RGC Ref.: N_HKU713/15
NSFC Ref. : 81561168023
(please insert ref. above)

The Research Grants Council of Hong Kong
NSFC/RGC Joint Research Scheme
Joint Completion Report

(Please attach a copy of the completion report submitted to the NSFC by the Mainland researcher)

Part A: The Project and Investigator(s)

1. Project Title

A comprehensive functional ultrasound imaging framework: the assessment of vascular mechanics for the diagnosis of cardiovascular diseases

2. Investigator(s) and Academic Department/Units Involved

	Hong Kong Team	Mainland Team
Name of Principal Investigator *(with title)*	Dr. Wei-Ning Lee	Dr. Jianwen Luo
Post	Associate Professor	Professor
Unit / Department / Institution	Electrical and Electronic Engineering/The University of Hong Kong	Biomedical Engineering/ Tsinghua University
Contact Information	wnlee@eee.hku.hk +852-39172703	luo_jianwen@mail.tsinghua.edu.cn
Co-investigator(s) *(with title and institution)*	N.A.	Professor Yanping Cao (Engineering Mechanics/ Tsinghua University) Dr. Linxue Qian (Sonography/ Beijing Friendship Hospital)

3. Project Duration

	Original	Revised	Date of RGC/ Institution Approval *(must be quoted)*
Project Start date	2016/01/01	N.A.	
Project Completion date	2019/12/31	N.A.	
Duration *(in month)*	48	N.A.	
Deadline for Submission of Completion Report	2020/12/31	N.A.	

Part B: The Completion Report

5. Project Objectives

5.1 Objectives as per original application

1. Develop a comprehensive functional ultrasound imaging framework to quantify and map vascular anisotropy and mechanics.
2. Establish a computational model of the vessel with material anisotropy to validate the proposed imaging framework.
3. Validate the framework in vessel-mimicking phantoms *in vitro*.
4. Investigate the feasibility of the framework in normal and pathological human vessels in a clinical setting.

5.2 Revised Objectives

Date of approval from the RGC: N.A.

Reasons for the change: N.A.

6. Research Outcome

Major findings and research outcome
(maximum 1 page; please make reference to Part C where necessary)

(1) Shear waves, whether induced by acoustic radiation force or other vibration sources, propagate in a guided mode along different radii at different speeds due to the unique geometry of the artery (i.e., thin-walled hollow cylinder in normal cases). Therefore, a geometric correction method was proposed (Part C: Guo et al. 2017). In addition, the shear wave propagation in the thin arterial wall was found to be significantly modified by the surrounding media (Parc C: Lee et al. 2018).
(2) Multi-directional shear moduli of the arterial wall were estimated and provided to estimate the degree of arterial anisotropy in a completely non-destructive way for the first time (Part C: Guo et al. 2018).
(3) Arterial wall was found to stiffen during systole (artery expansion) and soften during diastole (recoil). The degree of stiffening and softening is described as mechanical nonlinearity. We proposed a novel graphical representation for this nonlinearity by a strain-shear modulus loop. For the first time, such a loop was established as a qualitative and quantitative measure for arterial functional analysis (Part C: Wang et al. 2019).
(4) Fluid-structure interaction modeling and 3D-printed vessel-mimicking phantoms were established for anisotropic artery with branches. These two altogether serve as a versatile tool to investigate blood flow and arterial wall behavior comprehensively (Part C: Dong et al. 2020).
(5) Noninvasive estimation of luminal pressure changes with our derived mathematical equations realized by the proposed imaging framework is demonstrated to be feasible and accurate (Part C: Wang and Lee 2020).
(6) A new type of spontaneous wave propagating along the longitudinal axis of the arterial wall due to blood ejection from the left ventricle into the arterial network via aorta was discovered. Wave theory, computational modeling and experimental data analysis from human subjects were all done (Part C: Ran et al. 2020). Complementing existing indices, this may serve as a new indicator of arterial health.

Potential for further development of the research and the proposed course of action
(maximum half a page)

The research has great potential in both basic science and commercialization. In terms of basic science, nonlinearity of the artery was scarcely examined, not to mention its noninvasive assessment. Whether degree of anisotropy and degree of nonlinearity of the arterial wall are more sensitive than arterial wall deformation, stiffness, and blood pressure, to detect early arterial malfunction in a multitude of arterial pathologies, e.g., hypertension, atherosclerosis, aging, and diabetes, should be investigated. This requires continuous and

closer collaboration with the Mainland team as we have complementary strengths and resources.

In terms of commercialization, our developed ultrasound imaging framework is compatible with state-of-the-art ultrasound systems and programmable. Offline processing can be packaged into a software application for user-interactive data analysis. This will greatly aid clinicians' diagnosis and even monitoring of arterial conditions. Publicity of our developed framework and talking with prominent ultrasound system manufacturers will be indispensable.

7. The Layman's Summary

(describe <u>in layman's language</u> the nature, significance and value of the research project, in no more than 200 words)

The research project aims at developing an ultrasound imaging framework that can make comprehensive assessment of the arterial health in a completely noninvasive and quick way. This is both a fundamental and translational research project. We have revealed and analyzed unique and complex elastic wave behaviors in the arterial wall which has a hollow cylindrical structure and is surrounded by soft biological tissues. The analysis permits us to quantify arterial stiffness in the circumferential direction accurately and unprecedentedly. We have proposed and examined a novel graphical indicator of arterial nonlinearity for better sensitivity to arterial health condition. We have discovered a new fast elastic wave that propagates in the artery once every heartbeat and demonstrated its direct association with the longitudinal wall stiffness in full scope from wave theory to computational models and living carotid arteries in healthy human subjects. The research overall has advanced our understanding of dynamic arterial properties and realized a safe ultrasound imaging framework that not only assesses arterial anisotropy, deformation, stiffness, nonlinearity, and luminal pressure change, but is also compatible with state-of-the-art ultrasound imaging systems to aid clinical diagnosis and prognosis.

<u>Part C: Research Output</u>

8. Peer-reviewed journal publication(s) arising <u>directly</u> from this research project

(Please attach a copy of each publication and/or the letter of acceptance if not yet submitted in the previous progress report(s). All listed publications must acknowledge RGC's funding support by quoting the specific grant reference.)

The Latest Status of Publications				Author(s) *(**bold** the authors belonging to the project teams and denote the corresponding author with an asterisk*)*	Title and Journal/ Book *(with the volume, pages and other necessary publishing details specified)*	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of this Joint Research Scheme *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
Year of publication	Year of Acceptance *(For paper accepted but not yet published)*	Under Review	Under Preparation *(optional)*						

2017				**Y. Guo, H. Lo, and W.-N. Lee***	"Transmural Transverse Stiffness Estimation in Vascular Shear Wave Imaging: A Simulation and Phantom Study," *Applied Physics Letters*, vol. 110, 193701, 2017.	Yes (2018)	No	Yes	Yes
2018				**Y. Guo, Y. Wang, E. J.-H. Chang, and W.-N. Lee***	"Multi-directional estimation of arterial stiffness using vascular guided wave imaging (VGWI) with geometry correction," *Ultrasound in Medicine and Biology*, vol. 44, No. 4, pp. 884-896, 2018.	Yes (2018)	No	Yes	Yes
2018				**W.-N. Lee*, E. J.-H. Chang, Y. Guo, and Y. Wang**	"Experimental Investigation of Guided Wave Imaging in Thin Soft Media in Various Coupling Conditions," *Ultrasound in Medicine and Biology*	Yes (2018)	Yes	Yes	Yes

2019				**Y. Wang, H. Li, Y. Guo, and W.-N. Lee***	"Bidirectional Ultrasound Elastographic Imaging Framework for Non-invasive Assessment of the Non-linear Behavior of a Physiologically Pressurized Artery," *Ultrasound in Medicine and Biology*, vol. 45, no. 5, pp. 1184-1196, 2019.	Yes (2018)	No	Yes	Yes
2019				Y. Zhang, H. Li, W.-N. Lee*	"Imaging Heart Dynamics with Ultrafast Cascaded-wave Ultrasound (uCUS)," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 66, No. 9, pp. 1465-1479, 2019.	No	Yes	Yes	Yes

2020				Y. Wang and W.-N. Lee*	"Non-invasive Estimation of Localized Dynamic Luminal Pressure Change by Ultrasound Elastography in Arteries with Normal and Abnormal Geometries," *IEEE Trans. Biomedical Engineering* (early access)	No	Yes	Yes	Yes
2020				J. Dong, Y. Zhang, and W.-N. Lee*	"Walled vessel-mimicking phantom for ultrasound imaging using 3D printing with a water-soluble filament: design principle, fluid-structure interaction (FSI) simulation, and experimental validation," *Physics in Medicine and Biology*, vol. 65, 085006, 2020.	No	Yes	Yes	Yes
2020		1		Y. Zhang, J. Dong, Z. Zhen, S.-Y. Liao, H.-F. Tse, K. H. Yiu, and W.-N. Lee*	"Ultrasound Angiography with Tissue Echoes Filtering and Adaptive Image Formation," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*	No	Yes	Yes	No

2020		1		D. Ran, J. Dong, H. Li, and W.-N. Lee*	"A New Spontaneous Mechanical Wave for In Vivo Assessment of Arterial Wall Anisotropy," *American Journal of Physiology*, 2020 (Manuscript #: H-00756-2020)	No	Yes	Yes	No
			1	J. Dong and W.-N. Lee*	"Guidelines for computational modelling of fluid-structure interaction for anisotropic artery"	No	No	Yes	No

9. Recognized international conference(s) in which paper(s) related to this research project was/were delivered *(Please attach a copy of each delivered paper. All listed papers must acknowledge RGC's funding support by quoting the specific grant reference.)*

Month/Year/ Place	Title	Conference Name	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of this Joint Research Scheme *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
Oct/2016/Vermont, USA	"Bi-Plane Arterial Wall Stiffness Estimation Using Shear Wave Imaging: A Simulation and Phantom Study"	*International Tissue Elasticity Conference*, Vermont, New England, USA, Oct 16-19, 2016.	Yes	No	Yes	No

April/2017/Melbourne, Australia	"Shear Wave Elastography for the Characterization of Arterial Wall Stiffness: A Thin-Plate Phantom and Ex Vivo Aorta Study"	*Proc. In IEEE International Symposium on Biomedical Imaging*, Melbourne, Australia, April 18-21, 2017.	Yes	No	Yes	Yes
May/2017/Eindhoven, The Netherlands	"MEMS pressure sensor array wearable for Traditional Chinese Medicine pulse-taking"	*2017 IEEE 14th International Conference on Wearable and Implantable Body Sensor Networks (BSN)*. IEEE, 2017, 59-62.	Yes	No	Yes	Yes
September/2017/ Washington DC, USA	"Estimation of arterial transverse stiffness using vascular guided wave imaging (VGWI) in comparison with pulse wave imaging (PWI)"	*IEEE International Ultrasonics Symposium*, Washington D.C., U.S.A., Sep 6-9, 2017.	Yes	No	Yes, on the poster	No
September/2017/ Washington DC, USA	"Multi-plane estimation of the third- and fourth-order elastic constants of soft material"	*IEEE International Ultrasonics Symposium*, Washington D.C., U.S.A., Sep 6-9, 2017.	Yes	No	Yes, on the poster	No
September/2017/ Washington DC, USA	"Experimental investigation of Shear Wave Imaging in Thin Soft Media in Various Coupling Conditions"	*IEEE International Ultrasonics Symposium*, Washington D.C., U.S.A., Sep 6-9, 2017.	Yes	No	Yes, on the poster	No
December/2017/Hong Kong	"Assessment of Direction-dependent Strain-Stiffness Relationship of Physiologically Pressurized Artery Using Ultrasound Elastographic Imaging"	*5th International Conference on Biomedical Ultrasound*, Hong Kong, Dec 2-4, 2017.	Yes	No	Yes	No

March/2018/ New York, USA	"Assessment of Direction-dependent Strain-Stiffness Relationship of Physiologically Pressurized Artery Using Ultrasound Elastographic Imaging"	2018 American Institute of Ultrasound in Medicine (AIUM) Convention, New York, USA, March 24-28, 2018.	Yes	Yes	Yes, appeared in the presentation slides	No
Sep/2018/ Avignon, France	"A comparison study of mapping stiffness distribution of partially stiffened porcine aorta,"	International Tissue Elasticity Conference, Avignon, France, Sep 9-12, 2018.	No	Yes	Yes, appeared in the presentation slides	No
Oct/2018/ Kobe, Japan	"Bi-directional Ultrasound Assessment of Nonlinear Mechanical Behavior of Physiologically Pressurized Artery in Both Normal and Hardening Conditions"	*IEEE International Ultrasonics Symposium*, Kobe, Japan, Oct 22-25, 2018.	No	Yes	Yes, on the poster	No
Oct/2019/ Glasgow, Scotland	"Non-invasive estimation of localized intraluminal pressure in the artery by an ultrasound elastographic imaging framework"	*IEEE International Ultrasonics Symposium*, Glasgow, Scotland, Oct 6-9, 2019.	No	Yes	Yes, on the poster	No
Oct/2019/ Glasgow, Scotland	"Influence of blood vessel wall nonlinearity on flow velocity: a fluid-structure interaction (FSI) simulation study with in vitro validation"	*IEEE International Ultrasonics Symposium*, Glasgow, Scotland, Oct 6-9, 2019.	No	Yes	Yes, on the poster	No
Oct/2019/ Glasgow, Scotland	"Noninvasive Coronary Angiography with Ultrafast Cascaded-wave Ultrasound"	*IEEE International Ultrasonics Symposium*, Glasgow, Scotland, Oct 6-9, 2019.	No	Yes	Yes, appeared on the poster	No

Dec/2019/ San Diego, California	"Computational and ultrafast ultrasound assessment of arterial bi-directional stiffness from spontaneous pulsatile waves"	*178th Meeting of the Acoustical Society of America*, San Diego, California, U.S.A., Dec 2-6, 2019 (**Student Travel Award**)	No	Yes	Yes, appeared in the presentation slides	No
Sep/2020/ Las Vegas, USA	"Wrist-side Pulse Sensing: Pilot Comparison between Ultrasound Imaging and a Wearable Pulse-taking Sensor"	*IEEE International Ultrasonics Symposium*, Las Vegas, USA, Sep 6-11, 2020.	No	Yes	Yes, on the poster	No
Sep/2020/ Las Vegas, USA	"Quantitative Assessment of Arterial Anisotropy by Spontaneous Pulsatile Waves"	*IEEE International Ultrasonics Symposium*, Las Vegas, USA, Sep 6-11, 2020.	No	Yes	Yes, on the poster	No

10. Student(s) trained *(Please attach a copy of the title page of the thesis.)*

Name	Degree registered for	Date of registration	Date of thesis submission/ graduation
Yuexin Guo	PhD	2013/09/01	2017/11 (graduation)
Yahua Wang	PhD	2016/09	2020/11 (graduation)
Jinping Dong	PhD	2016/09	2021/01 (submission)
Dan Ran	PhD	2017/09	2021/06 (submission)
Enoch J-.H. Chang	BEng	2013/09/01	2017/05 (graduation)
Ho Yuen Lo	BEng	2013/09/01	2017/05 (graduation)

11. Other impact *(e.g. award of patents or prizes, collaboration with other research institutions, technology transfer, etc.)*

This is a collaboration project with Tsinghua University in Beijing, China. Mr. Dong was awarded as a finalist at the 2018 International Tissue Elasticity Conference, a leading conference in our research field. Mr. Ran received a student travel grant from American Society of Acoustics, a leading acoustical society. Mr. Chang received an undergraduate student thesis prize in 2017.

12. Statistics on Research Outputs *(Please ensure the summary statistics below are consistent with the information presented in other parts of this report.)*

	Peer-reviewed journal publications	Conference papers	Scholarly books, monographs and chapters	Patents awarded	Other research outputs (Please specify)
No. of outputs arising directly from this research project [or conference]	7 published; 2 under review; 1 under preparation	16	0	0	2 (student awards)