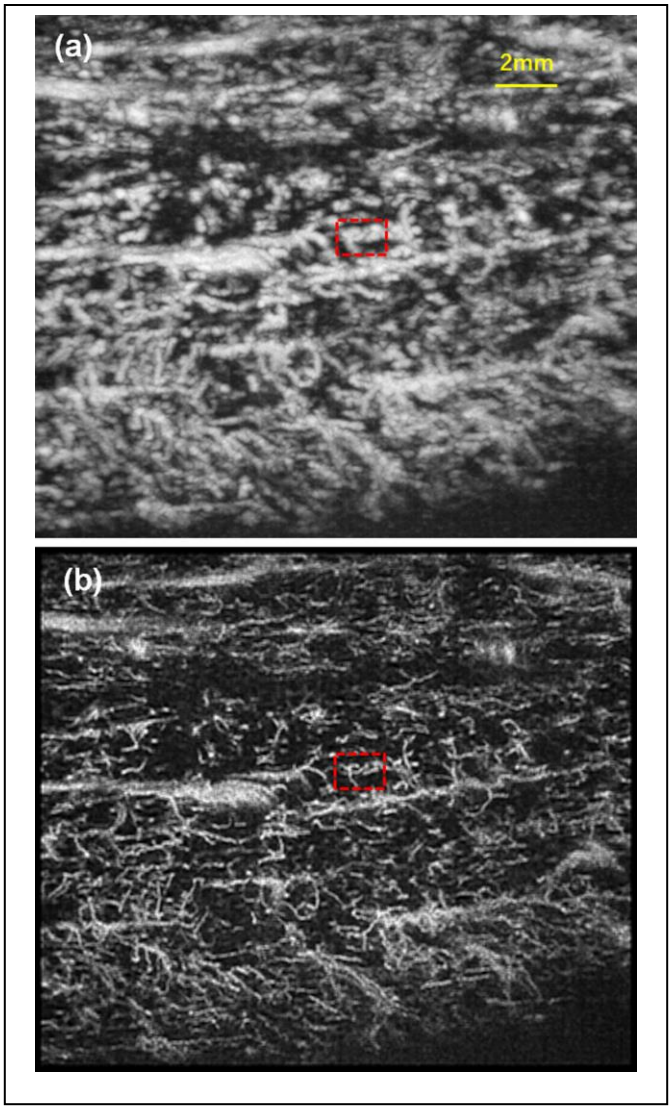

Fig. 3. The reconstructed results using 600 frames (120s-140s after microbubble injection) of the human quadriceps femoris muscle. (a) Maximum intensity projection (MIP), (b) ultrasound diffraction attenuation microscopy (UDAM).

while the proposed UDAM strategy achieves a much better spatial resolution.

To compare the FWHMs of MIP and UDAM images, we selected a small and typical region of interest (ROI) of the images in Fig. 3a and 3b (red dotted rectangles), which are zoomed and shown at the top of Fig. 4. The one-dimensional signals of a typical cross-section (the blue and orange dotedt lines) are plotted at the bottom of Fig. 4. In the Fig. 4b, we can easily observe several microvessels crossing over, while in the Fig. 4a the vessel structure is unclear. The FWHMs are significantly reduced to about 200μm and the three vessels across the dotted line can be easily separated in the UDAM image. This result suggests that the UDAM approach can distinguish microstructure beyond diffraction limitations.

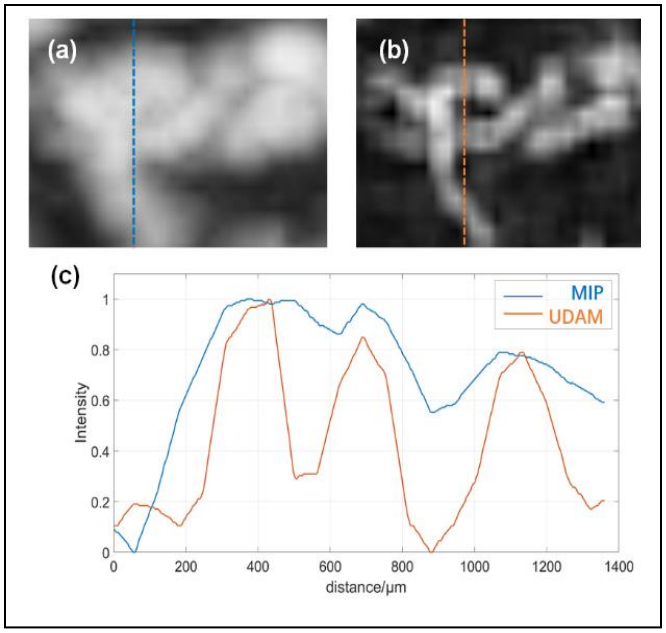

Fig. 4. The zoomed ROIs of the red dotted rectangles shown in the Fig.3 and the FWHMs. (a) the ROI of the MIP image, (b) the ROI of the UDAM image, (c) the one-dimensional signals of the color dotted line in the ROIs.

IV. Conclusions

In summary, we proposed a non-localizing ultrasound super-resolution method based on super-resolution radial fluctuations termed ultrasound diffraction attenuation microscopy. Then we demonstrated the feasibility of the UDAM method on fast ultrasound super-resolution blood flow imaging in human quadriceps femoris muscle. A clear and super-resolved vascular structure can be depicted under a single bolus injection of common contrast agent concentration. Super-resolution images can be reconstructed with only hundreds of CEUS frames in dozens of seconds at a clinically feasible acquisition frame rate of 30 Hz. We conclude from our study that UDAM is a novel, fast, and non-invasive imaging tool for the in vivo assessment of microvascular structures.

Acknowledgments

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