

Noninvasive Assessment of Arterial Stiffness in Small Animals Doppler Blood Flow Velocity Measurements for Cardiovascular Phenotyping in Mice



Prof. Anilkumar K. Reddy
Department of Medicine
Baylor College of Medicine
Houston, TX, USA

Normal and transgenic animal models are increasingly employed to study and elucidate the physiological mechanisms in aging and diseases, and many of these models are available only in mice. Because many of these genetic manipulations can alter cardiovascular physiology and function, it is important to measure (noninvasively, where feasible) the mechanical and functional properties of the cardiovascular system in small animals. Echocardiography with capability for Doppler velocimetry has been successfully used in the noninvasive assessment of left ventricular function but assessment of arterial stiffness in mice is limited.

In this presentation I will discuss the utility of 10 & 20 MHz pulsed Doppler system and small Doppler probes for the assessment of arterial stiffness and cardiac function in small animals. The utility of Doppler flow velocity measurement has been proven in mice for over the last 20 years and being noninvasive obviates the need for surgical implantation of transducers and allowing serial/longitudinal studies. The presentation will focus will be on the following areas: 1. Arterial stiffness and pulse wave velocity, 2. Cardiac systolic

and diastolic function -myocardial infarction & pressure overload, 3. Coronary flow reserve, and 4. Peripheral vascular function.

Short Biography

Prof. Anilkumar K. Reddy

Dr. Reddy is currently an Assistant Professor in the Department of Medicine at Baylor College of Medicine, Houston, Texas, USA and a Senior Scientist at Indus Instruments, Webster, Texas, USA. He got his BE-Electronics & Communication Eng. from Osmania University in India, MS-Biomedical Eng. From University of Akron, Akron, Ohio, USA and PhD-Bioengineering from Texas A&M University, College Station, Texas, USA.

In 1997, he began his career at Baylor College of Medicine as a postdoctoral associate in the section of Cardiovascular Sciences, Department of Medicine under the mentorship of Dr. Craig Hartley and transitioned to Instructor and Assistant Professor under the supervision of section chairman, Dr. Mark Entman.

His first project involved the design, construction, and testing of ultrasound Doppler instrumentation and data acquisition system for small animal cardiovascular research. The data and studies he will presenting today are the result of that system. Over the years he developed methods using modified and custom-made devices to measure systolic and diastolic blood pressure noninvasively in mice using pulsed Doppler plethysmography, determine aortic input impedance in mice to evaluate the systemic load on the left ventricle of a mouse, and noninvasively measure coronary flow velocity reserve in mice without image guidance. In 2005 he received the prestigious NIH Research Career Award to study the cardiovascular system in mice using aortic impedance. He has co-investigator on many research projects and small business grants from NIH. Dr. Reddy has a significant number of publications and has been a reviewer for NIH, NSF, AHA grant proposals, and a manuscript reviewer for several journals. He has made presentations at various institutes across the world that include Japan, Taiwan, China, Singapore, India, UK, Germany, and France.

Since 2013, Dr. Reddy has split his time between Baylor College of Medicine and Indus Instruments who had been his long-time collaborator, where he assists with development of research instrumentation and small business grant writing.

List of most relevant publications

Instrumentation & Methodology

1. **Reddy AK**, Jones AD, Martono C, Caro WA, Madala S, Hartley CJ. Pulsed Doppler signal processing for use in mice: Design and evaluation. *IEEE Transactions on Biomedical Engineering*, 52 (10): 1764-1770, 2005.
2. **Reddy AK**, Taffet GE, Li, Y-H, Lim S-W, Pham TT, Pocius JS, Entman ML, Michael LH, Hartley CJ. Pulsed Doppler signal processing for use in mice: Applications. *IEEE Transactions on Biomedical Engineering*, 52(10): 1771-1783, 2005.
3. **Reddy AK**, Madala S, Jones AD, Caro WA, Eberth JF, Pham TT, Taffet GE, Hartley CJ. Multi-channel pulsed Doppler signal processing for vascular measurements in mice. *Ultrasound in Medicine and Biology*, 35(12):2042-2054, 2009.
4. Hartley CJ, **Reddy AK**, Madala S, Entman ML, Michael LH, Taffet GE. Noninvasive ultrasonic measurement of arterial wall motion in mice – Innovative Methodology. *American Journal of Physiology Heart Circulatory Physiology*, 287: H1426-H1432, 2004.

Animal Studies

- Hartley CJ, **Reddy AK**, Madala S, Martin-McNulty B, Vergona R, Sullivan ME, Halks-Miller M, Taffet GE, Michael LH, Entman ML, Wang Y-X. Hemodynamics changes in apolipoprotein E-knockout mice. *American Journal of Physiology, Heart Circulatory Physiology* 279:H2326-H2334, 2000.
- Hartley CJ, Taffet GE, **Reddy AK**, Entman ML, Michael LH. Noninvasive cardiovascular phenotyping in mice. *Institute for Laboratory Animal Research* 43(3):147-158, 2002.
- **Reddy AK**, Taffet GE, Madala S, Michael LH, Entman ML, Hartley CJ. Noninvasive blood pressure measurement in mice using pulsed Doppler ultrasound. *Ultrasound in Medicine and Biology* 29(3):379-385, 2003.
- Li Y-H, **Reddy AK**, Taffet GE, Michael LH, Entman ML, Hartley CJ. Peripheral vascular adaptations to transverse aortic banding in mice. *Ultrasound in Medicine and Biology*, 29(9):1281-1289, 2003.
- **Reddy AK**, Li Y-H, Pham TT, Ochoa LN, Treviño MT, Hartley CJ, Michael LH, Entman ML, Taffet GE. Measurement of aortic input impedance in mice: Effect of age on aortic stiffness. *American Journal of Physiology, Heart and Circulatory Physiology*, 285:H1464-H1470, 2003.
- Li Y-H, **Reddy AK**, Ochoa LN, Pham TT, Hartley CJ, Michael LH, Entman ML, Taffet GE. Effect of age on peripheral vascular response to transverse aortic banding in mice. *Journal of Gerontology Biological Sciences*, 58A (10):895-899, 2003.
- **Reddy AK**, Li Y-H, Pham TT, Taffet GE, Michael LH, Entman ML, and Hartley CJ. Indices of aortic stiffness in mice. *Proceedings of IEEE-EMBS*, 25(1):276-278, 2003.
- Hartley CJ, **Reddy AK**, Michael LH, Pocius JS, Pham TT, Entman ML, and Taffet GE. Estimating arterial properties from Doppler signals in mice. *Proceedings of IEEE-EMBS*, 25(1):268-271, 2003.
- **Reddy AK**, Taffet GE, Prchal JF, Michael LH, Entman ML, and Hartley CJ. Effect of cellular elements on the pressure-velocity relationship in mice. *Proceedings of IEEE-EMBS*, 26(2):3720-3722, 2004.
- Schillinger KJ, Tsai SY, Taffet GE, **Reddy AK**, Marian AJ, Entman ML, Oka K, Chan L, O'Malley BW. Regulatable atrial natriuretic peptide gene therapy for hypertension. *Proceedings of National Academy of Sciences*, 102(39): 13789-13794, 2005.
- Hartley CJ, **Reddy AK**, Madala S, Michael LH, Entman ML, Taffet GE. Effects of isoflurane on coronary blood flow velocity in young, old, and ApoE^{-/-} mice measured by Doppler ultrasound. *Ultrasound in Medicine and Biology*, 33(4):512-521, 2007.
- **Reddy AK**, Amador-Nogues D, Darlington GJ, Scholz BA, Michael LH, Hartley CJ, Entman ML, Taffet GE. Cardiac function in young and old *Little* mice. *Journal of Gerontology-Biological Sciences*, 62A(12):1319-1325, 2007.
- Bujak M, Ren G, Chatila K, Dobaczewski M, **Reddy AK**, Taffet GE, Wang X-F, and Frangogiannis NG. Smad3 null mice exhibit attenuated ventricular remodeling following myocardial infarction. *Circulation*, 116: 2127-2138, 2007.
- Hartley CJ, **Reddy AK**, Madala S, Michael LH, Entman ML, Taffet GE. Doppler estimation of reduced coronary flow reserve in mice with pressure overload cardiac hypertrophy. *Ultrasound in Medicine and Biology*, 34(6):892-901, 2008.
- Eberth JF, Gresham VC, **Reddy AK**, Popovic N, Wilson E, Humphrey JD. Importance of pulsatility in hypertensive carotid artery growth and remodeling. *Journal of Hypertension*, 27(10): 2010-2021, 2009.

- Hartley CJ, **Reddy AK**, Madala S, Entman ML, Taffet GE. Feasibility of Doppler velocity measurements to estimate volume pulsations of an arterial segment. *Ultrasound in Medicine and Biology*, 36(7):1169-1175, 2010.
- Erez A, Chen Y, Shchelochkov OA, Nagamani SCS, Premkumar MH, Campeau PM, Garg HK, Mian A, Bertin TK, Black JO, Zeng H, Tang Y, **Reddy AK**, Summar M, O'Brien WE, Mitch WE, Aschner JL, Marini JC, Bryan NS, Lee B. Argininosuccinate lyase is essential for systemic nitric oxide production. *Nature Medicine*, 17: 1619-1626, 2011.
- Hartley CJ, **Reddy AK**, Madala S, Entman ML, Michael LH, Taffet GE. Doppler velocity measurements from large and small arteries of mice. *American Journal of Physiology, Heart and Circulatory Physiology*, 301: H269-H278, 2011.
- Gurha P, Abreu-Goodger C, Wang T, Ramirez MO, Drumond AL, van Dongen S, Chen Y, Bartonicek N, Enright AJ, Lee B, Kelm RJ Jr, **Reddy AK**, Taffet GE, Bradley A, Wehrens XH, Entman ML, Rodriguez A. Targeted deletion of microRNA-22 promotes stress-induced cardiac dilation and contractile dysfunction. *Circulation*, 125: 2751-2761, 2012.
- **Reddy AK**, Hartley CJ, Thuy T, Pham, Darlington G, Entman ML, Taffet GE. Young *Little* mice express a premature cardiovascular aging phenotype. *Journal of Gerontology- A Biological Sciences and Medical Sciences*, 69:152-159, 2014.
- Grimes KM*, Reddy AK*, Lindsey ML, Buffenstein R. And the beat goes on: attenuated cardiovascular aging in the longest-lived rodent, the naked mole-rat. (*-Equal contribution authors), *American Journal of Physiology, Heart Circulatory Physiology*, (APSselect article) 307:H284-H291, 2014.
- Zhou H, Ran Y, Da Q, Shaw TS, Shang D, **Reddy AK**, López JA, Ballantyne CM, Ware J, Wu H, Peng Y. Defective association of the platelet glycoprotein Ib-IX complex with the glycosphingolipid-enriched membrane domain inhibits murine thrombus and atheroma formation. *Journal of Immunology*, 197:288-295, 2016.
- Hinton Jr. AO, Yang Y, Quick AP, Xu P, Reddy CL, Yan X, Reynolds CL, Tong Q, Zhu L, Xu J, Wehrens XHT, Xu Y, **Reddy AK**. SRC-1 regulates blood pressure and aortic stiffness in a female mice. *PLoS ONE*, 11(12):e0168644, 2016.

Relevant publications from our group

- Hartley, C. J., L. H. Michael, and M. L. Entman. Noninvasive measurement of ascending aortic blood velocity in mice. *Am. J. Physiol.* 268 (Heart Circ. Physiol. 37): H499-H505, 1995.
- Hartley, C.J., G.E. Taffet, L.H. Michael, T.T. Pham, and M.L. Entman. Noninvasive determination of pulse-wave velocity in mice. *Am.J.Physiol.Heart Circ.Physiol.* 273: H494-H500, 1997.
- Taffet, G. E., C. J. Hartley, X. Wen, T. T. Pham, L. H. Michael, and M. L. Entman. Noninvasive indexes of cardiac systolic and diastolic function in hyperthyroid and senescent mouse. *Am. J. Physiol.* 270 (Heart Circ. Physiol. 39): H2204-H2209. 1996.
- Michael LH, Ballantyne CM, Zachariah JP, Gould KE, Pocius JS, Taffet GE, Hartley CJ, Pham TT, Daniel SL, Funk E, Entman ML. Myocardial infarction and remodeling in mice: effect of reperfusion. *Am J Physiol.* 1999 Aug;277(2 Pt 2):H660-8.