Program Digest, 2019 IEEE International Ultrasonics Symposium (IUS)
Glasgow, Scotland, October 6-9, 2019

Non-Contrast Perfusion Detection with ARFI Variance of Acceleration (VoA) Imaging: Phantom and *In Vivo* Results

Ramya Varadarajan
Joint Department of Biomedical Engineering
University of North Carolina and North Carolina State University
Chapel Hill, NC, USA

Gabriela Torres
Joint Department of Biomedical Engineering
University of North Carolina and North Carolina State University
Chapel Hill, NC, USA

Md. Murad Hossain
Joint Department of Biomedical Engineering
University of North Carolina and North Carolina State University
Chapel Hill, NC, USA

Caterina M. Gallippi
Joint Department of Biomedical Engineering
University of North Carolina and North Carolina State University
Chapel Hill, NC, USA

Abstract*— Low blood SNR makes detecting small vessels, measuring slow flow rates, and assessing blood perfusion without contrast administration challenging. A potential approach is to use Variance of Acceleration (VoA) imaging, which has been demonstrated previously in humans *in vivo* for monitoring subcutaneous bleeding and delineating intraplaque hemorrhage. We hypothesize that, without the addition of contrast agents, VoA can detect slow flow in small vessels for perfusion assessment. Experiments were performed on an ATS 700-D 527 calibrated flow phantom (vessel diameter of 1 mm, flow rates of 0-53 cm/s) and in the surgically exteriorized right kidneys of 3 pigs (2M/1F, mean body weight of 74.4 ± 9.3 kg) at baseline and after inducing ischemia. In the phantom, logVoA increased in the vessel with increasing flow rate, and it remained constant in the background. LogVoA values were higher in the background with versus without the ARF excitation. Similarly, logVoA values were higher in the vessel, particularly for flow rates < 12 cm/s, with versus without ARF excitation. Vessel CNR by logVoA was higher with versus without ARF excitation for flow rates < 12 cm/s, and CNR by logVoA was greater than CNR by power Doppler for all flow rates. Additionally, logVoA was statistically significantly greater at baseline than ischemia in all three in vivo pig kidneys. Finally, logVoA delineates a 1.25 mm-diameter vessel in a pig renal cortex *in vivo*, while power Doppler does not. These results suggest that logVoA could support contrast-free detection of slow blood flow in small vessels and *in vivo* perfusion assessment.

Keywords—ARFI imaging, perfusion detection, non-contrast imaging.

I. Introduction

Blood perfusion is diagnostically relevant as a measure of tissue and organ health. The liver, kidney, heart, and muscles require a steady supply of blood flow to their capillary beds for optimal health and function [1]. Other tissues in the body are similarly affected by lack of oxygen, so tissue perfusion is an important metric that may indicate irregularities and diseases in a wide variety of tissue types. Ischemia in the kidneys, for example, can lead to ischemic renal disease. This condition is characterized by a reduction in glomerular filtration rate, potentially leading to severe complications such as acute renal failure [2].

The current clinical standard for visualizing perfusion using ultrasound imaging is by Power Doppler (PD). PD relies on measuring frequency shifts induced by tissue motion, thus detecting the relative amount of blood flow in each part of the tissue. However, PD is limited in its abilities to assess vascularization in small vessels [3]. PD exhibits decreased spatial resolution and signal-to-noise ratio in smaller vessels, limiting its utility. Further, measuring purely lateral blood flow also lowers PD performance as the ultrasound beam and the direction of flow are aligned [4].

Contrast agents are often used to circumvent this issue. Contrast agents, typically made of gas microbubbles, increase the amount of harmonic signal and echogenicity, improving the spatial resolution of tissue [5]. However, patients with poor renal health, diabetes mellitus, hypertension, and other conditions are at a higher risk of developing complications from contrast agent use [6]. Furthermore, patients who require contrast agents during a sonography procedure typically receive a 2.3 mL dose, which amounts to an added cost of $44.76 USD; factoring in procedure times, contrast agent-aided ultrasound imaging sessions may cost patients an average of $1.42 USD per minute [7]. Given these demerits, an unmet need exists for a contrast agent-free alternative to estimating tissue perfusion that still overcomes some of the traditional limitations of Power Doppler.

Variance of Acceleration (VoA) is a parameter derived from an Acoustic Radiation Force Impulse (ARFI)-induced displacement [8]. VoA is calculated as the variance of the second time derivative of displacement over time kernel, and then the decadic logarithm of VoA is calculated to yield logVoA. Previously, log VoA has been used in vivo to monitor subcutaneous bleeding [8] and delineating carotid intraplaque components in a clinical study [9, 10]. Given that logVoA is a function of signal-to-noise ratio and cross correlation coefficient, it is useful for identifying regions with both variations of echogenicity and decorrelation. We hypothesize

that VoA can be useful for detecting tissue perfusion in small vessels without the addition of contrast agents.

II. Methods

A. Phantom Experiments

An ATS 700-D 527 calibrated flow phantom, manufactured by ATS Laboratories (Bridgeport, CT), was used in a setup to mimic blood flow through a small vessel. The rubber-based tissue mimic is calibrated for a sound velocity of 1,450 m/s with wave attenuation of 0.5 dB/cm/MHz at 23°C. However, the rate of fluid flow is unaffected by this discrepancy. The vessel is 1 mm in diameter, and logVoA was measured for blood flow rates between 3.7 and 21.2 cm/s, with an accuracy of ± 0.2% in flow rate reading. Fluid flow was laminar for all measured flow rates.

The blood mimicking fluid used in this study was ATS 707-Doppler Test Fluid, with a viscosity of 1.66 ± 0.10 cSt and a density of 1.04 ± 0.01 g/cc, as measured at room temperature. The scattering particles are 30 ± 3 μm in diameter, with a fluid concentration of 1.7 ±0.1 particles per cc. The flow pump was connected to the phantom using PVC tubing 10 mm in diameter, so the system was given adequate time to equilibrate and adjust to new flow rates over the course of the experiment.

B. In Vivo Protocol

The University of North Carolina at Chapel Hill Institutional Animal Care and Use Committee approved all animal experiments reviewed in this study. The experiments included 2 male and 1 female pig with a mean body weight of 74.4 ± 9.3 kg at the time of study, and all pigs were anesthetized with telazol (2-3 mg/kg intramuscular) prior to procedure. The pigs were also administered atropine sulfate (0.03 mg/kg SQ) before endotracheal intubation to reduce pharyngeal secretion. Finally, the pigs were administered isoflurane (4-5%) via inhalation to induce anesthesia, which was maintained for the duration of the experiment. Intravenous fluid (0.9% NaCl) was infused at 5 mL/kg/hr, while an ear vein catheter introduced saline infusion at 5 mL/min. A pressure catheter (SPR-350S, Millar Inc., Houston, TX, USA) was placed in the femoral artery to monitor blood pressure using LabChart (AD instruments, Colorado Springs, CO, USA). Pigs were prepared with an aseptic as instructed by the Division of Laboratory Animal Medicine guidelines, and the right kidney of each pig was exposed using laparotomy incisions. Finally, each kidney was excised with a combination of sharp and blunt dissection.

Each kidney was imaged at baseline condition with normal blood flow in all renal vessels. The transducer was held in place during data acquisition using a stereotactic clamp. The transducer was placed along the kidney with the lateral field-of-view aligned across the direction of the nephrons in the cortex. Following this, each kidney was also imaged in an ischemic condition with the renal artery ligated to prevent blood flow into the kidney, with the same transducer orientation.

C. ARFI Imaging

Data were acquired for phantoms with and without an ARFI excitation using a Siemens Acuson Antares and VF7-3 linear array transducer in the calibrated flow phantom. ARFI excitation pulses were generated at 300 cycles at 4.21 MHz, while tracking pulses were two cycles at 6.15 MHz at a focal depth of either 23 or 25 mm.

For the *in vivo* experiments, ARFI data were acquired using a Siemens S3000 Helix and a 9L4 linear array transducer in the right kidneys of 3 pigs, following surgical removal. ARFI excitation pulses were generated at 4.0 MHz for 70 us, focused at 36 mm. The tracking pulses were generated at 6.0 MHz, focused at the same depth.

The collected radio frequency (RF) data were used to measure ARFI-induced displacement calculated with a normalized cross correlation algorithm of kernel size 1.5λ [11], followed by two-stage interpolation and linear motion filtering [12, 13]. The acquired data was processed using MATLAB (Mathworks Inc., Natick, MA). VoA was calculated as the variance of the second time derivative of displacement (i.e. acceleration) through time [14].

RF signal-to-noise ratio (SNR) was derived as μ/σ, where μ is the amplitude of the signal in each pixel per frame, and σ is the average signal amplitude in the anechoic region, representing the noise component of the signal [10]. Finally, Power Doppler was also calculated for each image as a point of comparison for the log VoA method.

The contrast-to-noise ratio was calculated for logVoA, SNR, cross-correlation coefficient, and Power Doppler, using the equation,

$$CNR = \frac{|\mu_v - \mu_b|}{\sqrt{\sigma_v^2 + \sigma_b^2}}$$

where v and b represent the vessel and background regions, respectively, μ represents the analyzed parameter, and σ represents the variance in given parameter.

The positions of vessels and image backgrounds were manually segmented on each B-mode image using the ROIpoly function on MATLAB.

Additionally, logVoA, ARFI peak displacement, and Power Doppler were compared for differentiating between baseline and ischemic conditions, as well as in parametric 2D images for identifying small vessels in the kidney.

III. Results and Discussion

Figure 1 shows the B-Mode, Power Doppler and logVoA images of the phantom in its lateral view, in which a 1 mm diameter vessel is indicated by the orange arrow. This vessel can be identified in the B-Mode image, as well as in the logVoA image, but not in Power Doppler. Figure 2 shows that in the phantom, logVoA remained constant in the background but increased in the vessel with increasing flow rate. LogVoA values were higher in the background with versus without the ARF excitation. Similarly, logVoA values were higher in the vessel, particularly for flow rates < 12 cm/s, with versus without ARF excitation. Vessel CNR by logVoA was higher with versus without ARF excitation for flow rates < 12 cm/s, and CNR by logVoA was greater than CNR by Power Doppler for all flow rates.

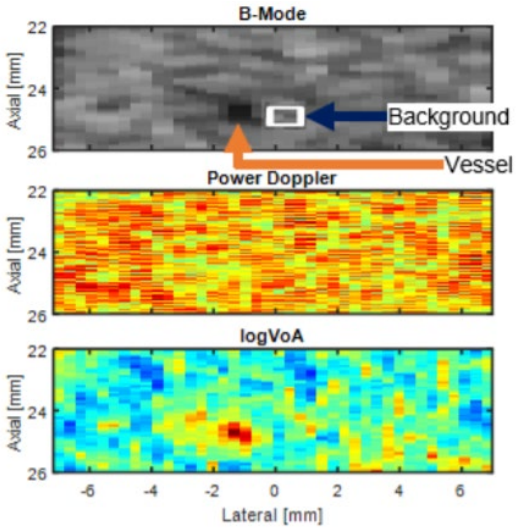

Fig. 1. 2D parametric images of calibrated blood-mimicking flow phantom. From top to bottom: B-Mode, Power Doppler, and logVoA. ROIs indicate background (blue), and vessel (orange).

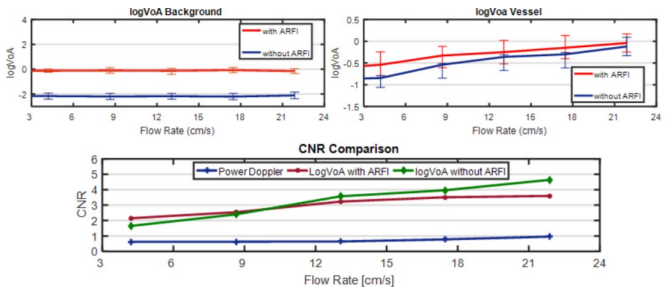

Fig. 2. logVoA of calibrated blood-mimicking flow phantom: comparison of with vs. without ARFI push, in background and vessel ROIs. CNR comparison between logVoA with/without ARFI, and Power Doppler.

Figure 3 shows that logVoA (measured in a 2x20 mm ROI centered at the focus) was statistically significantly greater at baseline than ischemia in all three in vivo pig kidney cortex. This demonstrates the potential of using logVoA as a marker of perfusion, as ischemic tissue experience reduced blood flow compared to healthy vessels. As indicated by the phantom experiment, logVoA increases with blood flow rate, so we expect an ischemic vessel to have a significantly lower logVoA. This expectation is validated in our *in vivo* results.

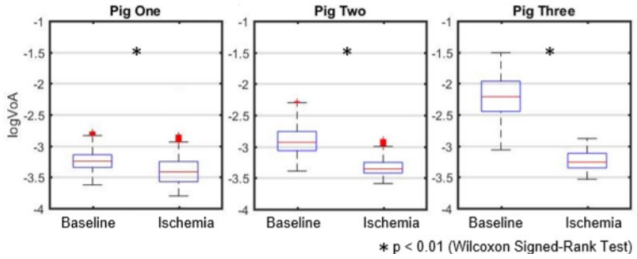

Fig. 3. logVoA of *in vivo* pig renal cortex during baseline and ischemia.

Figure 4 shows B-Mode, Power Doppler, and logVoA images across the renal cortex of one of the pigs with the renal artery ligated. The logVoA image delineates a 1.25 mm-diameter vessel in a pig renal cortex in vivo (arrow), while they cannot be identified in the B-Mode and Power Doppler images. These images were acquired with the artery ligated, which demonstrates that there was still blood flow into the kidney even in the ischemic condition.

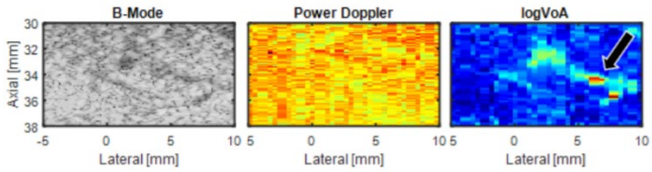

Fig. 4. Vessel Identification: *in vivo* pig renal cortex during ischemia. From left to right: B-Mode, normalized Power Doppler, and logVoA.

A limitation to the phantom study is that the vessel in the flow phantom was of a fixed diameter and could not be manipulated to test diameter effects on logVoA performance. Similarly, the blood mimicking fluid was held constant over the course of the experiment. Another experimental variable could have been variation in the amount of scatterers in the mixture over time to see how echogenicity affects logVoA association with blood flow.

IV. Conclusion

This study demonstrates that logVoA improves perfusion detection in small vessels compared to Power Doppler. This study also showed that only logVoA differentiated a small vessel from the background tissue *in vivo*, which was not possible using B-mode or Power Doppler. These results suggest that logVoA could support contrast-free detection of slow blood flow in small vessels and perfusion assessment, *in vivo*.

Acknowledgment

The authors thank Siemens Healthcare, Ultrasound Division for in-kind support. This work was supported by UNC Glaxo Foundation Fellowship and NIH grants R01HL092944, R01NS074057, R01DK107740, K02HL105659, and T32HL069768. The authors also appreciate the contribution K. A. Yokoyama for help with manuscript editing.

REFERENCES

[1] Frohlich ED, Quinlan PJ. Coronary heart disease risk factors: public impact of initial and later-announced risks. Ochsner J. 2014;14(4):532–537.

[2] Preston, RA., and Murray E. "Ischemic Renal Disease." Journal of Hypertension, vol. 15, no. 12, 1997, pp. 1365–1377., doi:10.1097/00004872-199715120-00001.

[3] Pinter SZ, Lacefield JC. Detectability of small blood vessels with high‐frequency power Doppler and selection of wall filter cut‐off velocity for microvascular imaging. Ultrasound Med Biol 2009; 35:1217‐1228.

[4] Xu, T, et al. "In Vivo Lateral Blood Flow Velocity Measurement Using Speckle Size Estimation." Ultrasound in Medicine & Biology, vol. 40, no. 5, May 2014, pp. 931–937., doi:10.1016/j.ultrasmedbio.2013.11.017.

[5] Calliada, F, et al. "Ultrasound Contrast Agents." European Journal of Radiology, vol. 41, no. 3, May 2002, p. 175., doi:10.1016/s0720-048x(02)00022-0.

[6] Pasternak JJ, Williamson EE. Clinical pharmacology, uses, and adverse reactions of iodinated contrast agents: a primer for the non-radiologist. Mayo Clin Proc. 2012;87(4):390-402.

[7] Lorusso A, Quaia E, Poillucci G, Stacul F, Grisi G, Cova MA. Activity-based cost analysis of contrast-enhanced ultrasonography (CEUS) related to the diagnostic impact in focal liver lesion characterisation. Insights into Imaging. 2015;6(4):499-508. doi:10.1007/s13244-015-0402-4.

[8] Geist, RE., et al. "Experimental Validation of ARFI Surveillance of Subcutaneous Hemorrhage (ASSH) Using Calibrated Infusions in a Tissue-Mimicking Model and Dogs." Ultrasonic Imaging, vol. 38, no. 5, 27 Nov. 2015, pp. 346–358., doi:10.1177/0161734615617940.

[9] Torres, G, et al. "In Vivo Delineation of Human Carotid Plaque Features with ARFI Variance of Acceleration (VoA)." 2017 IEEE International Ultrasonics Symposium (IUS), 2017, doi:10.1109/ultsym.2017.8091836.

[10] Torres, G, et al. "In Vivo Delineation of Human Carotid Plaque Features with ARFI Variance of Acceleration (VoA)." 2017 IEEE International Ultrasonics Symposium (IUS), Mar. 2019, doi:10.1109/ultsym.2017.8091836.

[11] Pinton GF, Dahl JJ, Trahey GE. "Rapid tracking of small displacements with ultrasound." IEEE Trans Ultrason Ferroelectr Freq Control, 53 (2006), pp. 1103-1117

[12] Nightingale K, Soo MS, Nightingale R, Trahey GE. "Acoustic radiation force impulse imaging: in vivo demonstration of clinical feasibility." Ultrasound Med Biol, 28 (2002), pp. 227-235

[13] Fahey BJ, Palmeri ML, Trahey GE. "The impact of physiological motion on tissue tracking during radiation force imaging." Ultrasound Med Biol, 33 (2007), pp. 1149-1166

[14] Torres G, Czernuszewicz TJ, Homeister JW, Caughey MC, Huang BY, Lee ER, Zamora CA, Farber MA, Marston WA, Huang DY, Nichols TC. Delineation of Human Carotid Plaque Features In Vivo by Exploiting Displacement Variance. IEEE transactions on ultrasonics, ferroelectrics, and frequency control. 2019 Feb 11;66(3):481-92.