A-mode ultrasound methods for measurement of arterial structure and functional properties: a window to early vascular ageing

(PhD Viva Voce)

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Research Guide: Dr. Jayaraj Joseph

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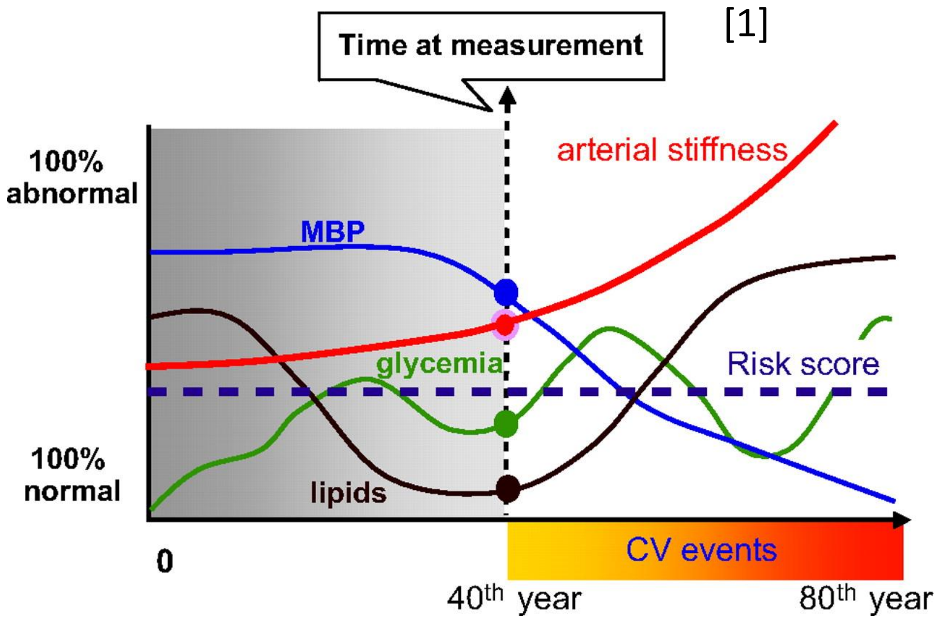
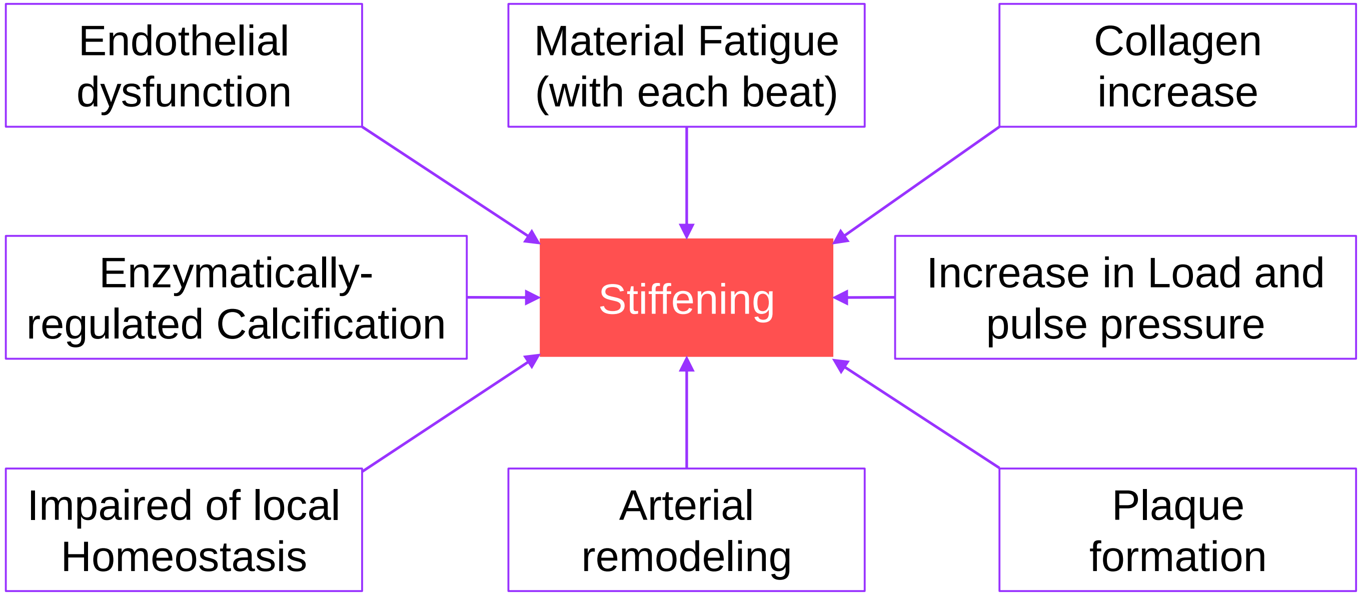
1.1. Arterial stiffening: Hallmark of Vascular Ageing

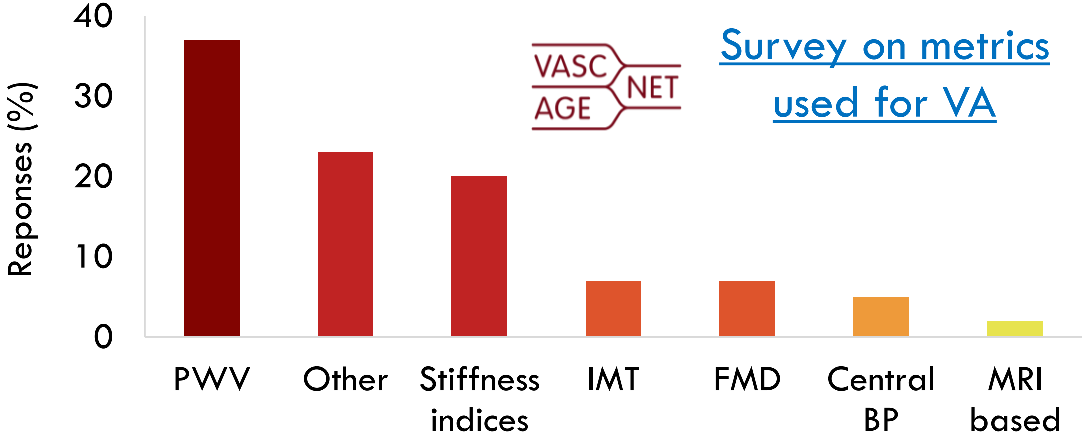




"Arterial stiffening **continually increases with age** and is an **integrator of all the damages** done to arterial wall in previous years" [1]

1. P. M. Nilsson et al., "Vascular Aging: A Tale of EVA and ADAM in Cardiovascular Risk Assessment and Prevention," Clinical Hypertension, vol. 27, no. 6, pp. 341–345, Nov. 2007

1.2. Technology gaps in VA assessment: Motivation

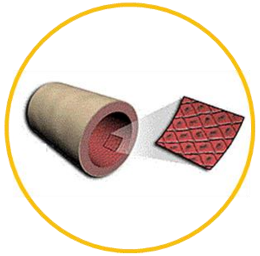


Survey on metrics used for VA

Motivation: One automated device, multiple vascular health markers

Solution: A-Mode ultrasound methods and system

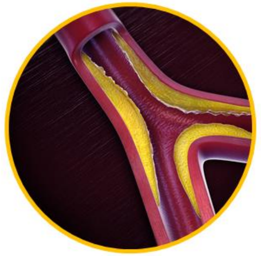
State-of-the-art



Endothelial function

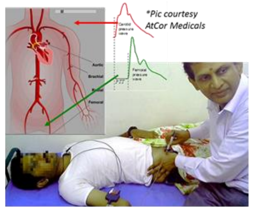
Arterial stiffness

Central blood pressure



Diameter and Wall thickness

Endothelial function: Imaging and dedicated devices (FMD/LFMC)

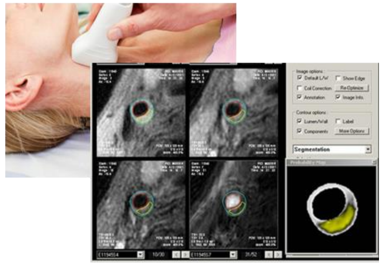


Regional stiffness: Tonometry (CF-PWV, CAVI)

Local stiffness indices: Ultrasound (AC, Ep, β, Local PWV)

Invasive catheters

Calibration based non-invasive methods



Dedicated geometric assessment software packages

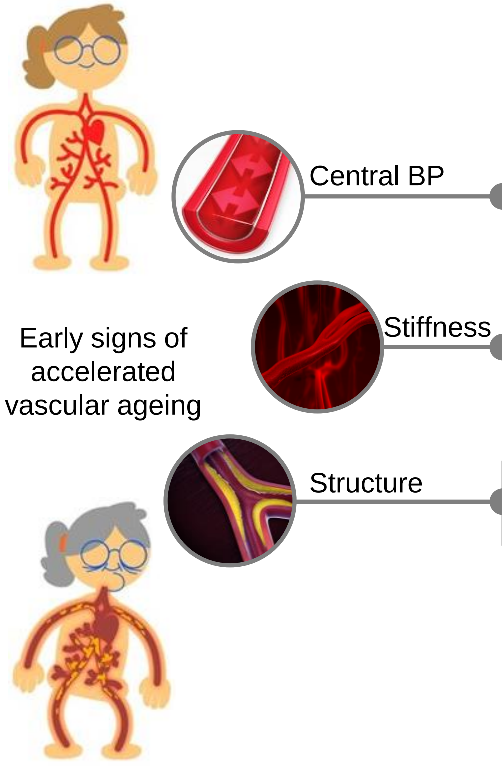
Gaps

- X No single device for comprehensive assessment
- X Equipment setup capital is high and non scalable
- X Demand technically skilled expert
- X Some require offline analysis
- X Not suitable for routine clinical use
- X Legal constraints on Imaging systems in India

1.3. Goal and contribution of the work

Goal: High Frame Rate multimodal A-mode ultrasound system and methods for automated measurement of structural and functional vascular health markers.

Scientific contribution



- Carotid Blood Pressure

- Local PWV
- Incremental Local PWV

- Regional PWV

- Diameter and its changes
- IMT and its changes

High-frame rate ultrasound system for calibration-free CBP using structure and local PWV

High-frame rate ultrasound system and method

Multimodal ultrasound system and method

Signal processing methods for
- Auto-recognition of walls
- Auto-tracking of wall motion
- Diameter and IMT measurement

6 Patents (pending)

Research Publications (**55**) and Awards

Journals based on thesis = 5
- *Computer Methods and Programs in Biomedicine (IF = 7.02)*
- *IEEE Transactions on UFFC (IF = 3.26)*
- *Ultrasonics (IF = 4.06)*
- *Journal of Hypertension (IF = 4.84)*
- *Blood Pressure (IF = 2.03)*

Journals Co-authored = 3
- *Physiological Measurement (IF = 2.68)*
- *IEEE RBME (IF = 7.07)*
- *Biomedical Physics & Engineering Express (IF = 1.46)*

Conference proceedings = 47 (18 based on thesis)
(IEEE EMBC, IEEE MeMeA, IEEE Sensors, RGC, IEEE CinC, ARTERY)

Award = 1
Best poster award in international peer reviewed conf. for vascular researchers and clinicians

Research Objectives: To develop & validate

01 Method for robust arterial wall-recognition and tracking from A-mode ultrasound frames

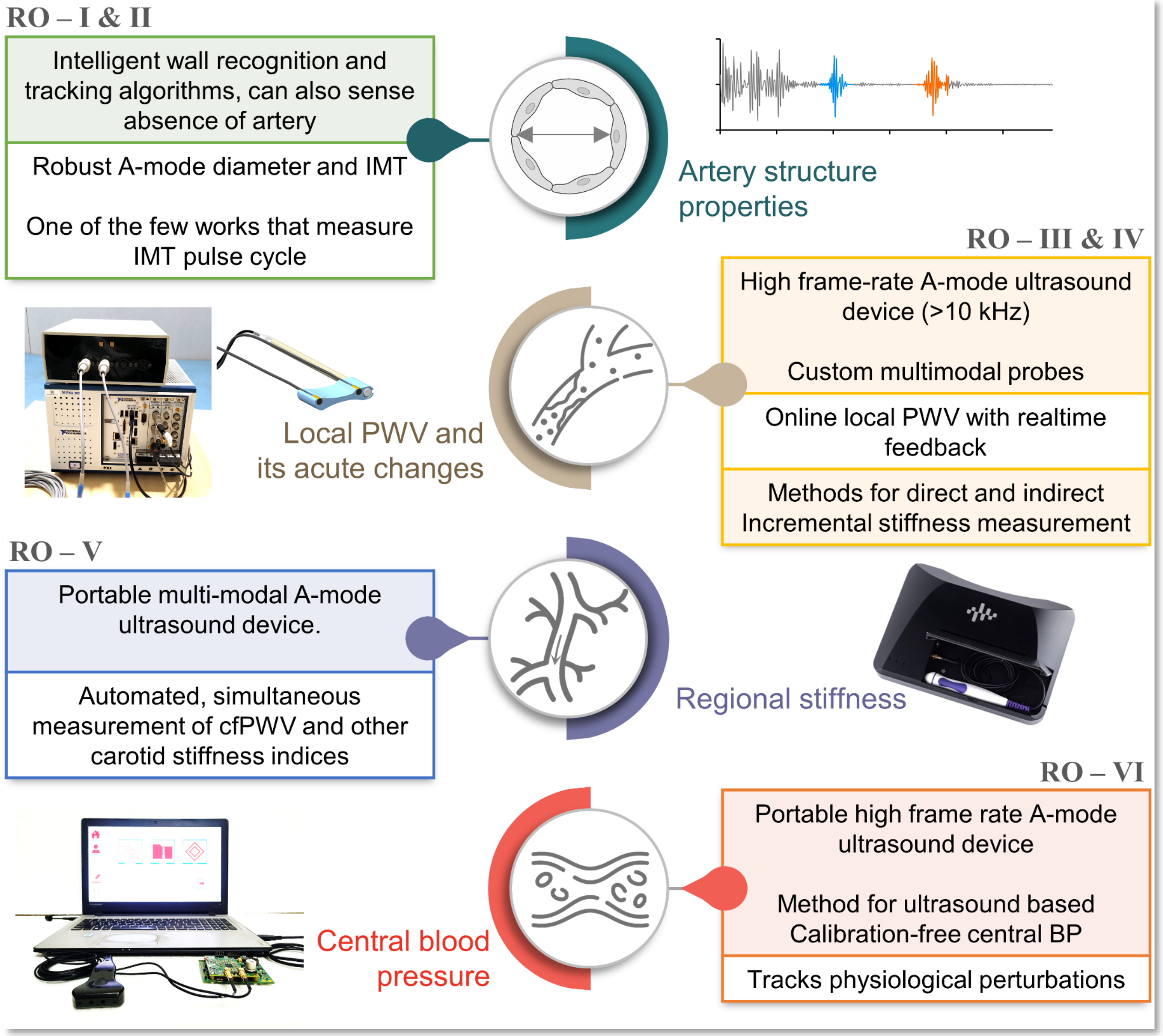
02 Method for diameter and wall thickness using A-scan ultrasound measurement

03 High frame-rate A-scan multimodal ultrasound system and probes

04 Method for local PWV and its pressure-dependent variations using A-scan ultrasound

05 Method for regional stiffness measurement using A-scan ultrasound

06 Method for carotid pressure measurement : feasibility study using LBNP intervention



500+ In-vivo measurements, including interventional studies

8 Journal articles (5 part of thesis)

47 Conference publications (18 part of thesis)

6 Patents pending

RO-1. Arterial Wall Detection & Tracking

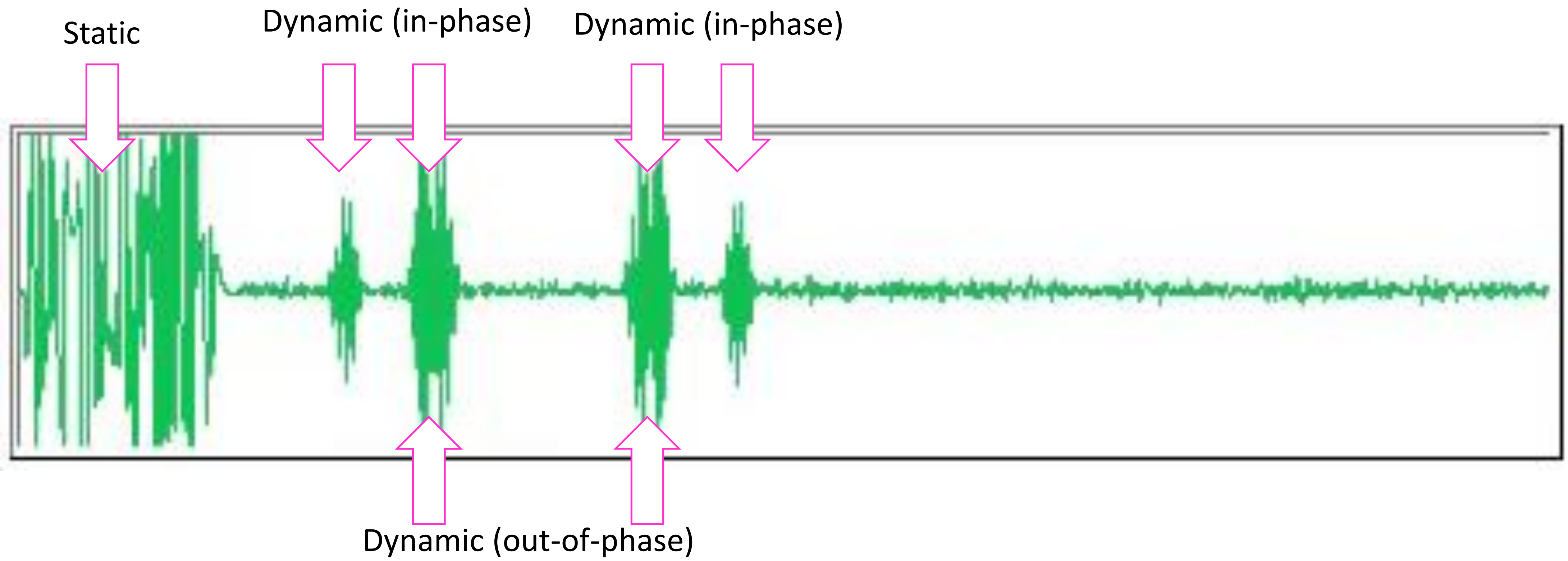
Raj, K. V., Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2022). Time-warping for robust automated arterial wall-recognition and tracking from single-scan-line ultrasound signals. **Ultrasonics**, 126, 106828.

Raj, K. V., Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2022). Time-warping for robust automated arterial wall-recognition and tracking from single-scan-line ultrasound signals. Ultrasonics, 126, 106828.

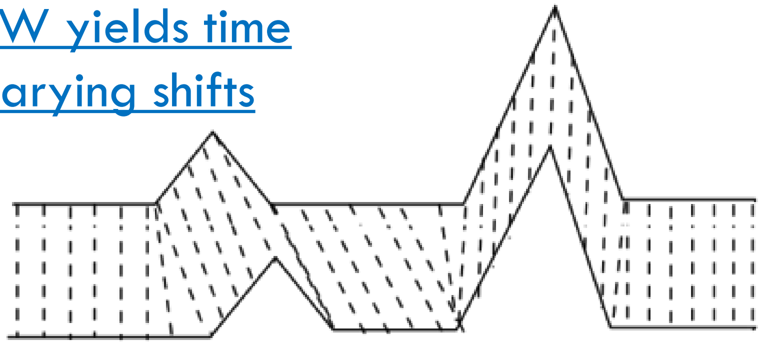
Raj, K. V., Joseph, J., Nabeel, P. M., & Sivaprakasam, M. (2020). A Dynamic Time Warping Method for Improved Arterial Wall-Tracking using A-mode Ultrasound Frames : A Proof-of-Concept. IEEE Symposium on Medical Measurements and Applications (MeMeA), 1–6. Bari.

Raj, K. V., Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2021). Phantom evaluation of a time warping based automated arterial wall recognition and tracking method. IEEE International Symposium on Medical Measurements and Applications (MeMeA),

2.1 Dynamic Time warping for recognition and tracking artery wall locations



[DTW yields time varying shifts]

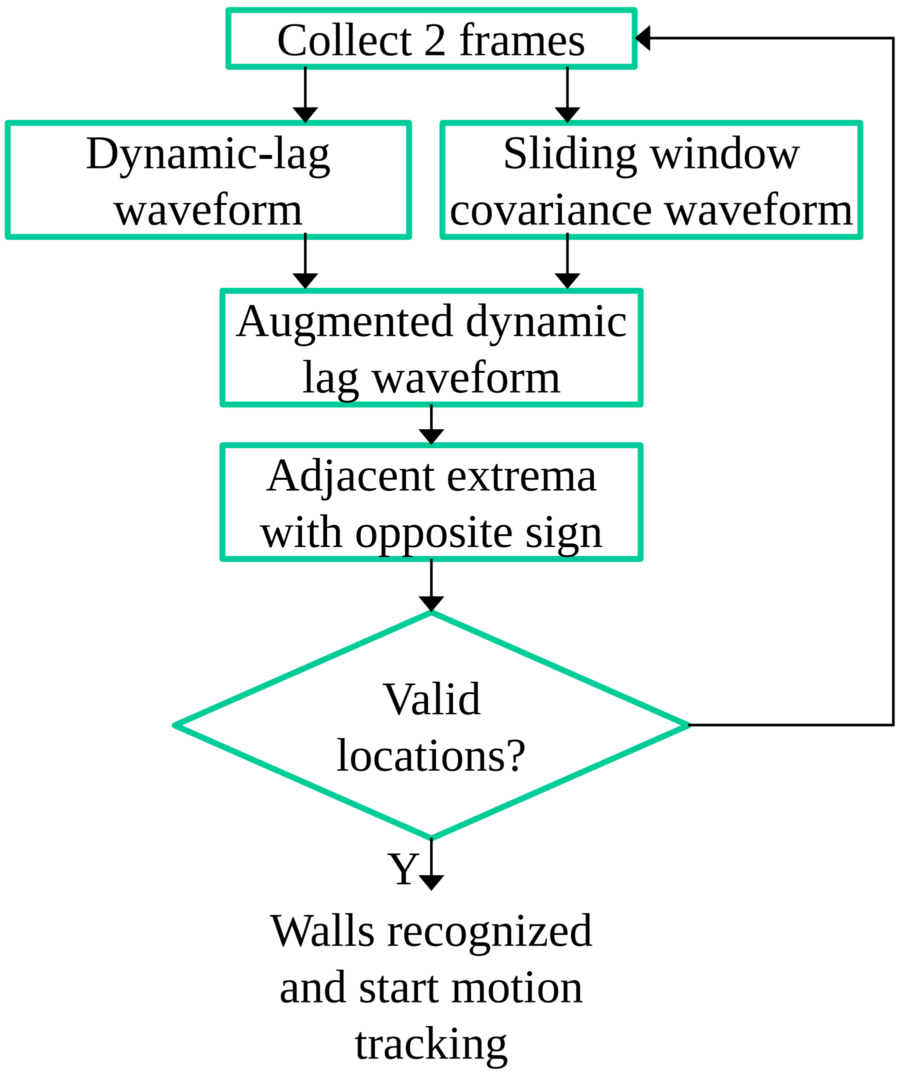


Warping

- Stretching
- Compressing
- Shifting

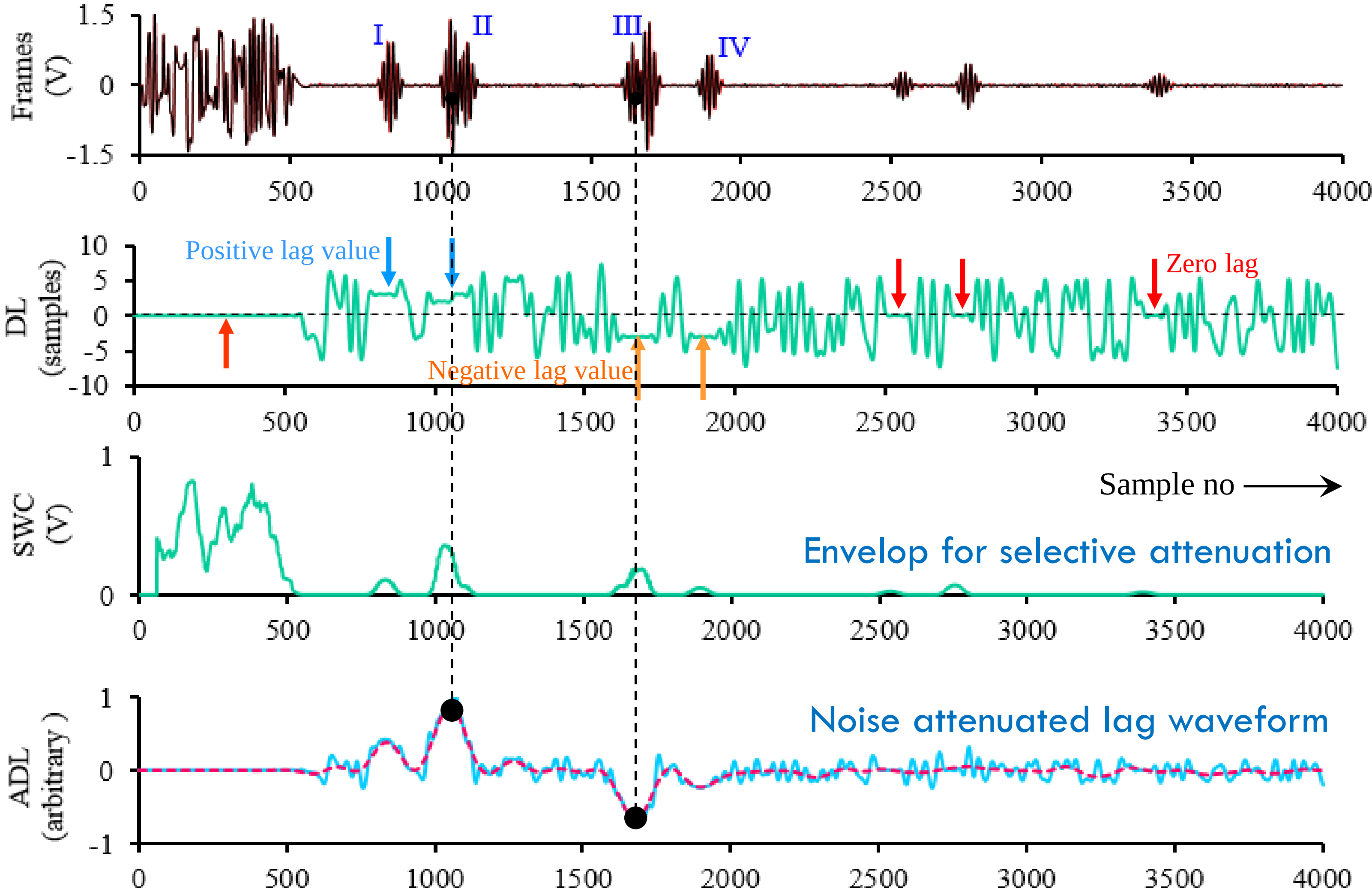
- Principle is based on finding the time varying shifts between two frames F_n and F_{n-1}
- Identify **adjacent** dynamic echoes moving **opposite in direction**

2.2. Wall recognition: Construction of dynamic lag waveform



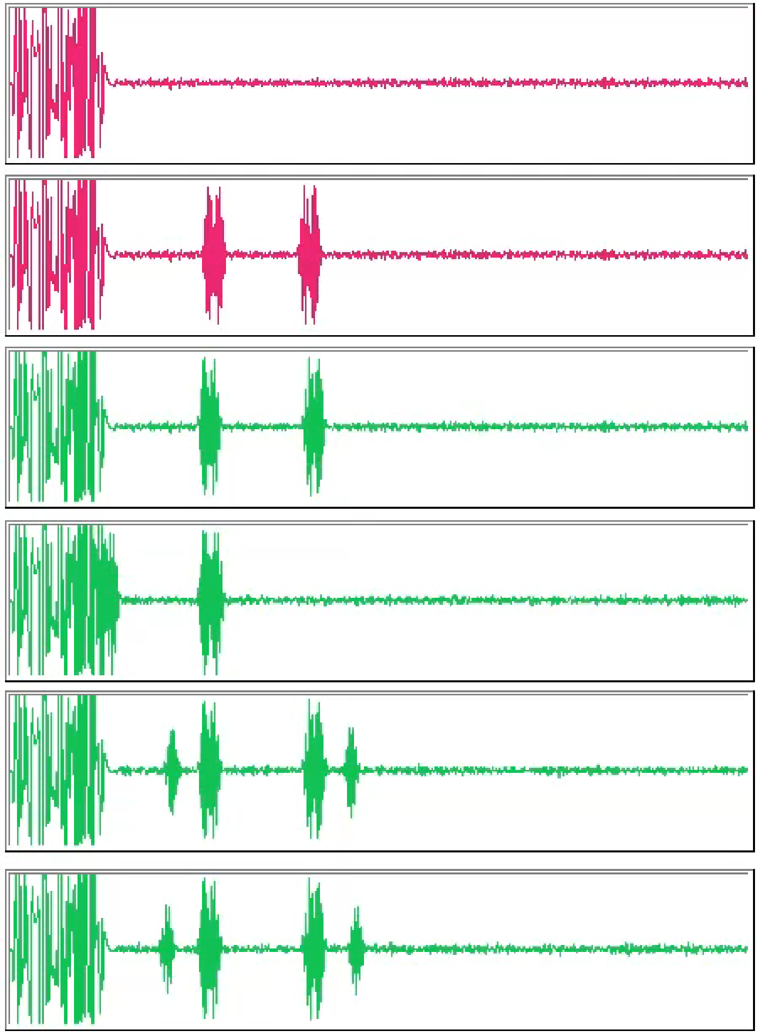
DTW based estimation of dynamic lag waveform

Alignment Error matrix → Accumulated Error matrix → Back-tracking for Dynamic lag waveform

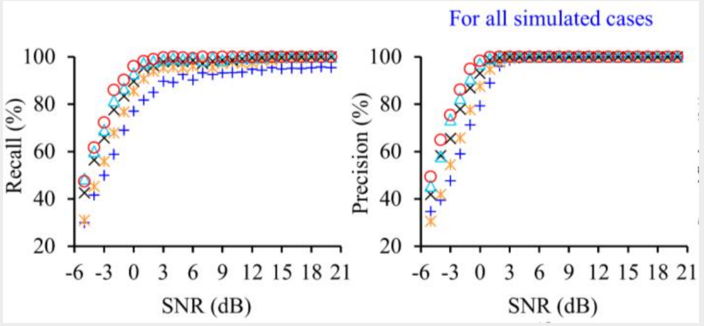


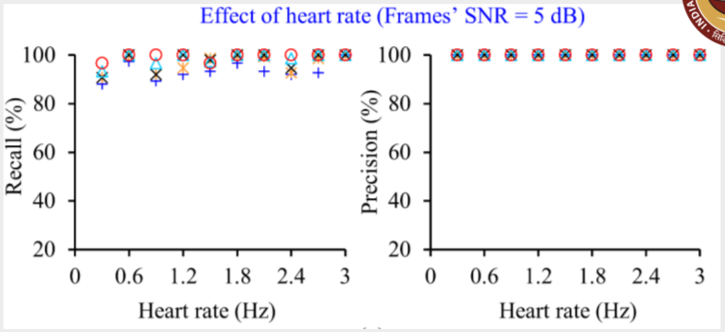
2.3. Wall recognition: Validation

Simulated frames with and without artery

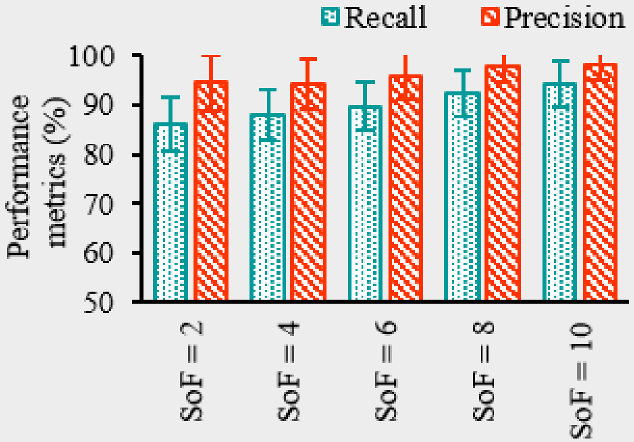


Validated on simulations (6 easy to difficult cases)





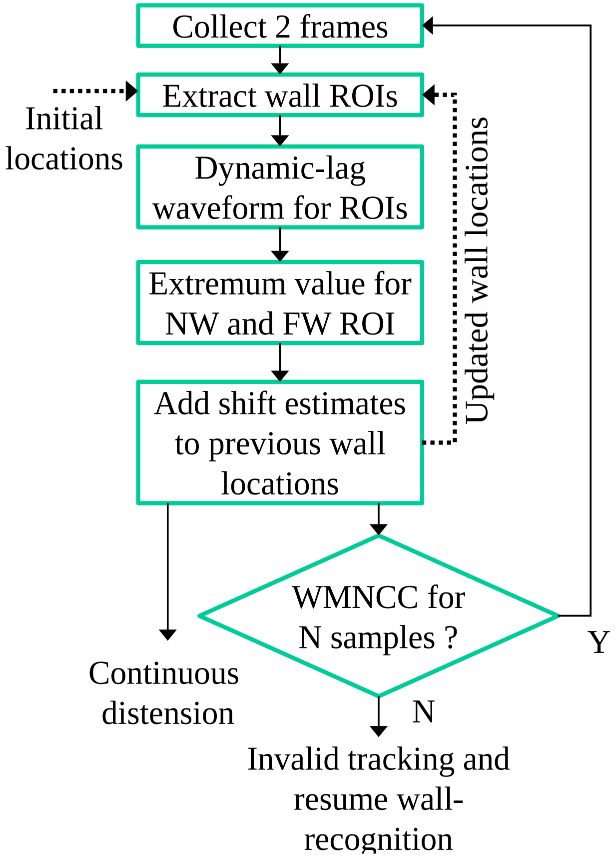
Validated on human subjects (N = 50)

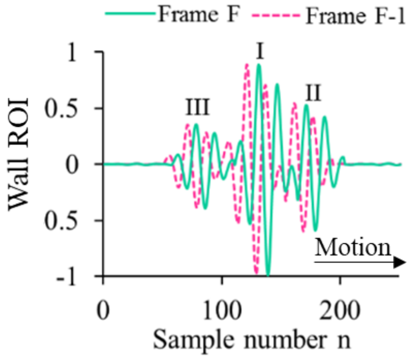


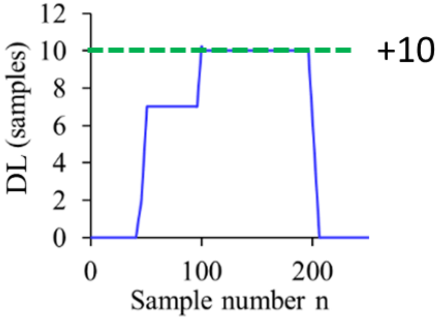
- Works for 2 difficult simulation cases, (i) absence of artery and (ii) overlap with hyperechoic echoes, where other methods fail
- 90% detection rate, 96% correct detections, in-vivo performance on par with best image-based methods

Raj, K. V., Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2022). Time-warping for robust automated arterial wall-recognition and tracking from single-scan-line ultrasound signals. **Ultrasonics**, 126, 106828.

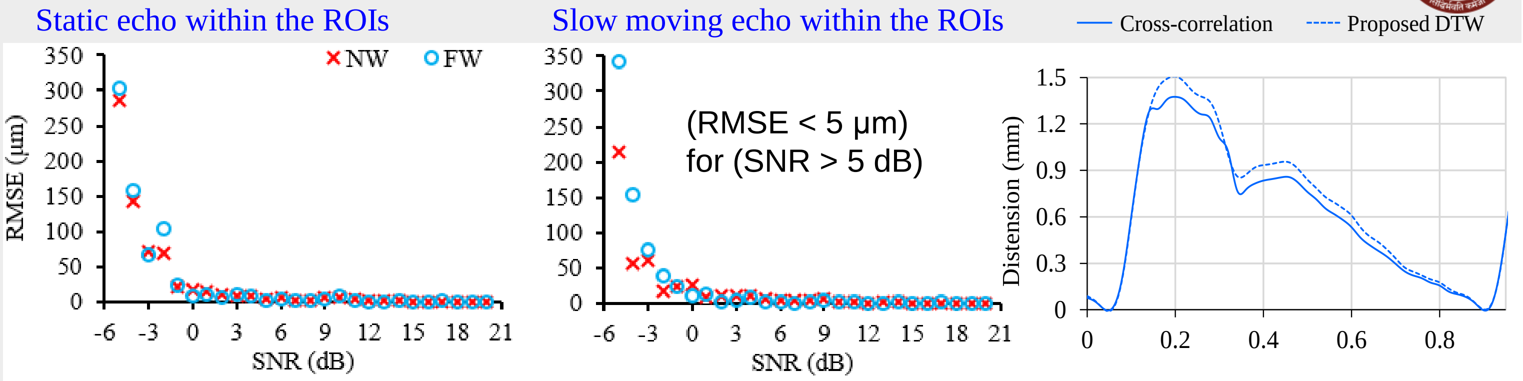
2.3. Wall tracking Algorithm



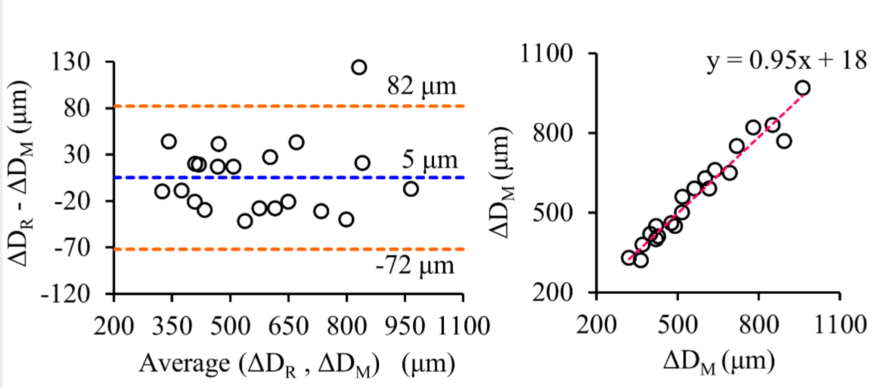




Validated on simulations



Validated on human subjects



- ✓ Insignificant bias = 5 μm ($p = 0.28$)
- ✓ No trend in BA plot
- ✓ Strong correlation ($R = 0.97$)

- Shift estimates of arterial walls not influenced by the motion of extra echoes in the ROI.
- Accurate tracking of arterial walls. Distension measurements comparable to Imaging reference

Raj, K. V., Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2022). Time-warping for robust automated arterial wall-recognition and tracking from single-scan-line ultrasound signals. **Ultrasonics**, 126, 106828.

RO-2. Arterial Diameter and IMT Measurement

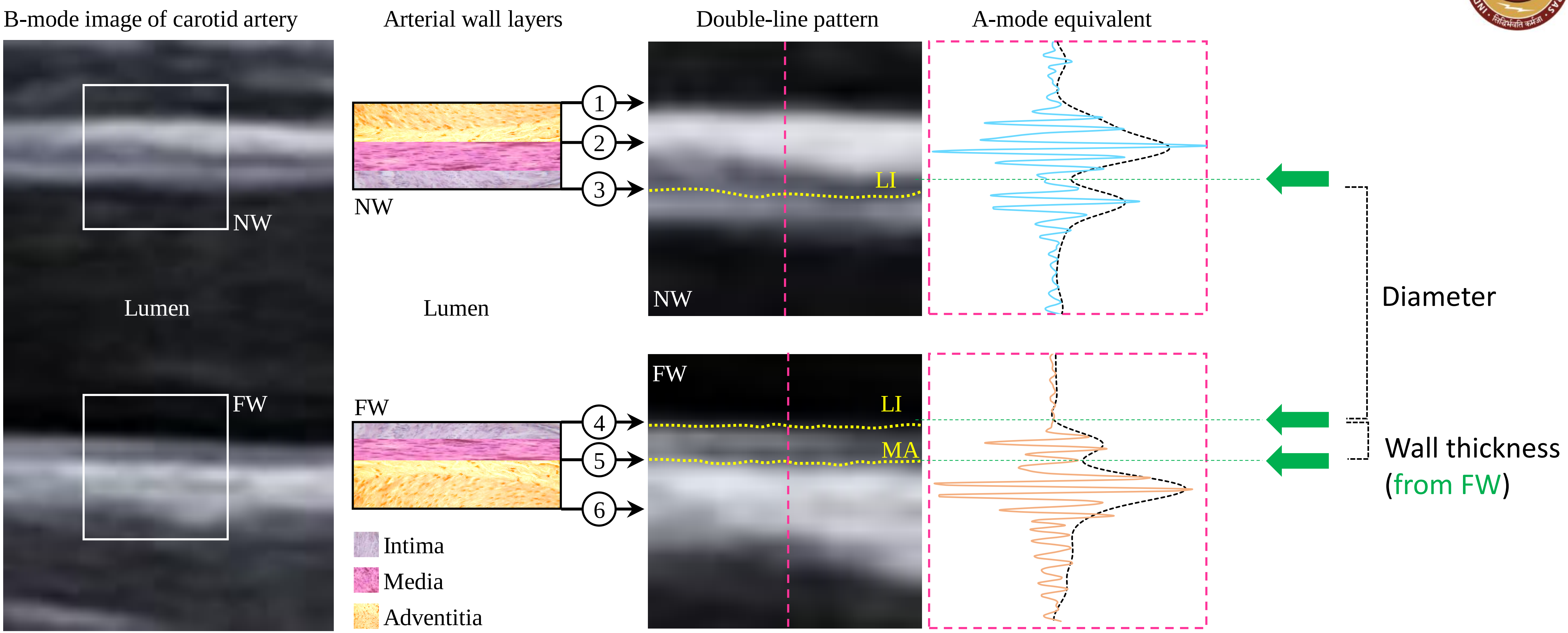
Raj, K. V., Joseph, J., Nabeel, P. M., & Sivaprakasam, M. (2020). Automated measurement of compression-decompression in arterial diameter and wall thickness by image-free ultrasound. **Computer Methods and Programs in Biomedicine**, 194, 1–12.

Raj, K. V., Joseph, J., Shah, M. I., & Sivaprakasam, M. (2017). An image-free ultrasound method to estimate artery wall thickness surrogate for screening. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6. Rochester.

Raj, K. V., Joseph, J., Nabeel, P. M., Frese, H., Sivaprakasam, M., & Shah, M. I. (2019). Analytic phase based approach for arterial diameter evaluation using A-mode ultrasound frames. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–5.

Raj, K. V., Nabeel, P. M., Shah, M. I., Sivaprakasam, M., & Joseph, J. (2021). Gaussian-Mixture Modelling of A-Mode Radiofrequency Scans for the Measurement of Arterial Wall Thickness. 43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 5598–5601.

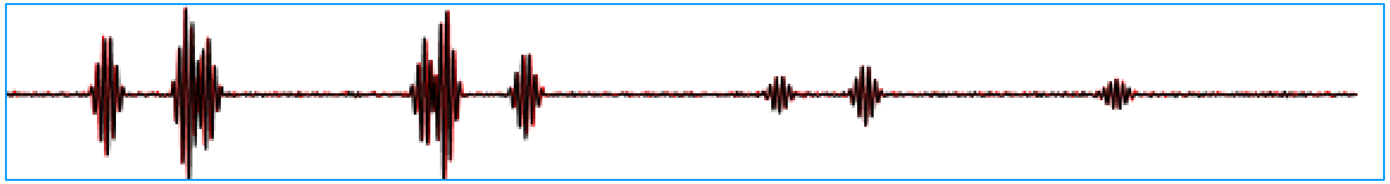
3.1. Clinical guideline on measuring diameter and wall thickness



Valid measurements [1]

1. J. Wikstrand et al., "Methodological considerations of ultrasound measurement of carotid artery intima–media thickness and lumen diameter," Clinical Physiology and Functional Imaging, vol. 27, no. 6, pp. 341–345, Nov. 2007

3.2. Measurement method's principle: Exploiting Unwrapped Phase

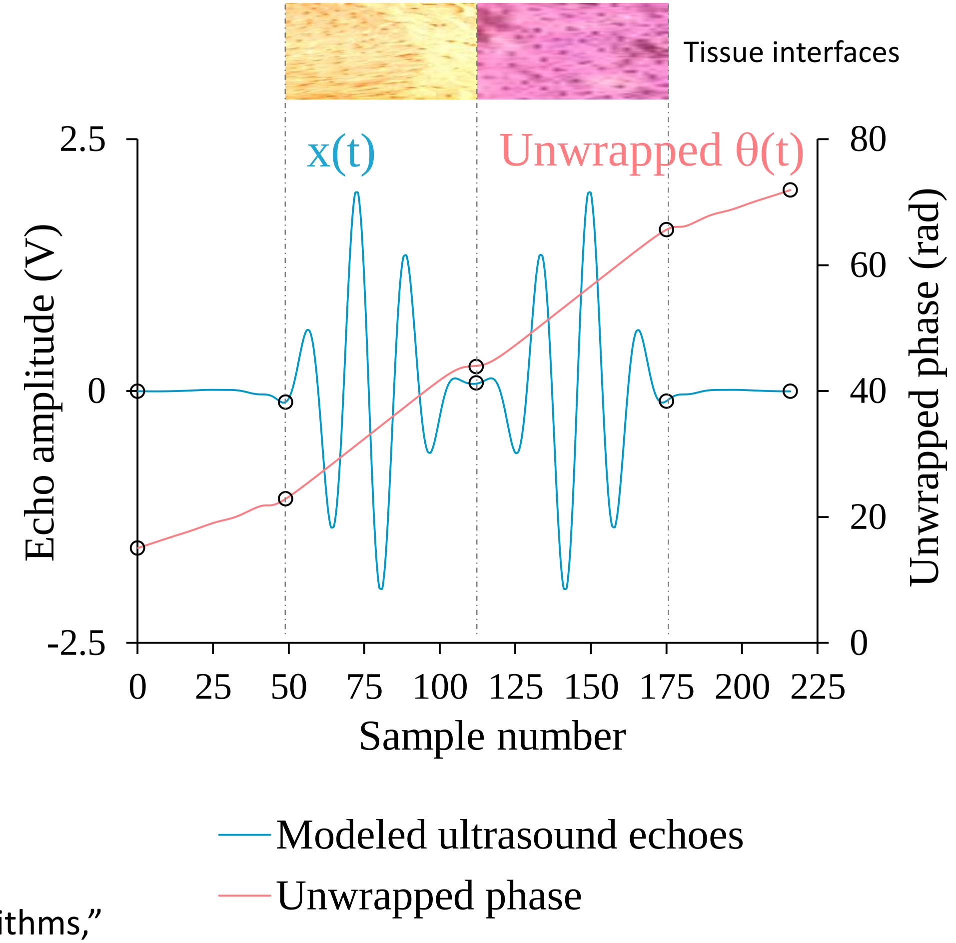


$$x(t) = \sum_k p_k(t) + n(t)\,.$$

$$p_k(t) = W_k\, e^{-\alpha(t-\tau_k)^2} \cos(2\pi f_c(t-\tau_k) + \theta_k)$$

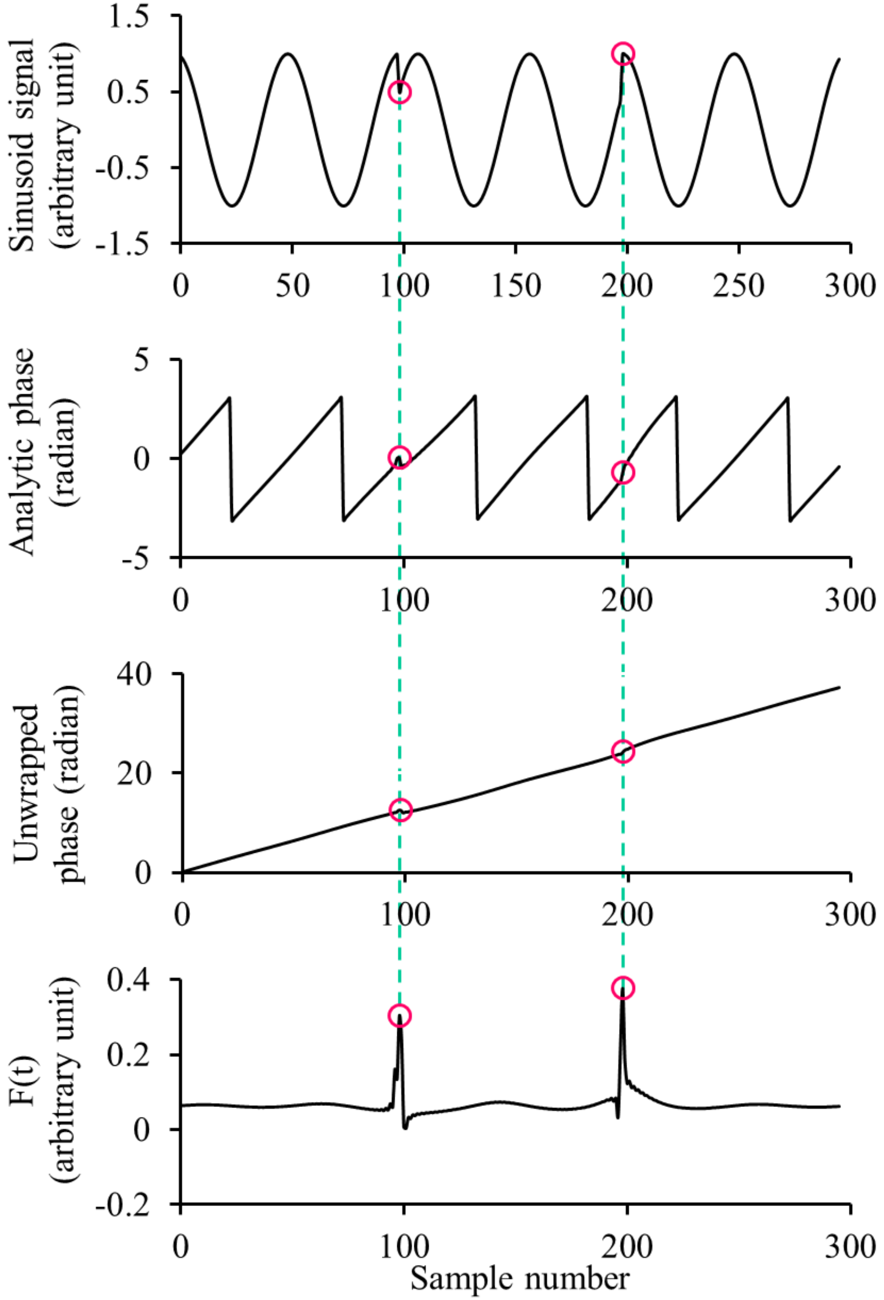
Sum of weighted and shifted gaussian sinusoids [1]

Breakpoints or knots of the piecewise linear unwrapped-phase signal locate the echoes' boundaries



1. R. Demirli et al., "Model-based estimation of ultrasonic echoes. Part I: Analysis and algorithms," Clinical IEEE Trans. Ultrason. Ferroelectr. Freq. Control, vol. 48, pp. 787–802, Nov. 2001

3.2. Measurement method's principle: Phase jumps and knots



Sinusoidal signal with phase jumps

Hilbert transform of x(t)

$$y(t) = \frac{1}{\pi}\int_{-\infty}^{\infty} \frac{x(\tau)}{t-\tau}\,d\tau$$

Analytic phase θ(t)

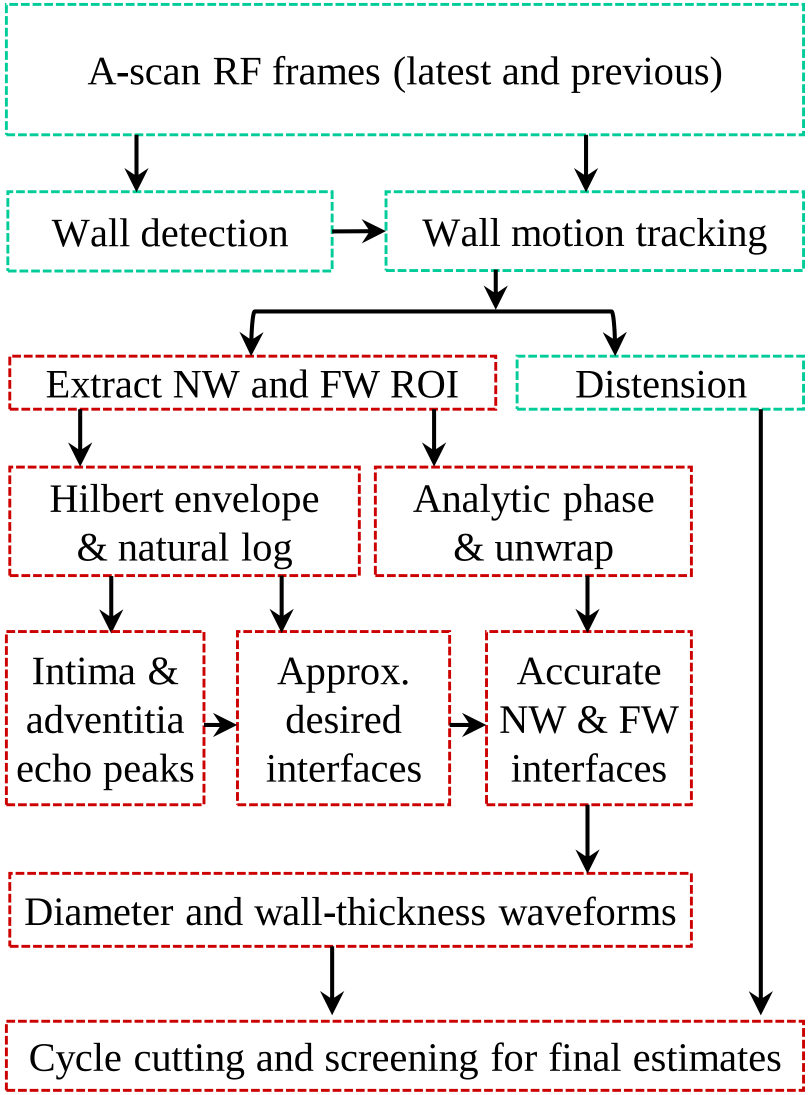
$$\theta(t) = \tan^{-1}\left(\frac{y(t)}{x(t)}\right)$$

Piecewise linear with breakpoints or knots

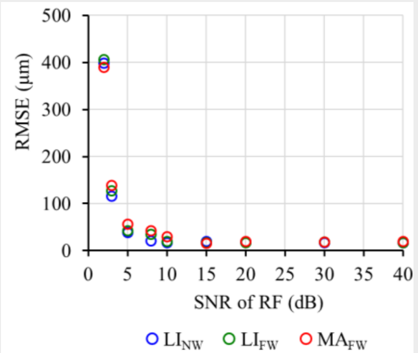
F(t) is the absolute version of unwrapped θ'(t) subtracted from its mean

3.3. Developed Algorithm: Validation

Analytic phase based method

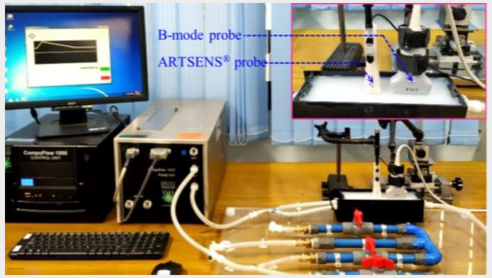


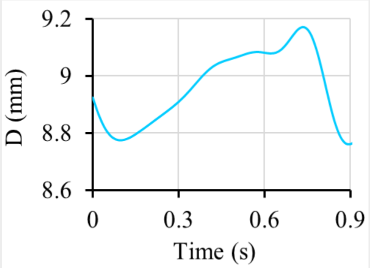
Validated on simulations

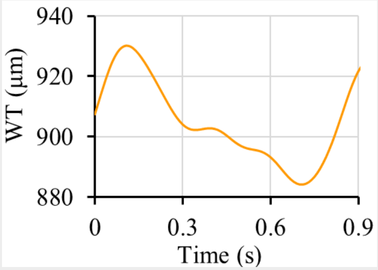


- ✓ Requires SNR ≥ 10 dB, for RMSE < 20 µm
- ✓ For SNR ≥ 5 dB, RMSE was still < 60 µm

Validated on flow phantom







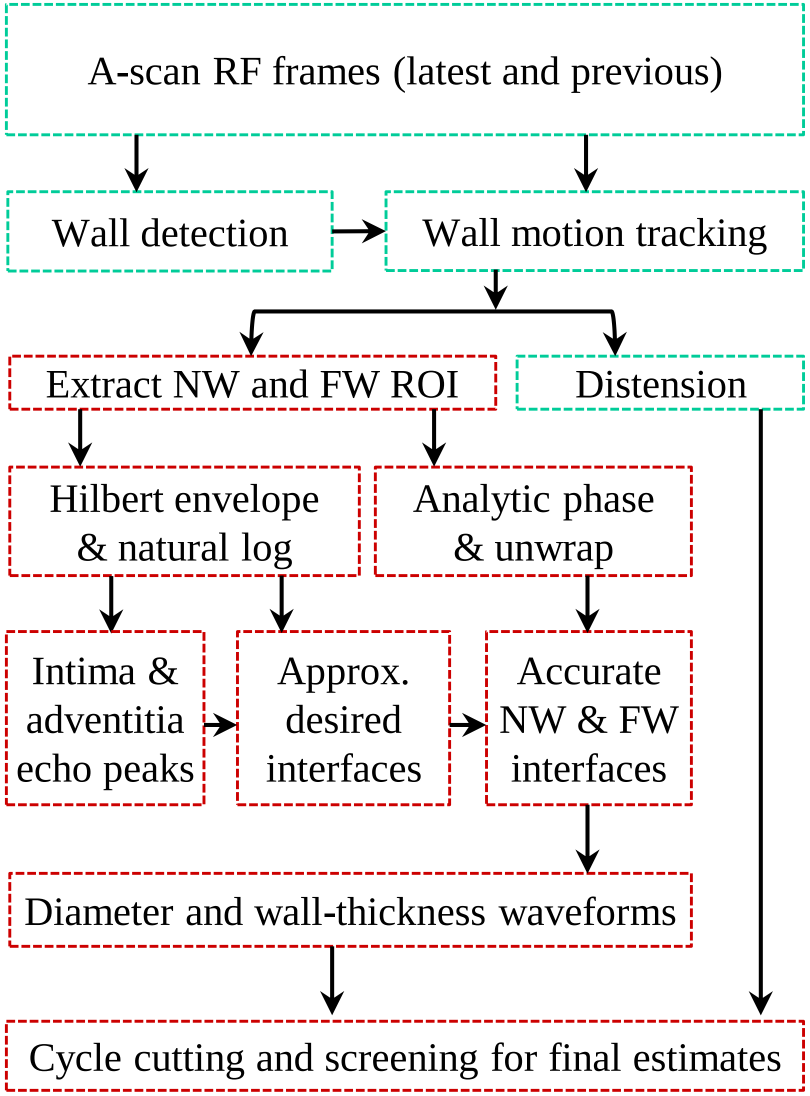
- Simultaneous B-mode measurements
  - ✓ Diameter: $r = 0.94$, $p < 0.001$
  - ✓ Wall thickness: $r = 0.87$, $p < 0.001$
- Instantaneous diameter and thickness
  - ✓ High repeatability (CoV < 3%)
  - ✓ Low errors, RMSE < 15 µm

- **Accurate identification** of the desired wall interfaces of interest, for frames with **SNR as small as 10 dB.**
- **Accurate and repeatable** measurements on phantom. **Continuous diameter and wall thickness** waveforms

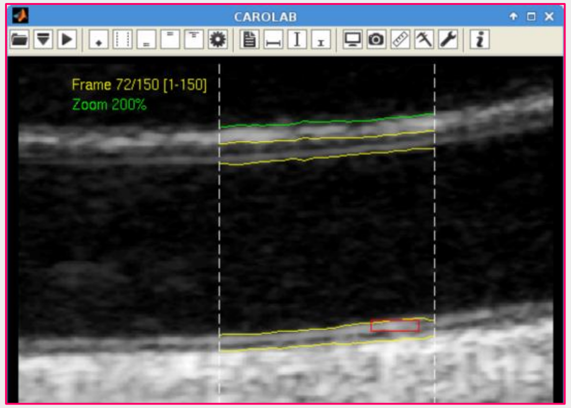
Raj, K. V., Joseph, J., Nabeel, P. M., & Sivaprakasam, M. (2020). Automated measurement of compression-decompression in arterial diameter and wall thickness by image-free ultrasound. **Computer Methods and Programs in Biomedicine**, 194, 1–12.

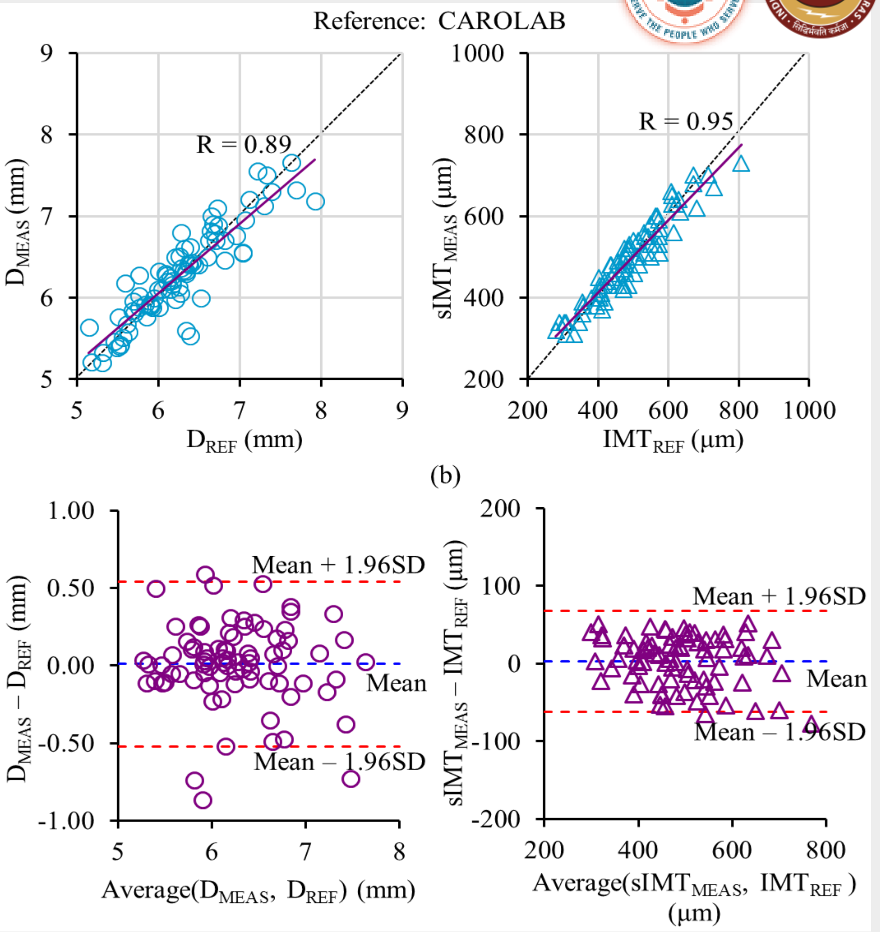
3.3. Developed Algorithm: Validation

Analytic phase based method



Validated on human subjects (N = 40)





Diameter

- ✓ Mean bias: -11 µm
- ✓ Bias significance, p = 0.37
- ✓ Abs error (%) = 2.8 ± 2.9
- ✓ RMSE = 264 µm

sIMT

- ✓ Mean bias: -2.8 µm
- ✓ Bias significance, p = 0.22
- ✓ Abs error (%) = 5.8 ± 3.7
- ✓ RMSE = 33 µm

Highly accurate measurements, on par with imaging methods in literature.

Raj, K. V., Joseph, J., Nabeel, P. M., & Sivaprakasam, M. (2020). Automated measurement of compression-decompression in arterial diameter and wall thickness by image-free ultrasound. **Computer Methods and Programs in Biomedicine**, 194, 1–12.

RO-3,4. High frame rate system and method for local pulse wave velocity

Raj, K. V., Nabeel, P. M., & Joseph, J. (2022). Image-Free Fast Ultrasound for Measurement of Local Pulse Wave Velocity: In Vitro Validation and In Vivo Feasibility. **IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control**, 69(7), 2248–2256.

Raj, K. V., Nabeel, P. M., Joseph, J., Shah, M. I., & Sivaprakasam, M. (2018). Evaluation of local pulse wave velocity using an image free ultrasound technique. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.

Raj, K. V., Nabeel, P. M., Joseph, J., & Sivaprakasam, M. (2019). Methodological and measurement concerns of local pulse wave velocity assessment. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.

Raj, K. V., Nabeel, P. M., Manoj, R., Shah, M. I., & Joseph, J. (2021). Phantom Assessment of an Image - free Ultrasound Technology for Online Local Pulse Wave Velocity Measurement. 43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 5610–5613.

Raj, K. V., Nabeel, P. M., Chandran, D., Sivaprakasam, M., & Joseph, J. (2022). High-frame-rate A-mode ultrasound for calibration-free cuffless carotid pressure: feasibility study using lower body negative pressure intervention. Blood Pressure, 31(1), 1–11.

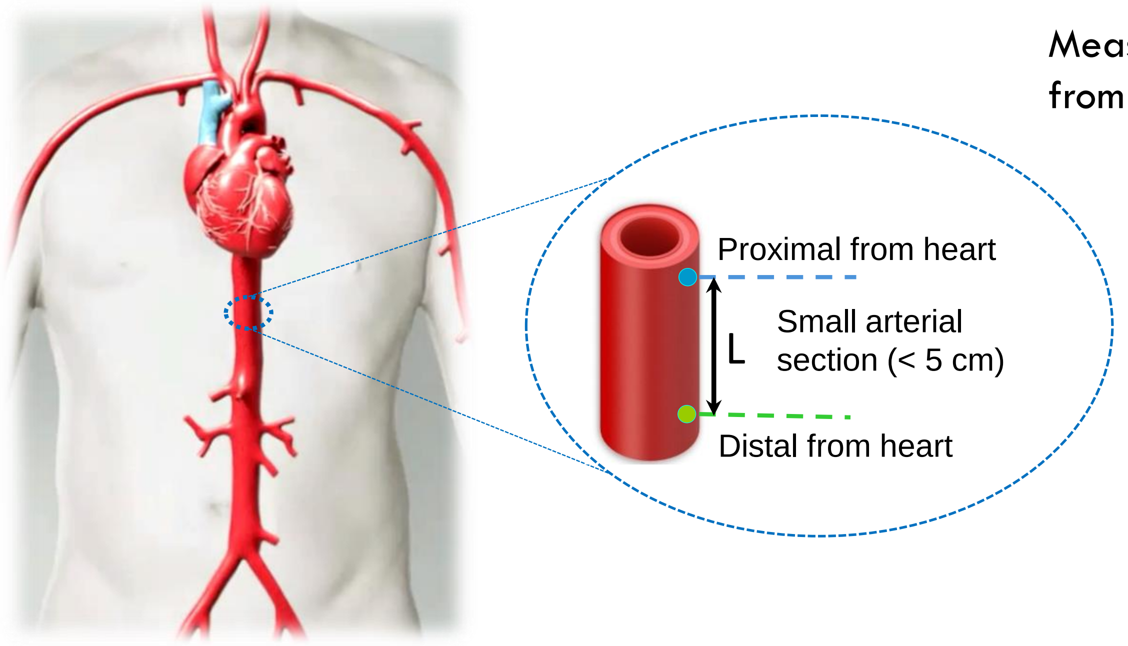
Raj, K. V., Nabeel, P. M., Joseph, J., & Sivaprakasam, M. (2018). Non-invasive assessment of arterial incremental elastic modulus variations within a cardiac cycle. 13th Russian-German Conference on Biomedical Engineering (RGC), 108–111.
Raj, K. V., Nabeel, P. M., Joseph, J., & Sivaprakasam, M. (2019). Incorporating Arterial Viscoelastic Modelling for the Assessment of Changes in Pulse Wave Velocity Within a Cardiac Cycle Using Bramwell-Hill Equation. Computing in Cardiology (CinC), 46, 1–4.

Raj, K. V., Nabeel, P. M., Joseph, J., Frese, H., & Sivaprakasam, M. (2019). Multimodal Image-Free Ultrasound Technique for Evaluation of Arterial Viscoelastic Properties: A Feasibility Study. 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 5034–5037.

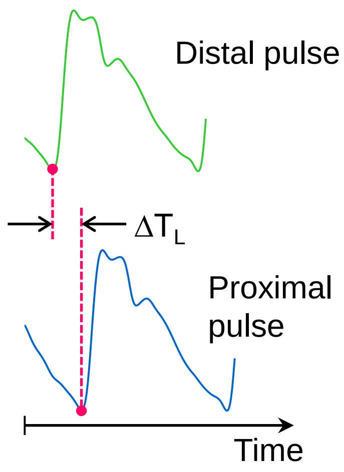
Raj, K. V., Nabeel, P. M., Joseph, J., Chandran, D., & Sivaprakasam, M. (2020). P.41 Measurement of Pressure-dependent Intra-Beat Changes in Carotid Pulse Wave Velocity using Image-Free Fast Ultrasound. Artery Research, 26(Supplement 1), S63.

Raj, K. V., Manoj, R., Ishwarya, S., Nabeel, P. M., Joseph, J. (2022). Comparison of Approximated and Actual Bramwell-Hill Equation Implementation for Local Pulse Wave Velocity: Ex-vivo Study. 44th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 5034–5037.

4.1. Local PWV: Definition and Measurement



Measure delay between pulses from two nearby sites



Local pulse wave velocity is speed with which blood pulse traverses across a small segment of artery

$$\text{Local PWV} = \frac{L}{\Delta T_L}$$

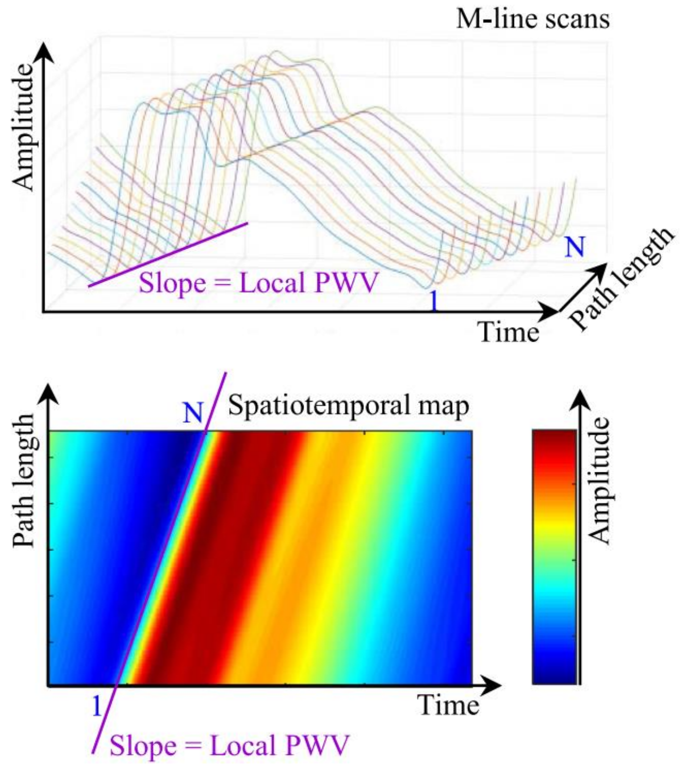
Say,
PWV = 3 – 10 m/s, L = 50 mm,

ΔT measured would be 5 – 20 ms

➔ Need high sampling rate

Imaging systems measure accurate blood pulse directly from the artery as diameter or flow but are limited by the low scanning rate

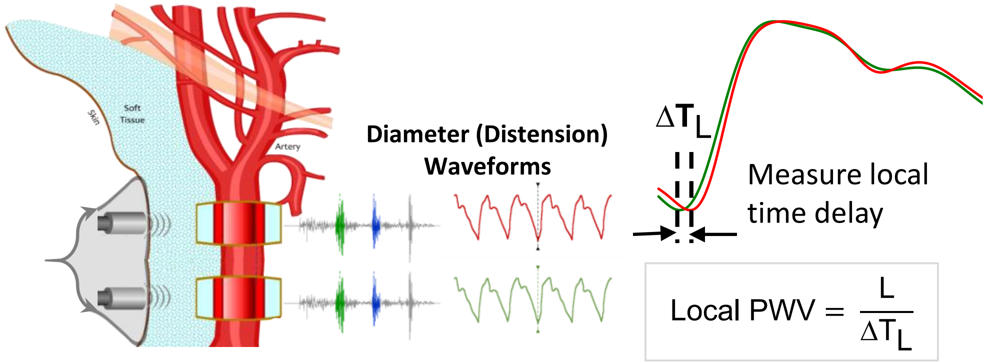
Advanced ultrafast imaging systems in literature implement variants of transit time method



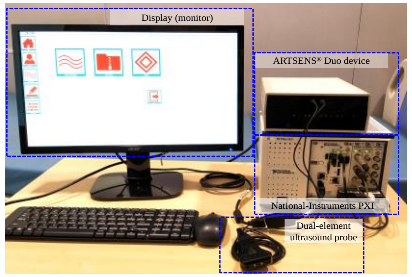
1. Expensive and complex devices
2. Non-real time (post-processing)
3. No feedback of recording quality even with use of GPUs.

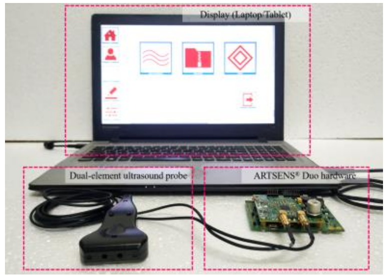
4.2. Developed High frame rate ultrasound system for local PWV

Measurement principle



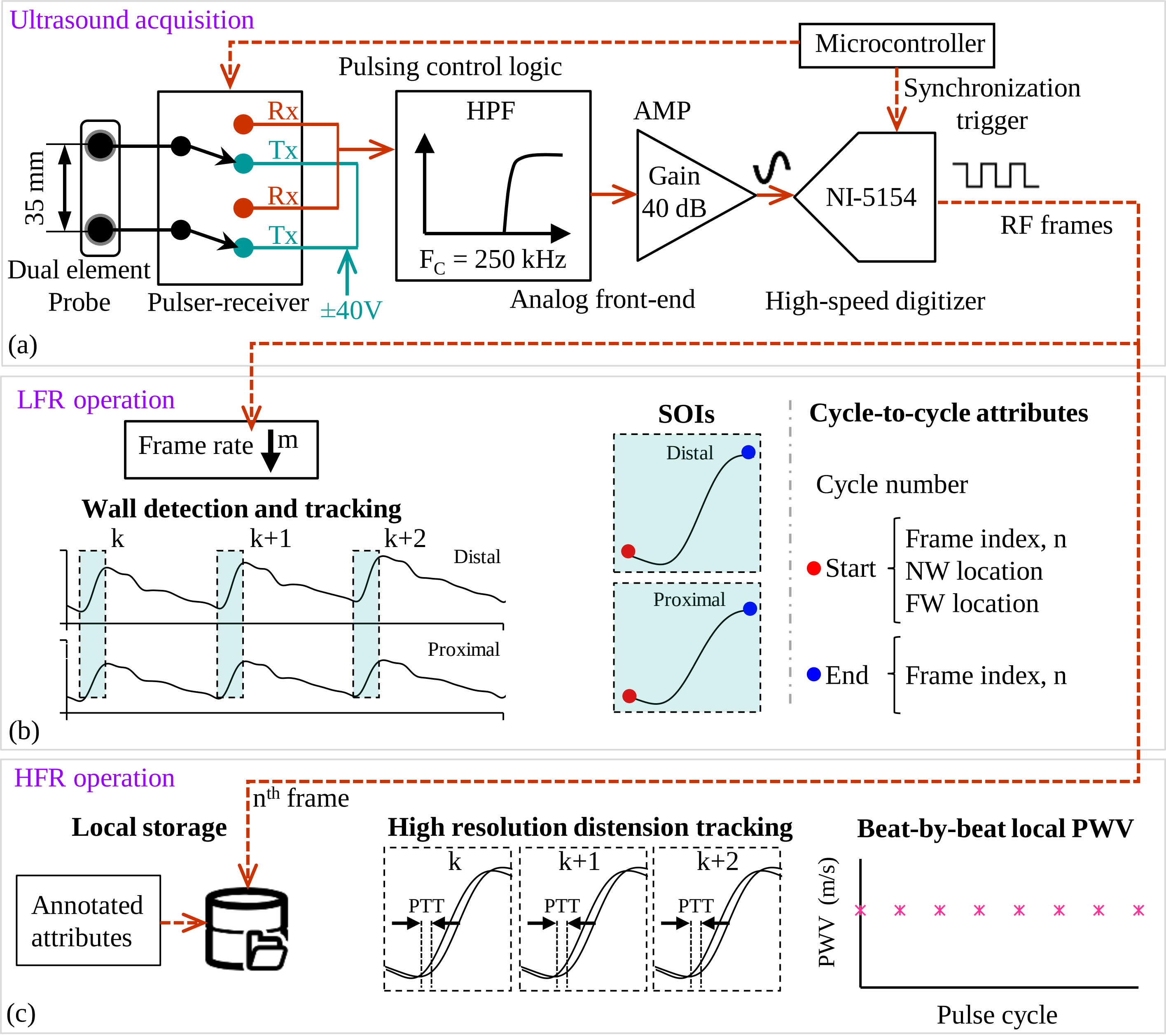
High frame rate system prototypes





- ✓ Earlier discussed detection and tracking algorithms used for carotid distension pulses
- ✓ Real-time feedback for tracked waveforms
- ✓ Implemented selective segment processing scheme for online PWV measurements

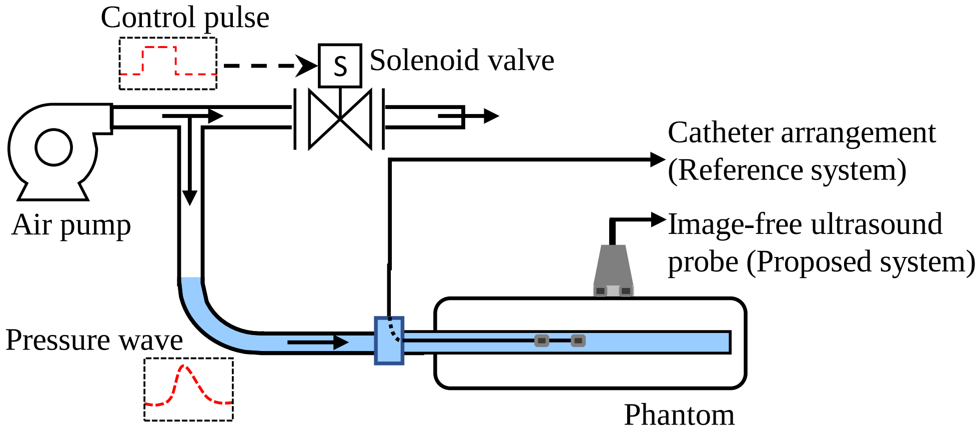
Measurement system schematic



4.3. System characterization

Phantom setup with invasive reference

Experimental validation setup

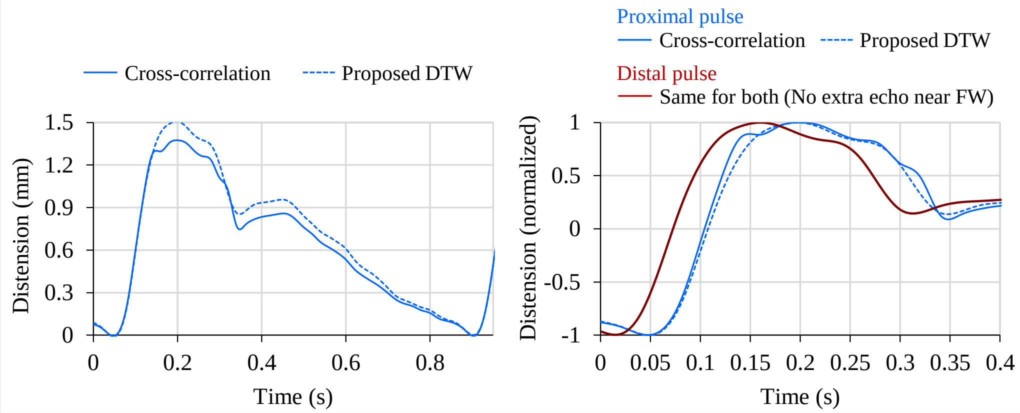


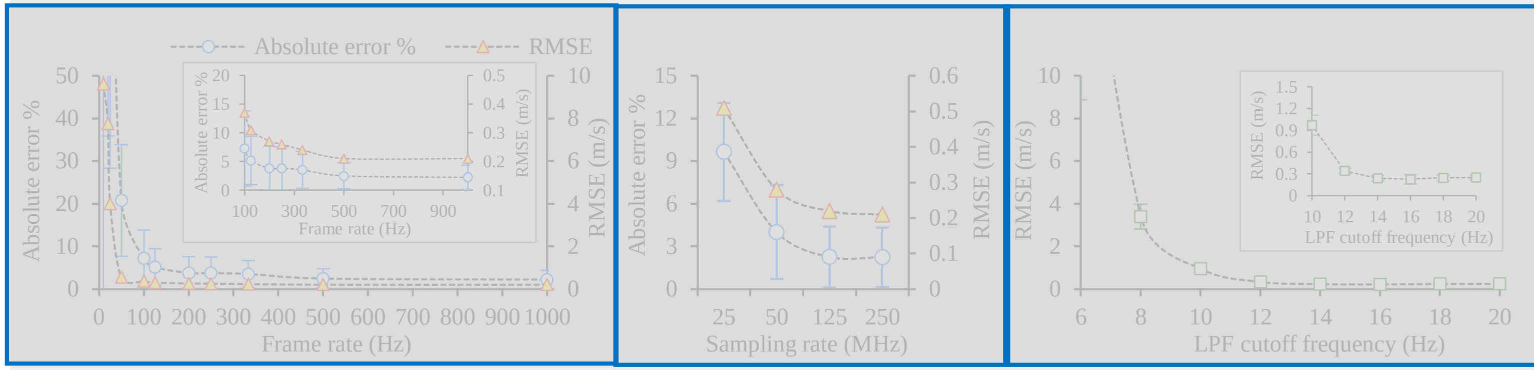
Synchronized beat-to-beat invasive and non-invasive local PWV measurements

- ✓ Pulses were emulated to provide steeper ascent than descent
- ✓ Foot to peak systolic 27% to 42% of total cycle
- ✓ At normal heart rate ascend time = 280 ms, and descend was 550 ms
- ✓ At higher HR (>100 bmp) systolic times were kept closer to 40%

In-vitro design characterization (against invasive reference)

- Tissue transit delay
- Inter-channel delay
- Tracking algorithm
- Frame rate
- Sampling rate
- Pulse filter parameters





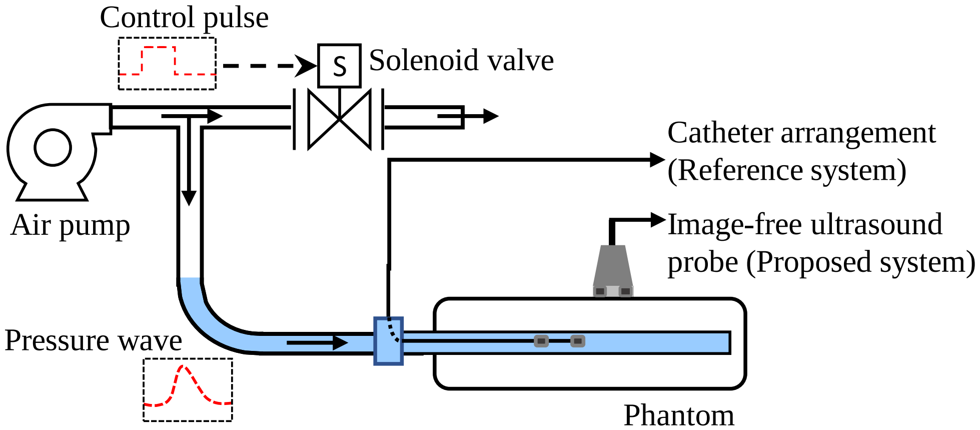
High frame rate system was characterized for Local PWV measurement over a desired range of 3 to 11 m/s

Raj, K. V., Nabeel, P. M., & Joseph, J. (2022). Image-Free Fast Ultrasound for Measurement of Local Pulse Wave Velocity: In Vitro Validation and In Vivo Feasibility. **IEEE Transactions on Ultrasonics, Ferroelectrics, and Control**, 69(7), 2248–2256.

4.4. Local PWV: Validation

Phantom setup with invasive reference

Experimental validation setup



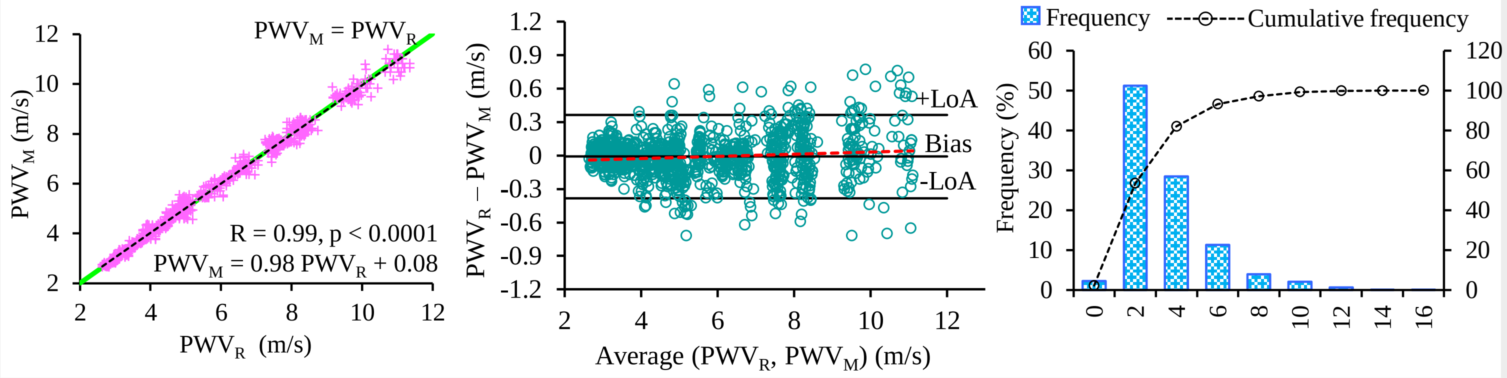
Synchronized beat-to-beat invasive and non-invasive local PWV measurements

In-vivo measurements

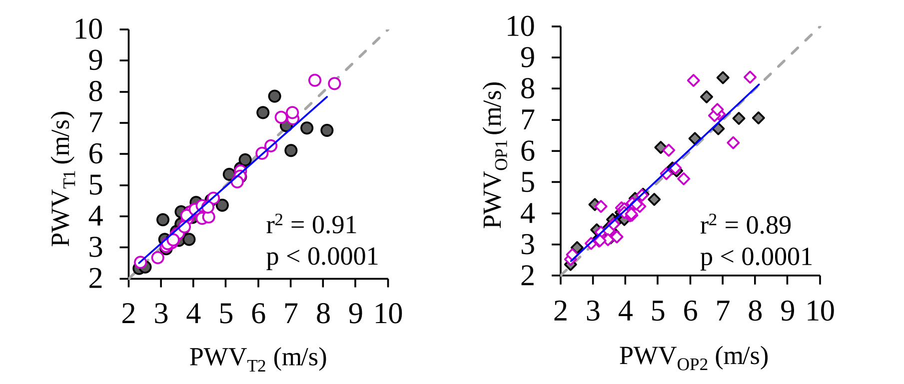
(N = 33)

- Healthy young (M = 19)
- Left common carotid
- Age : 20 – 52 years

In-vitro accuracy (against invasive reference)



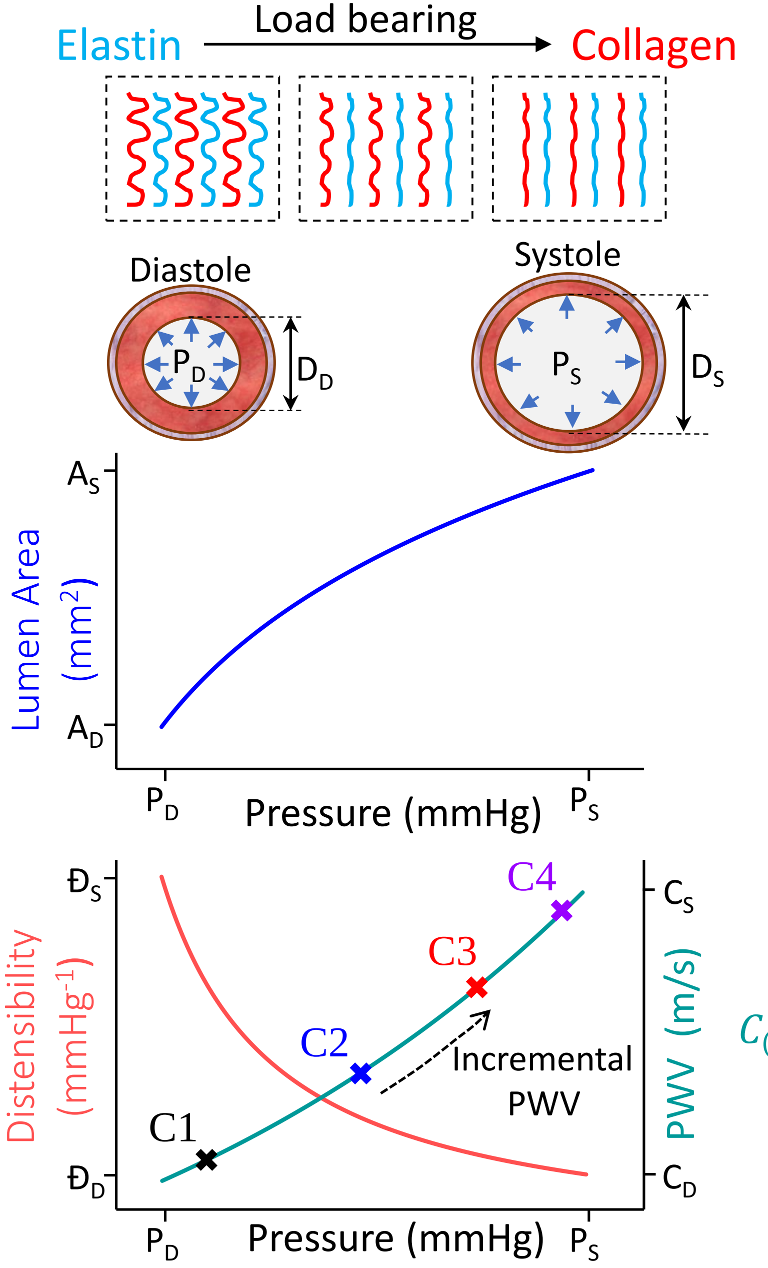
In-vivo reliability (operator repeatability and reproducibility, N = 66)



With the optimal design parameters (frame-rate = 500 Hz, RF sampling rate = 125 MHz, LPF cutoff frequency = 14 Hz, and order = 4) performance was validated in-vitro for accuracy and in-vivo for repeatability and reproducibility

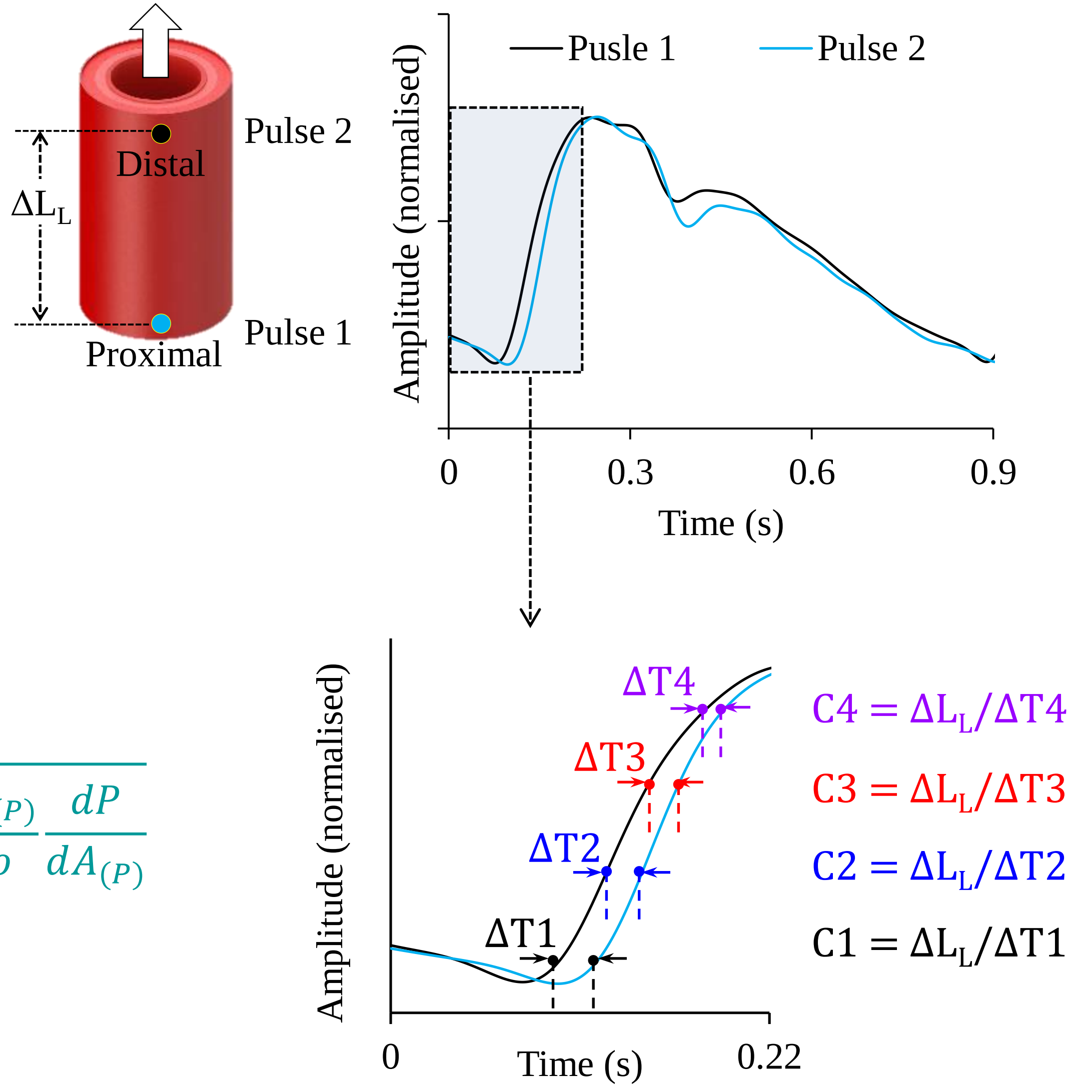
Raj, K. V., Nabeel, P. M., & Joseph, J. (2022). Image-Free Fast Ultrasound for Measurement of Local Pulse Wave Velocity: In Vitro Validation and In Vivo Feasibility. **IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control**, 69(7), 2248–2256.

4.5. Intra-cardiac cycle changes in PWV: Concept



$$C_{(P)} = \sqrt{\frac{A_{(P)}}{\rho}\frac{dP}{dA_{(P)}}}$$

<u>Two-point method for</u>
<u>Incremental local PWV</u>

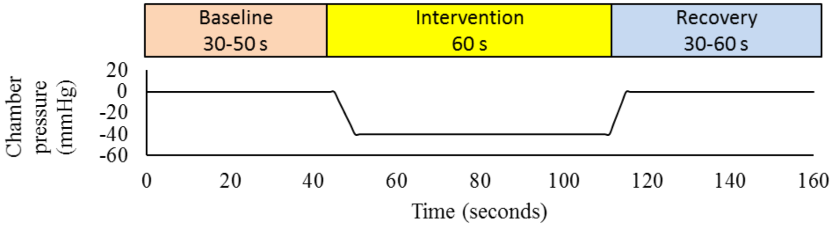


4.6. Pressure dependent changes in local PWV

In-vivo study (under LBNP intervention)

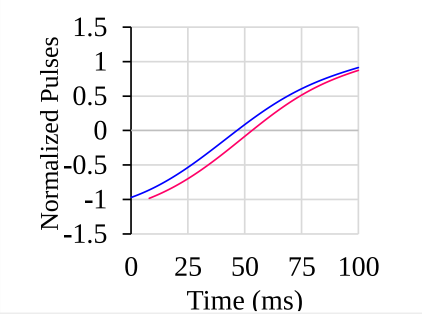
(N = 8)

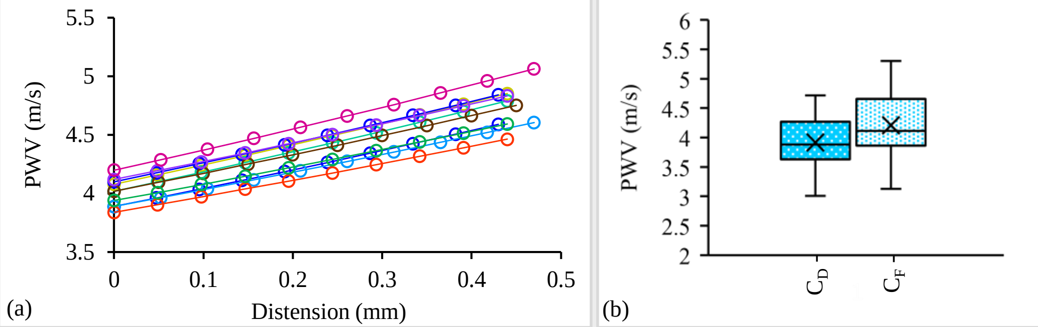
- Healthy male
- Left common carotid
- Age : 21 – 30 years

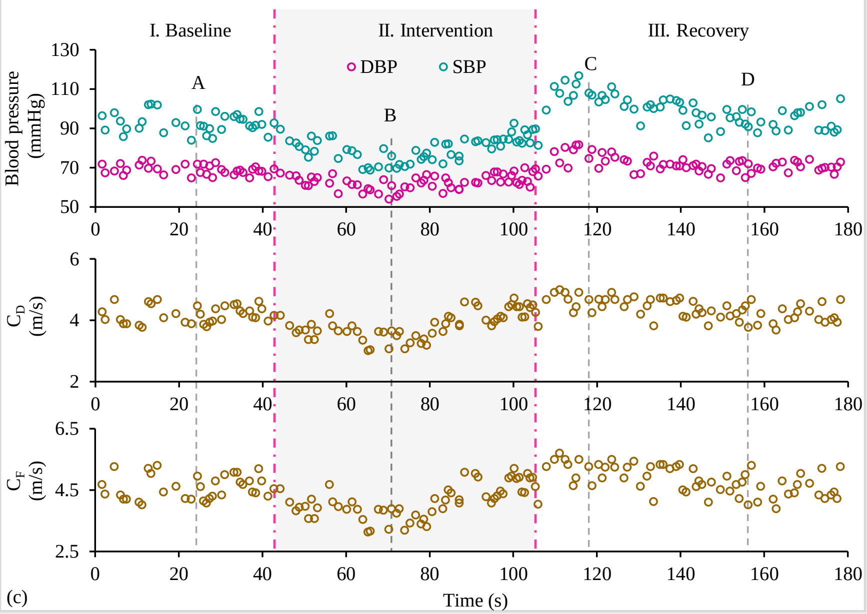


Experiment design

- **Continuous BP:** ADI NIBP system
- **Continuous PWV:** Image-free high framerate ultrasound
- **Intervention:** -40 mmHg lower body negative pressure







- Systolic PWV was greater than diastolic PWV
- Measured reliably the beat to beat changes as well due to physiological perturbation by LBNP

Forward wave separation allows reliable systolic and diastolic PWV measurement, which otherwise is challenging

Raj, K. V., Nabeel, P. M., Chandran, D., Sivaprakasam, M., & Joseph, J. (2022). High-frame-rate A-mode ultrasound for calibration-free cuffless carotid pressure: feasibility study using lower body negative pressure intervention. **Blood Pressure,** 31(1), 1–11.

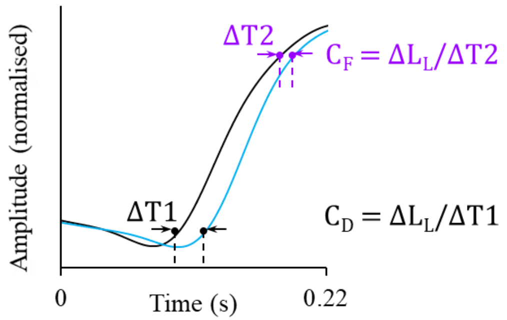
RO-6. High frame rate system for calibration-free central BP: validation

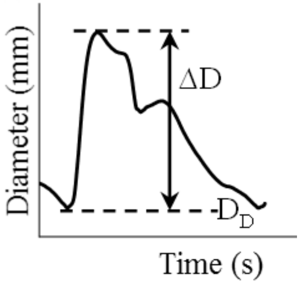
Raj, K. V., Nabeel, P. M., Chandran, D., Sivaprakasam, M., & Joseph, J. (2022). High-frame-rate A-mode ultrasound for calibration-free cuffless carotid pressure: feasibility study using lower body negative pressure intervention. **Blood Pressure**, 31(1), 1–11.

5.1. Central BP using HFR system

Calibration free blood pressure

Intra-cardiac changes in local PWV & Diameter



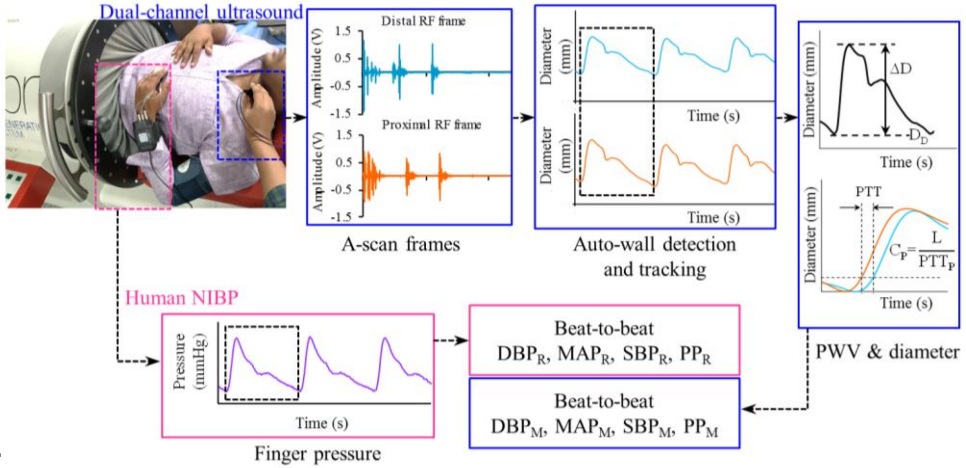


$$\beta = \frac{\ln\left(\frac{C_F^2 D_D}{C_D^2 D_F}\right)}{\left(\frac{D_F}{D_D} - 1\right)}$$

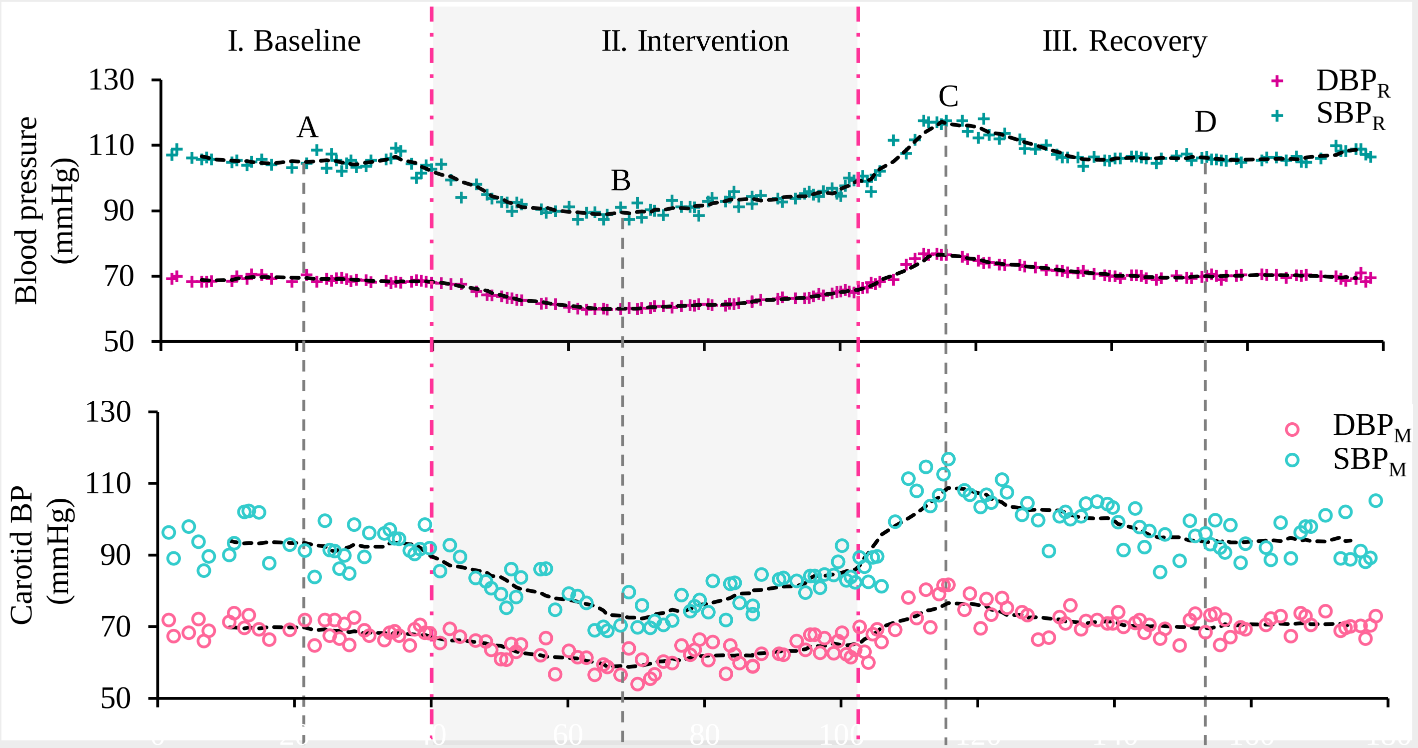
$$DBP = \frac{2\rho C_D^2}{\beta}$$

$$SBP = DBP\ e^{\beta\left(\Delta D/D_D\right)}$$

In-vivo validation



In-vivo performance (tracking ability under LBNP intervention)



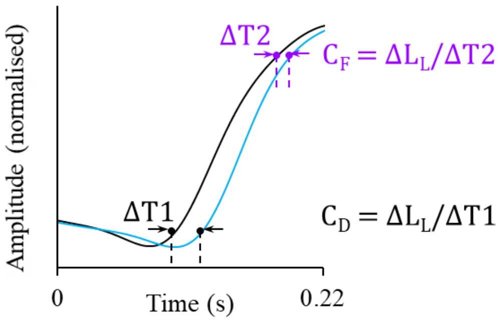
Device tracked expected physiological difference in response of central versus peripheral pressure.

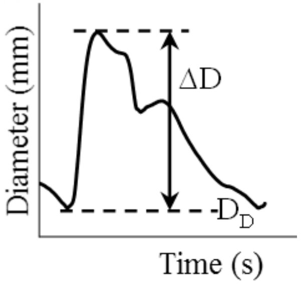
Raj, K. V., Nabeel, P. M., Chandran, D., Sivaprakasam, M., & Joseph, J. (2022). High-frame-rate A-mode ultrasound for calibration-free cuffless carotid pressure: feasibility study using lower body negative pressure intervention. **Blood Pressure**, 31(1), 1–11.

5.1. Central BP using HFR system

Calibration free blood pressure

Intra-cardiac changes in local PWV & Diameter



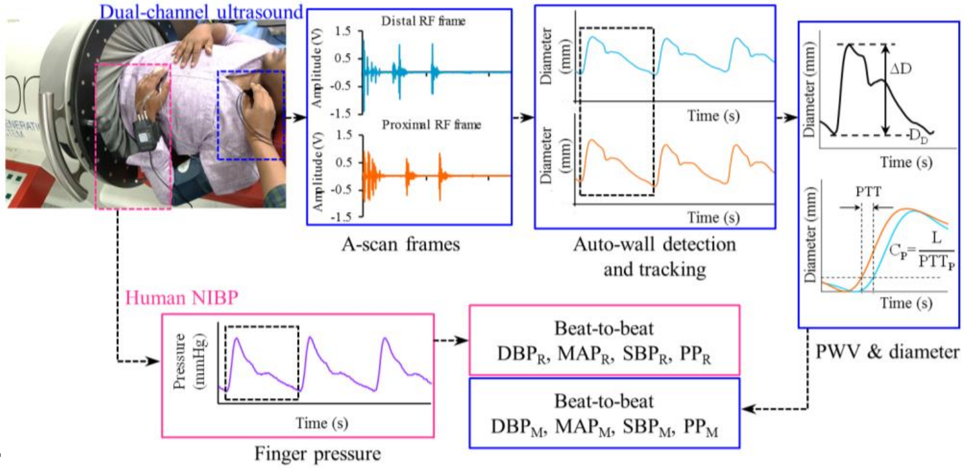


$$\beta = \frac{\ln\left(\frac{C_F^2 D_D}{C_D^2 D_F}\right)}{\left(\frac{D_F}{D_D} - 1\right)}$$

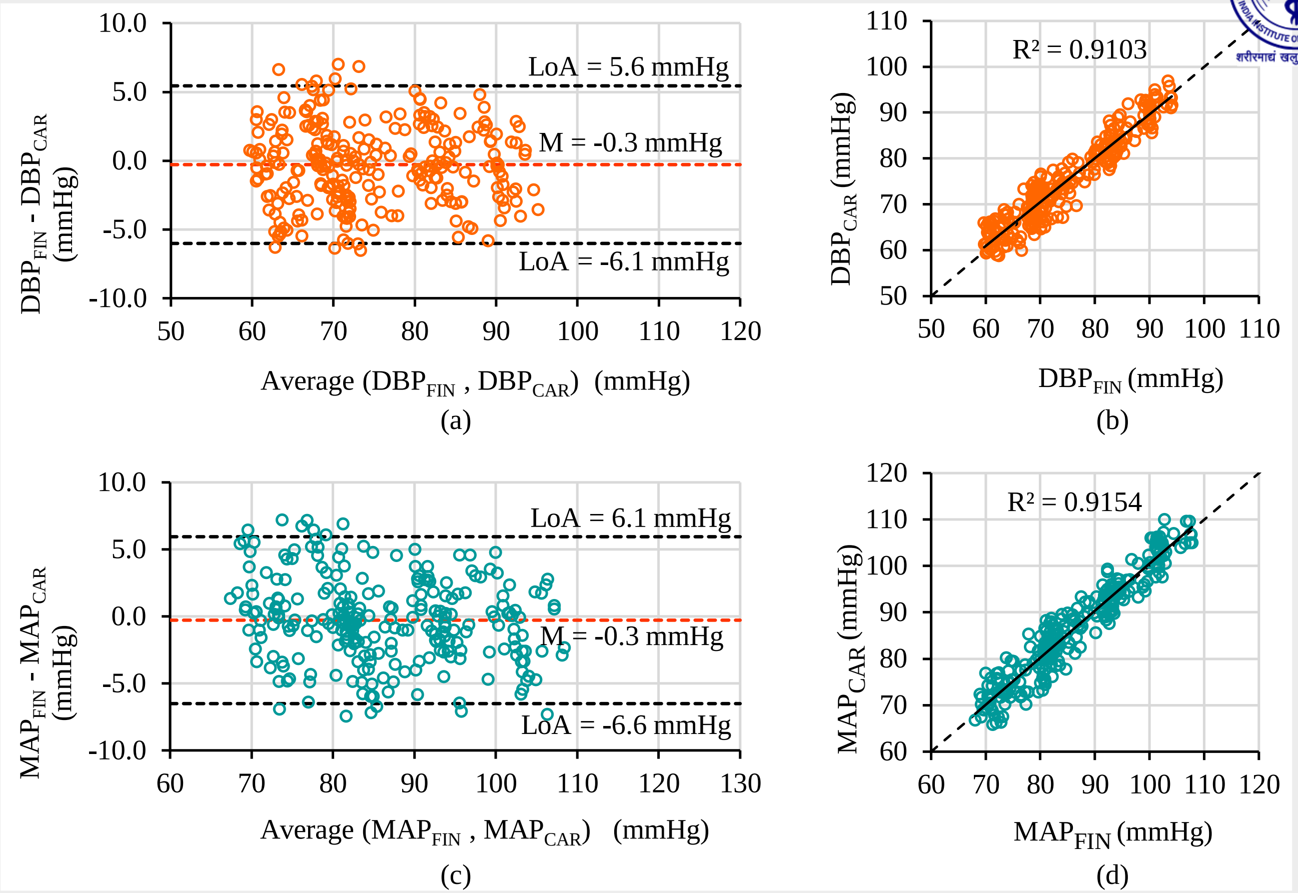
$$DBP = \frac{2\rho C_D^2}{\beta}$$

$$SBP = DBP\ e^{\beta\left(\Delta D / D_D\right)}$$

In-vivo validation



In-vivo performance (accuracy performance)



Accurate BP with error limits < 7 mmHg, even when heart rate is changing due to LBNP intervention

Raj, K. V., Nabeel, P. M., Chandran, D., Sivaprakasam, M., & Joseph, J. (2022). High-frame-rate A-mode ultrasound for calibration-free cuffless carotid pressure: feasibility study using lower body negative pressure intervention. **Blood Pressure**, 31(1), 1–11.

Conclusion

(Structural properties : RO – I and II)

- **Signal processing methods** for
  - Auto-recognition of walls
  - Auto-tracking of wall motion
  - Diameter and IMT measurement

(Functional properties RO – III and VI)

- **Multimodal ultrasound system** and method for regional stiffness measurement
- **High-frame rate ultrasound system** and method for local PWV and its incremental nature
- **High-frame rate ultrasound system for calibration-free CBP** using structure and local PWV

Chap No.	RO covered	Topic	No. of Journals	No. of conf.
1	Introduction			
2	Literature review			
3	RO-1	DTW methods for wall recognition and tracking	1	2
4	RO-2	Analytical phase methods for instantaneous Diameter and IMT	1	4
5	RO-3 and 4.1	High frame rate ultrasound system for Local PWV	1	4
6	RO-5	Multimodal ultrasound system Regional PWV	1	
7	RO-4.2	Measurement of pressure-dependent variations in local PWV		7
8	RO-6	High frame rate ultrasound system for Central BP	1	1
9	Conclusion			

Research outcomes

- Journals articles

1. **Raj, K. V**, Joseph, J., Nabeel, P. M., & Sivaprakasam, M. (2020). Automated measurement of compression-decompression in arterial diameter and wall thickness by image-free ultrasound. Computer Methods and Programs in Biomedicine, 194, 1–12.

2. **Raj, K. V**, Nabeel, P. M., Chandran, D., Sivaprakasam, M., & Joseph, J. (2022). High-frame-rate A-mode ultrasound for calibration-free cuffless carotid pressure: feasibility study using lower body negative pressure intervention. Blood Pressure, 31(1), 1–11.

3. **Raj, K. V**, Nabeel, P. M., & Joseph, J. (2022). Image-Free Fast Ultrasound for Measurement of Local Pulse Wave Velocity: In Vitro Validation and In Vivo Feasibility. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, 69(7), 2248–2256.

4. **Raj, K. V**, Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2022). Time-warping for robust automated arterial wall-recognition and tracking from single-scan-line ultrasound signals. Ultrasonics, 126, 106828.

5. Nabeel, P. M., **Raj, K. V**, & Joseph, J. (2022). Image-free ultrasound for local and regional vascular stiffness assessment: The ARTSENS Plus. Journal of Hypertension, 40(8), 1537–1544.

6. Joseph, J., **Raj, K. V**, Nabeel, P. M., Shah, M. I., Bhaskar, A., Ganesh, C., & Seshadri, S. (2020). ARTSENS® Pen — portable easy-to-use device for carotid stiffness measurement: technology validation and clinical-utility assessment. Biomedical Physics & Engineering Express, 6(2), 1–12.

7. Nabeel, P. M., **Raj, K. V**, Joseph, J., Abhidev, V. V., & Sivaprakasam, M. (2020). Local pulse wave velocity: theory, methods, advancements, and clinical applications. IEEE Reviews in Biomedical Engineering, 13, 74–112.

8. Manoj, R., **Raj, K. V**, Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2022). Arterial pressure pulse wave separation analysis using a multi-Gaussian decomposition model. Physiological Measurement, 43(5), 1–12.

Research outcomes

- Conference papers

1. **Raj, K. V**, Joseph, J., Shah, M. I., & Sivaprakasam, M. (2017). An image-free ultrasound method to estimate artery wall thickness surrogate for screening. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6. Rochester.
2. **Raj, K. V**, Nabeel, P. M., Joseph, J., & Sivaprakasam, M. (2017). Brachial artery stiffness estimation using ARTSENS. 39th Nnual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 262–265.
3. **Raj, K. V**, Nabeel, P. M., Joseph, J., & Sivaprakasam, M. (2018). Non-invasive assessment of arterial incremental elastic modulus variations within a cardiac cycle. 13th Russian-German Conference on Biomedical Engineering (RGC), 108–111.
4. **Raj, K. V**, Nabeel, P. M., Joseph, J., Shah, M. I., & Sivaprakasam, M. (2018). Measurement of Arterial Young's Elastic Modulus using ARTSENS Pen. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.
5. **Raj, K. V**, Nabeel, P. M., Joseph, J., Shah, M. I., & Sivaprakasam, M. (2018). Evaluation of local pulse wave velocity using an image free ultrasound technique. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.
6. **Raj, K. V**, Nabeel, P. M., Joseph, J., Venkatramanan, S., Shah, M. I., & Sivaprakasam, M. (2018). An In-Vivo Study on Intra-Day Variations in Vascular Stiffness using ARTSENS Pen. 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 4575–4578.
7. **Raj, K. V**, Nabeel, P. M., Joseph, J., & Sivaprakasam, M. (2019). Incorporating Arterial Viscoelastic Modelling for the Assessment of Changes in Pulse Wave Velocity Within a Cardiac Cycle Using Bramwell-Hill Equation. Computing in Cardiology (CinC), 46, 1–4.
8. **Raj, K. V**, Joseph, J., Nabeel, P. M., Frese, H., Sivaprakasam, M., & Shah, M. I. (2019). Analytic phase-based approach for arterial diameter evaluation using a-mode ultrasound frames. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–5.
9. **Raj, K. V**, Nabeel, P. M., Joseph, J., & Sivaprakasam, M. (2019). Methodological and measurement concerns of local pulse wave velocity assessment. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.
10. **Raj, K. V**, Abhidev, V. V., Nabeel, P. M., Joseph, J., Sivaprakasam, M., & Shah, M. I. (2019). Arterial Stiffness in Elastic and Muscular Arteries: Measurement using ARTSENS Pen. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–5.
11. **Raj, K. V**, Nabeel, P. M., Joseph, J., Frese, H., & Sivaprakasam, M. (2019). Multimodal Image-Free Ultrasound Technique for Evaluation of Arterial Viscoelastic Properties: A Feasibility Study. 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 5034–5037.
12. **Raj, K. V**, Joseph, J., Nabeel, P. M., & Sivaprakasam, M. (2020). A Dynamic Time Warping Method for Improved Arterial Wall-Tracking using A-mode Ultrasound Frames: A Proof-of-Concept. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6. Bari.
13. **Raj, K. V**, Nabeel, P. M., Joseph, J., Chandran, D., & Sivaprakasam, M. (2020). P.41 Measurement of Pressure-dependent Intra-Beat Changes in Carotid Pulse Wave Velocity using Image-Free Fast Ultrasound. Artery Research, 26(Supplement 1), S63.
14. **Raj, K. V**, Nabeel, P. M., Manoj, R., Shah, M. I., & Joseph, J. (2021). Phantom Assessment of an Image - free Ultrasound Technology for Online Local Pulse Wave Velocity Measurement. 43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 5610–5613.
15. **Raj, K. V**, Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2021). Phantom evaluation of a time warping based automated arterial wall recognition and tracking method. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.
16. **Raj, K. V**, Nabeel, P. M., Shah, M. I., Sivaprakasam, M., & Joseph, J. (2021). Gaussian-Mixture Modelling of A-Mode Radiofrequency Scans for the Measurement of Arterial Wall Thickness. 43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 5598–5601.
17. **Raj, K. V**, Manoj, R., Ishwarya, S., Nabeel, P. M., & Joseph, J. (2022). Operator Variabilities in Carotid Pulse Wave Velocity Measured by an Image-free Ultrasound Device. 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), 4018-4021.
18. **Raj, K. V**, Manoj, R., Ishwarya, S., Nabeel, P. M., & Joseph, J. (2022). Comparison of Approximated and Actual Bramwell-Hill Equation Implementation for Local Pulse Wave Velocity: Ex-vivo Study. 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), 3989-3992.

Research outcomes

- Conference papers

19. Nabeel, P. M., **Raj, K. V**, Joseph, J., & Sivaprakasam, M. (2018). Non-Invasive Assessment of Local Pulse Wave Velocity as Function of Arterial Pressure. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.
20. Nabeel, P. M., **Raj, K. V**, Joseph, J., & Sivaprakasam, M. (2018). Local pulse wave velocity and cuffless blood pressure assessment using ARTSENS. 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 1. Honolulu.
21. Nabeel, P. M., **Raj, K. V**, Jayaraj, J., & Mohanasankar, S. (2018). Local Evaluation of Variation in Pulse Wave Velocity over the Cardiac Cycle using Single-Element Ultrasound Transducer. 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 4560–4563.
22. Joseph, J., **Raj, K. V**, Nabeel, P. M., & Sivaprakasam, M. (2019). Image-free ultrasound technique for calibration-free cuffless blood pressure measurement. 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 1. Berlin.
23. Nabeel, P. M., **Raj, K. V**, Joseph, J., & Sivaprakasam, M. (2019). Determination of Incremental Local Pulse Wave Velocity Using Arterial Diameter Waveform: Mathematical Modeling and Practical Implementation Theoretical Analysis Modeling of incremental local PWV. Computing in Cardiology (CinC), 46(1), 1–4.
24. Manoj, R., **Raj, K. V**, Nabeel, P. M., Joseph, J., & Sivaprakasam, M. (2020). A Bi-modal Probe Integrated with A-mode Ultrasound and Force Sensor for Single-site Assessment of Arterial Pressure-Diameter Loop. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6. Bari.
25. Nabeel, P. M., **Raj, K. V**, Shah, M. I., Abhidev, V. V., Manoj, R., Sivaprakasam, M., & Joseph, J. (2021). An image-free ultrasound device for simultaneous measurement of local and regional arterial stiffness Indices. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.
26. Manoj, R., **Raj, K. V**, Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2021). Multi-gaussian model for estimating stiffness surrogate using arterial diameter waveform. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.
27. Manoj, R., **Raj, K. V**, Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2021). Separation of Forward-Backward Waves in the Arterial System using Multi-Gaussian Approach from Single Pulse Waveform. 43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 5547–5550.
28. Nabeel, P. M., **Raj, K. V**, Manoj, R., Abhidev, V. V., Sivaprakasam, M., & Joseph, J. (2021). High-Framerate A-Mode Ultrasound for Vascular Structural Assessments: In-Vivo Validation in a Porcine Model. 43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 5602–5605.
29. Manoj, R., **Raj, K. V**, Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2021). Evaluation of Nonlinear Wave Separation Method to Assess Reflection Transit Time: A Virtual Patient Study. 43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 5551–5554.
30. Navya, R. G, **Raj, K. V**, Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2022). High Frame-Rate A-Mode Ultrasound System for Jugular Venous Pulse Tracking: A Feasibility Study. 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), 4022-4025.
31. Manoj, R., **Raj, K. V**, Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2022). Evaluation of Pulse Contour Markers using an A-Mode Ultrasound: Association with Carotid Stiffness Markers and Ageing. 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), 4010-4013.
32. Manoj, R., **Raj, K. V**, Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2022). Estimation of Characteristic Impedance using Multi-Gaussian Modelled Flow Velocity Waveform: A Virtual Subjects Study. 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), 2274-2277.
33. Navya, R. G, **Raj, K. V**, Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2022). Jugular Venous Diameter Measurement Using A-Mode Ultrasound: A Feasibility Study. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.
34. Manoj, R., **Raj, K. V**, Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2022). Variation in Pulse Contour Markers on an Anesthetized Porcine During Pressure Perturbation: Association with Local and Regional Stiffness. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.
35. Manoj, R., **Raj, K. V**, Nabeel, P. M., Sivaprakasam, M., & Joseph, J. (2022). Assessment of Arterial Reflection Markers using an A-Mode Ultrasound Device. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.

Research outcomes

- Conference papers

36. Joseph, J., Nabeel, P. M., Shah, M. I., **Raj, K. V**, & Sivaprakasam, M. (2018). Live Demonstration of ARTSENS® Pen – An Image-Free Ultrasound Device for Automated Evaluation of Vascular Stiffness. IEEE Sensors, 1.
37. Manoj, R., Nabeel, P. M., **Raj, K. V**, Joseph, J., & Sivaprakasam, M. (2019). Cuffless evaluation of arterial pressure waveform using flexible force sensor: a proof of principle. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.
38. Joseph, J., Chandran, D. S., **Raj, K. V**, Abhidev, V. V., & Sivaprakasam, M. (2019). Image-Free Technique for Flow Mediated Dilation Using ARTSENS® Pen. 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 5051–5054.
39. Nabeel, P. M., Chilaka, V., **Raj, K. V**, Joseph, J., & Sivaprakasam, M. (2019). Deep Learning for Blood Pressure Estimation: An Approach using Local Measure of Arterial Dual Diameter Waveforms. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.
40. Chandran, D., Joseph, J., Sen, S., **Raj, K. V**, Nabeel, P. M., & Deepak, K. K. (2020). P.47 Feasibility Evaluation of Imaging-Free Ultrasound Technology to Measure Diameters of Brachial and Radial Arteries for Assessment of Endothelial Function. Artery Research, 26(Supplement 1), S70.
41. Manoj, R., Nabeel, P. M., **Raj, K. V**, Joseph, J., & Sivaprakasam, M. (2020). YI 2.5 Direct Measurement of Stiffness Index β of Superficial Arteries Without Blood Pressure Estimation. Artery Research, 26(Supplement 1), S18.
42. Poojitha, U. P., Ram, K., Nabeel, P. M., **Raj, K. V**, Joseph, J., & Sivaprakasam, M. (2020). Blood Pressure Estimation using Arterial Diameter : Exploring Different Machine Learning Methods. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6. Bari.
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45. Ramakrishna, P., Nabeel, P. M., **Raj, K. V**, Joseph, J., & Sivaprakasam, M. (2020). Cuffless Blood Pressure Estimation Using Features Extracted from Carotid Dual-Diameter Waveforms. 42nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 2719–2722. Canada.
46. Arathy, R., Nabeel, P. M., **Raj, K. V**, Abhidev, V. V., Sivaprakasam, M., & Joseph, J. (2021). Evaluation of Vascular Pulse Contour Indices over the Physiological Blood Pressure Ranges in an Anesthetized Porcine Model. 43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 5594–5597.
47. Ishwarya, S., Manoj, R., **Raj, K. V**, Nabeel, P. M., & Joseph, J. (2022). Hydrostatic Pressure Compensator for Evaluation of Carotid Stiffness using A-Mode Ultrasound: Design, Characterization, and In-Vivo Validation. IEEE International Symposium on Medical Measurements and Applications (MeMeA), 1–6.

Research outcomes

- **Patents filed**

1. J. Joseph, P. M. Nabeel, M. I. Shah, V. Raj Kiran, and M. Sivaprakasam, “Image-free ultrasound for non-invasive assessment of early vascular health markers,” Indian Patent 202041013190, Mar. 26, 2020.
2. J. Joseph, V. Raj Kiran, P. M. Nabeel, and M. Sivaprakasam, “Methods for identifying the boundaries of a blood vessel,” Indian Patent 202041017854, Apr. 27, 2020.
3. J. Joseph, V. Raj Kiran, P. M. Nabeel, and M. Sivaprakasam, “Method for tracing the motion of blood vessel boundaries,” Indian Patent 202041017855, Apr. 27, 2020.
4. P. M. Nabeel, J. Joseph, M. Sivaprakasam, and V. Raj Kiran, “Multi-modal ultrasound probe for calibration-free cuff-less evaluation of blood pressure,” European Patent 19816111.9A, Jul. 10, 2020.
5. P. M. Nabeel, J. Joseph, M. Rahul, V. Raj Kiran, and M. Sivaprakasam, “A system for non-invasive calibration-free blood pressure (BP) measurement,” Indian Patent 202041033513, Aug. 05, 2020.
6. J. Joseph, C. Dinu, P. M. Nabeel, V. Raj Kiran, and M. Sivaprakasam, “Augmented multimodal flow mediated dilatation,” Indian Patent 202041042567, Sep. 30, 2020.

- **Awards**

ARTERY
Association for Research into Arterial Structure and Physiology

ARTERY 20

Joint First Place:

Yolandi Breet – P.12 Investigating the role of glycemic markers in pulse pressure amplification in young adults: The African-PREDICT study

Raj Kiran – P.41 Measurement of pressure-dependent intra-beat changes in carotid pulse wave velocity using image-free fast ultrasound

THANK YOU

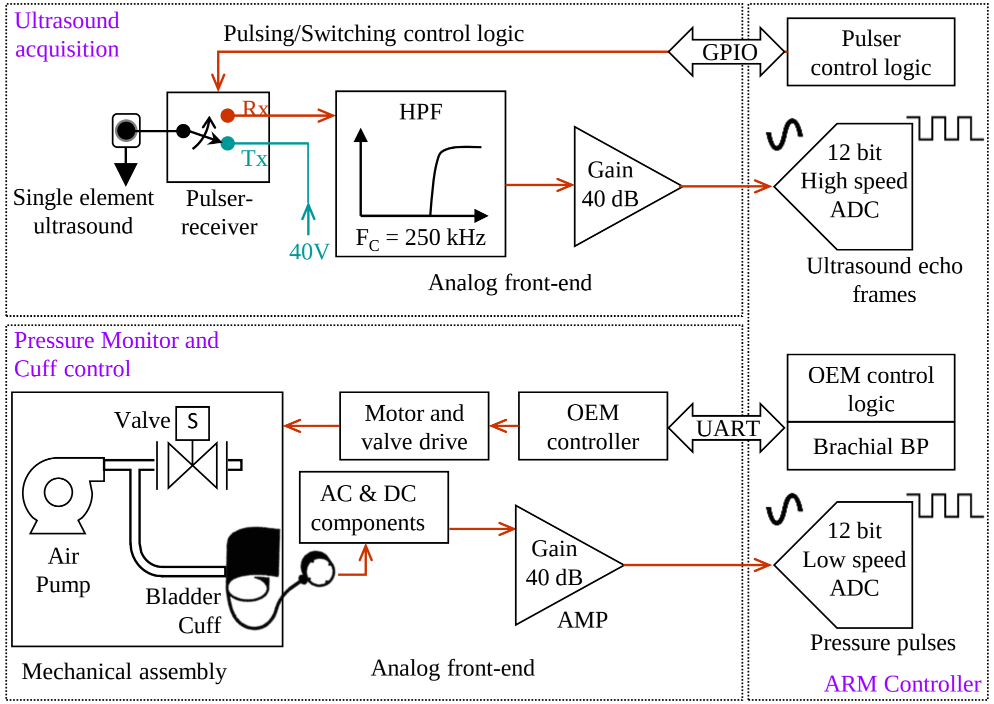
EXTRA SLIDES

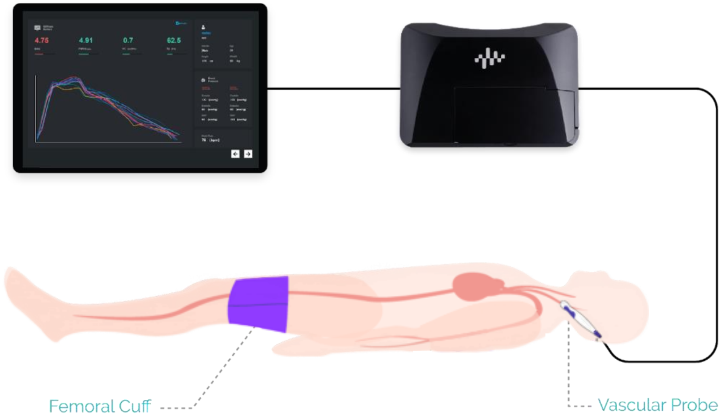
RO-5. Multimodal system for Regional PWV

Nabeel, P. M., **Raj, K. V,** & Joseph, J. (2022). Image-free ultrasound for local and regional vascular stiffness assessment: The ARTSENS Plus. Journal of Hypertension, 40(8), 1537–1544.

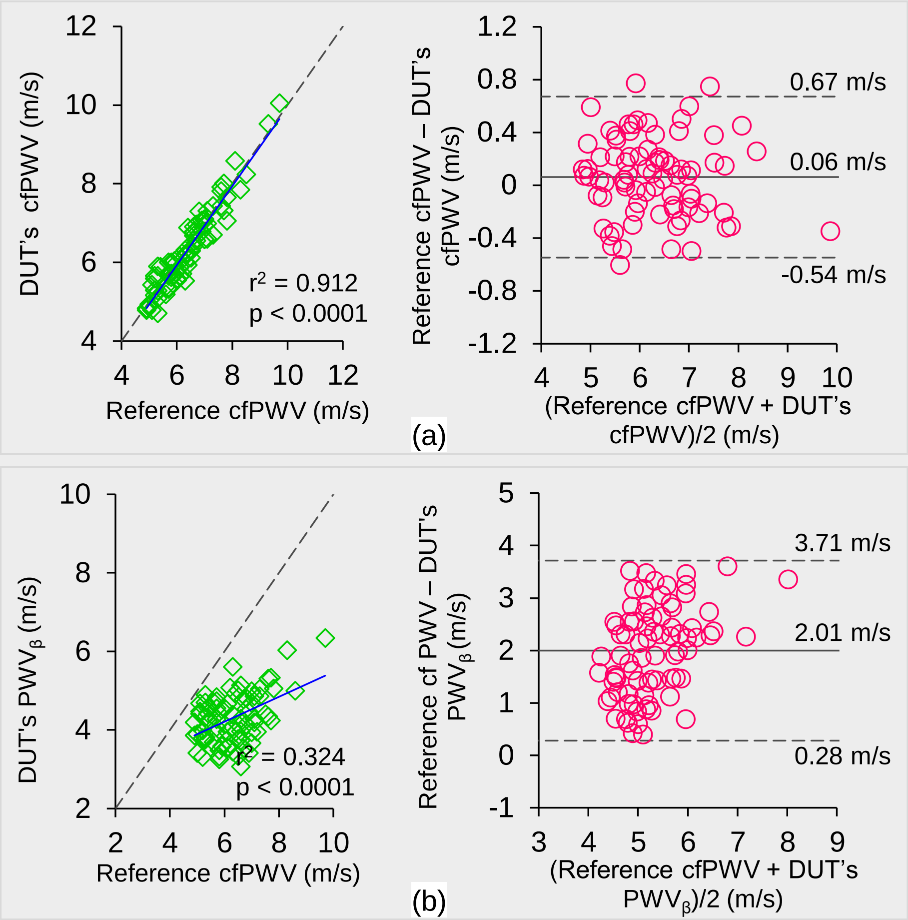
6.1. Multimodal ultrasound system for regional PWV

High frame rate system with cuff control





In-vivo performance (N =90)

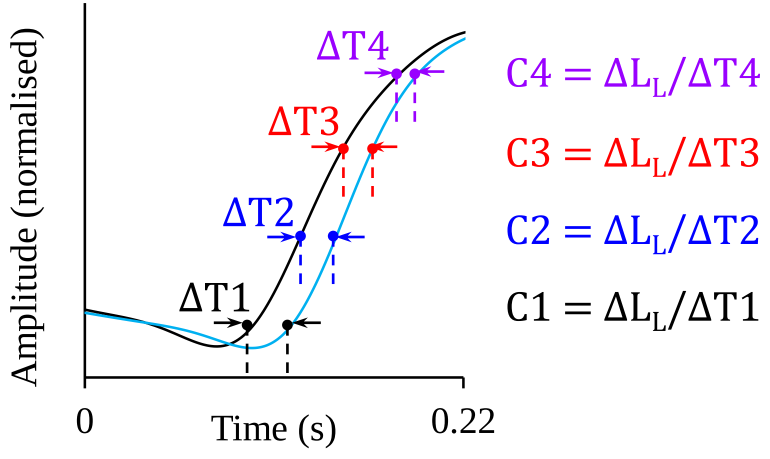


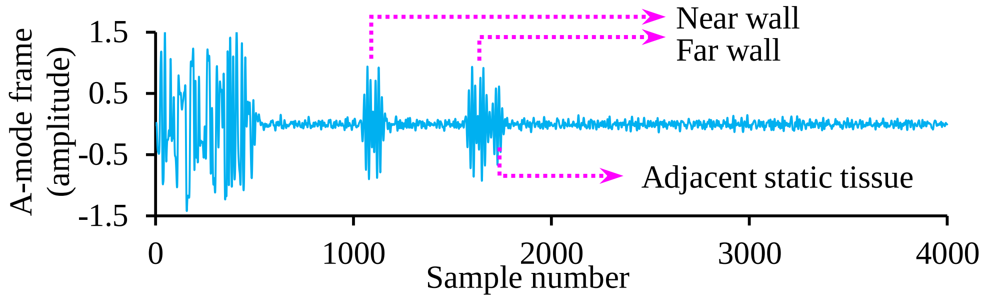
- Reference: SphygmoCor (FDA approved)
- Excellent performance according to ARTERY Society guidelines
- High operator repeatability (CoV < 5%)
- Accurate and on par with reference standard.

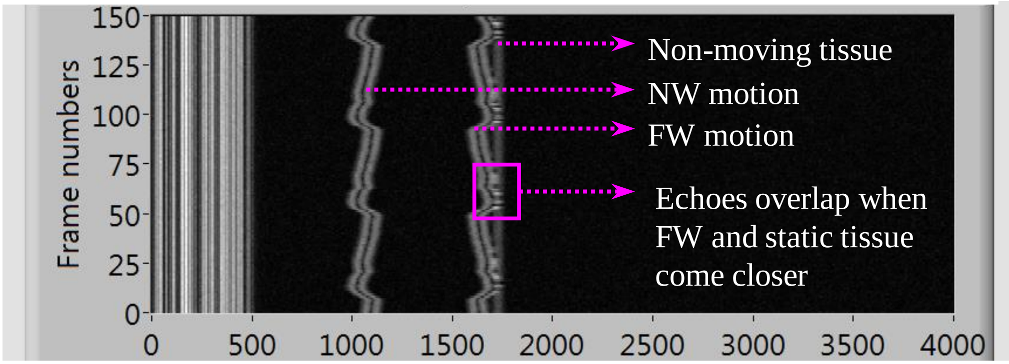
Online measurement of regional PWV was performed with high accuracy and repeatability

Nabeel, P. M*., **Raj, K. V***, & Joseph, J. (2022). Image-free ultrasound for local and regional vascular stiffness assessment: The ARTSENS Plus. **Journal of Hypertension**, 40(8), 1537–1544.

3.3. Direct measurement of intra-cardiac cycle PWV changes: Challenges



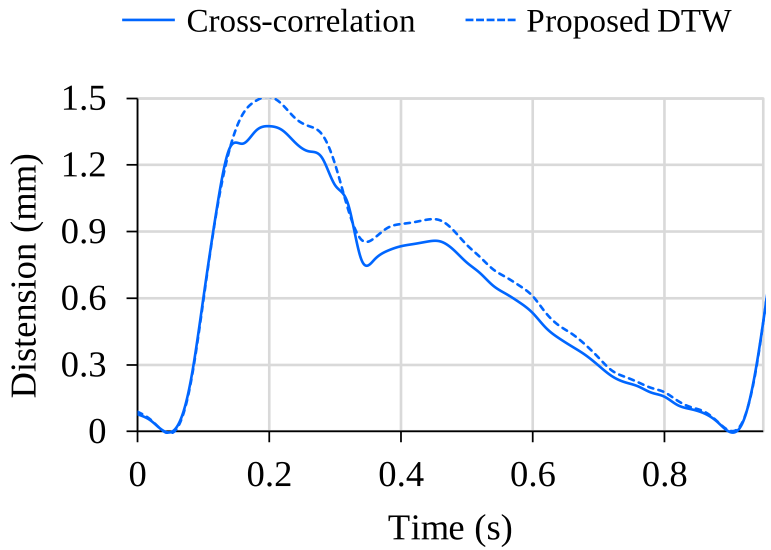


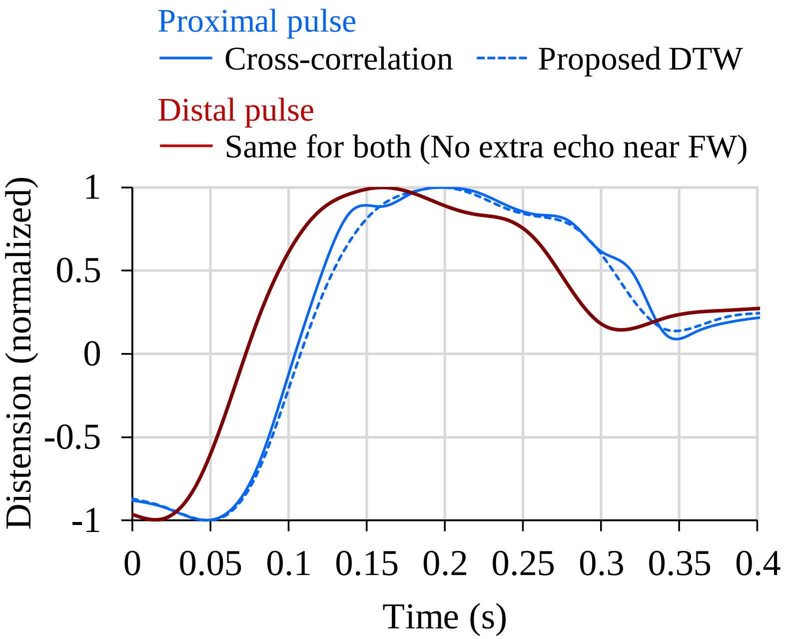


Challenge with wall-motion tracking

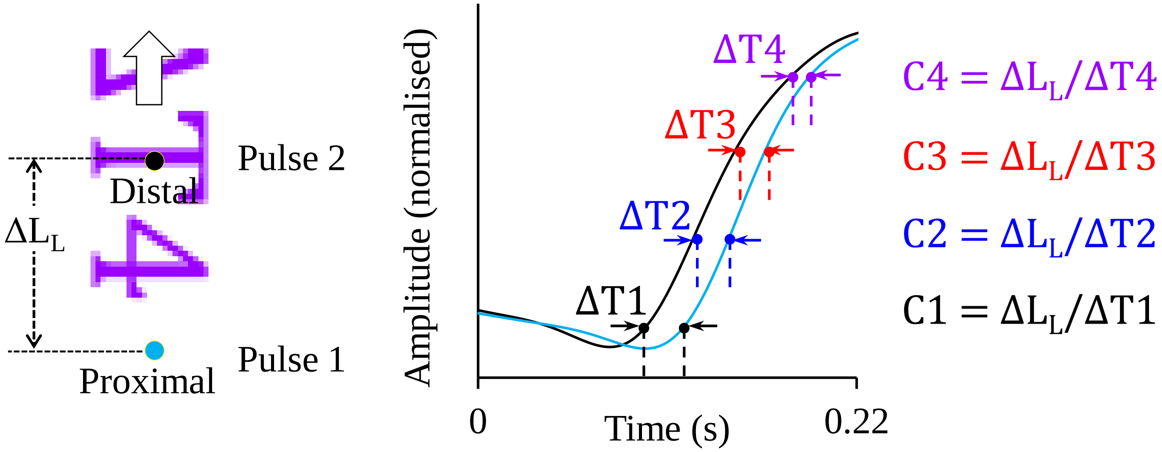
- Wall echo corrupted for one measurement site
- Pulse pair Morphology effected non-identically
- Under- or over-estimated PTTs

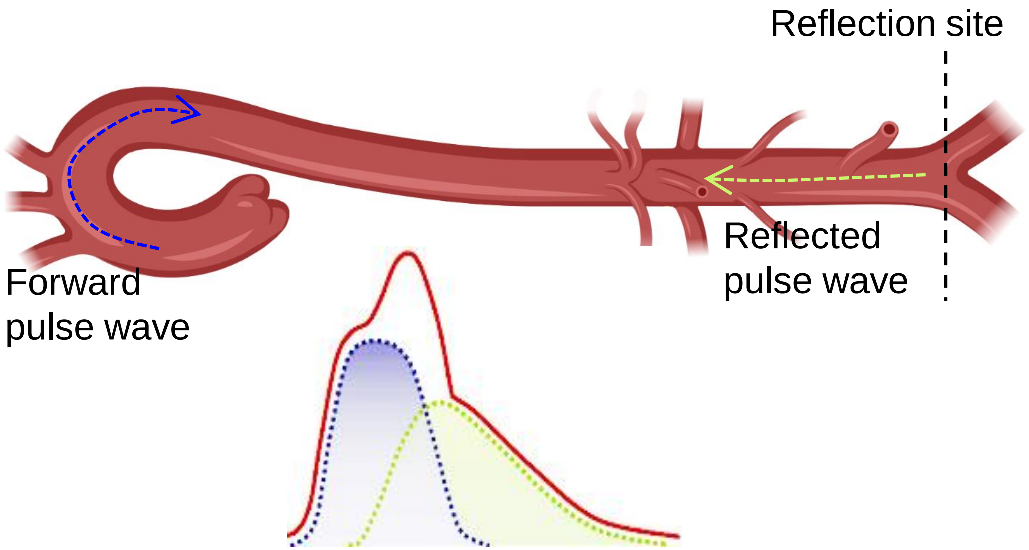
DTW method proposed in the first seminar is robust to such corruptions, yielding reliable pulse pair



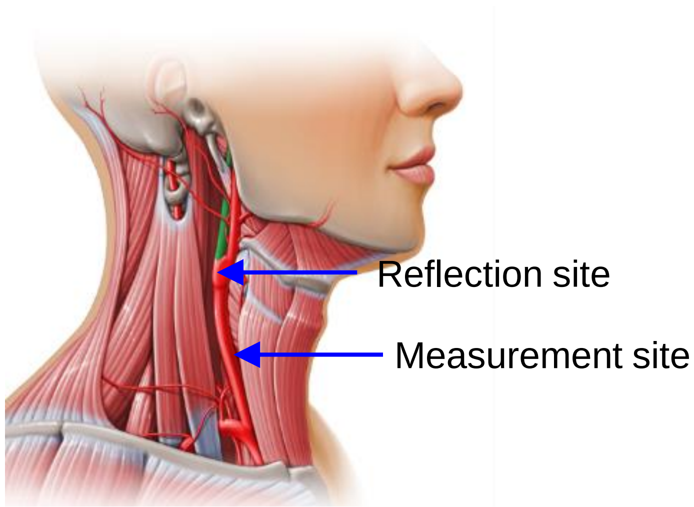


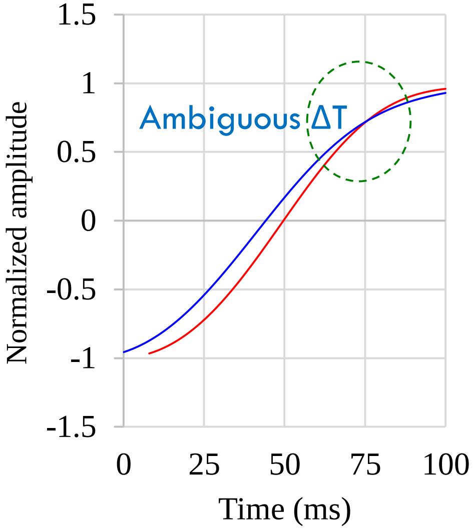
3.3. Direct measurement of intra-cardiac cycle PWV changes: Challenges





While performing carotid measurements





- **Early reflections** (~25ms from start of cycle)
- **Hold down pressure** at distal site creates an additional reflection point
- Proximal and distal pulse **effected differently** (in terms of amplitude and time at which the reflections start to effect)

3.3.1 Dealing with arterial wave reflections

Method of Characteristic Impedance

Vascular impedance (Z) describes the spectral relationship between arterial pressure P and flow rate Q of an artery.

$$P(t) = \bar{P} + \sum_{n=1}^{H} P_n \sin(n\omega t + \theta_n).$$

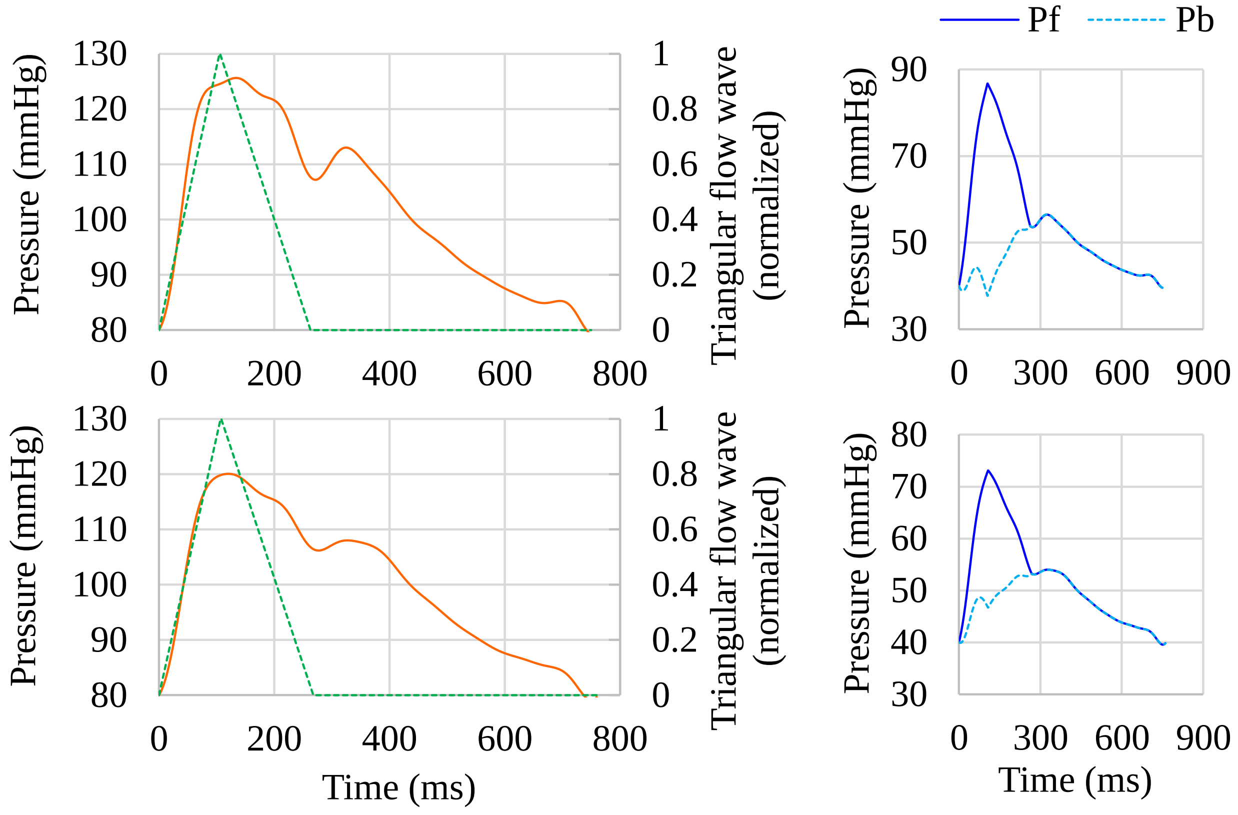
$$Q(t) = \bar{Q} + \sum_{n=1}^{H} Q_n \sin(n\omega t + \theta_n).$$

$$|Z_n| = |P_n|/|Q_n| \;\&\; \mathrm{Phase}(Z_n) = \tan^{-1}(P_n/Q_n)$$

Characteristic Impedance (Z_0) is the impedance seen for forward moving pulses = averaged ratio of higher harmonics of P and Q moduli

Forward and backward pulse waves

$$P_{f \text{ or } b} = \frac{1}{2}\,(P \pm Z_0 Q)$$

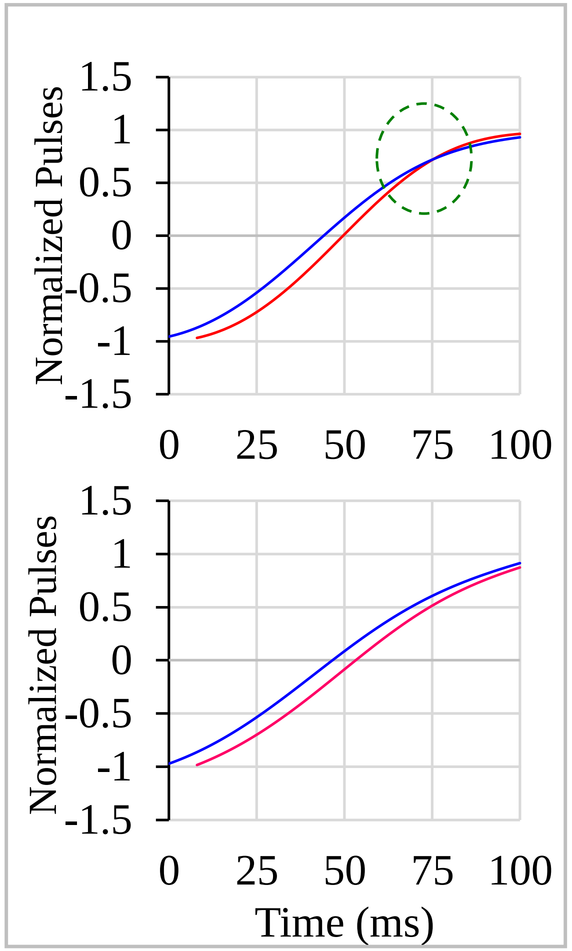


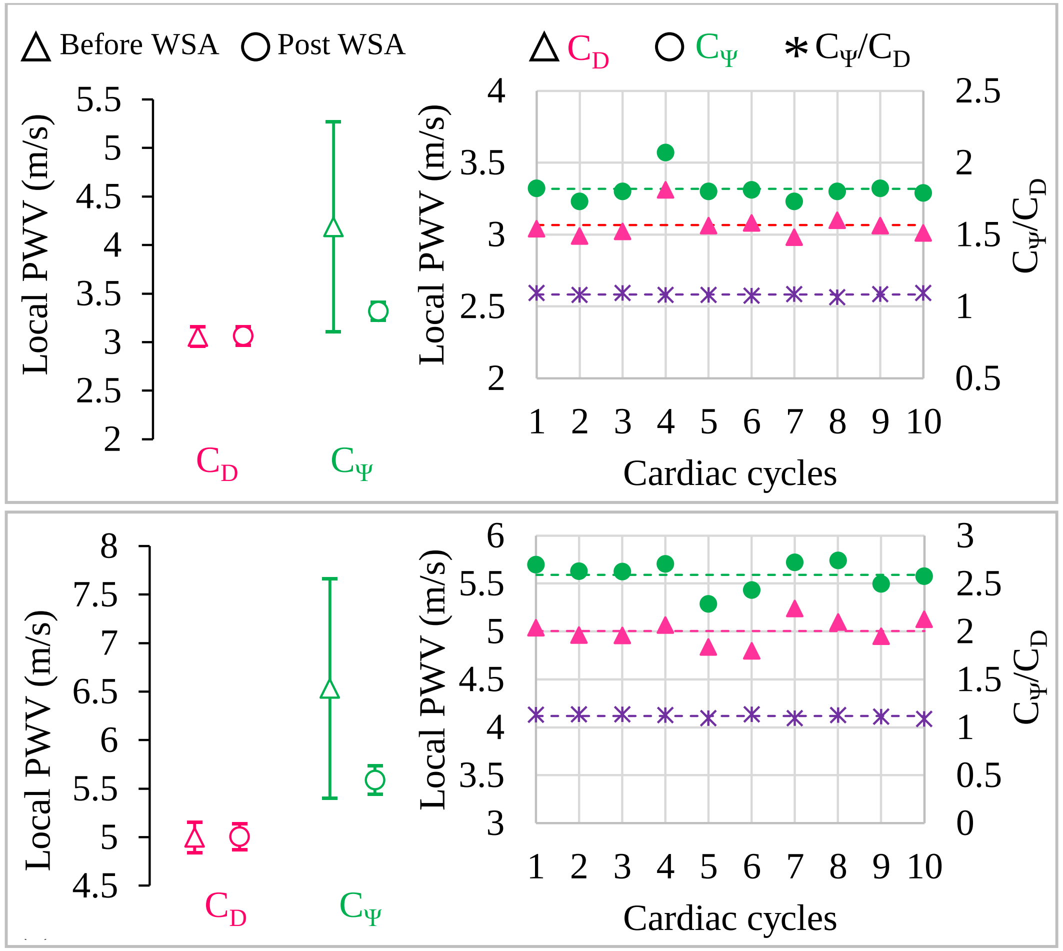
Pressure: Modeled from diameter
Flow: Modeled as triangular

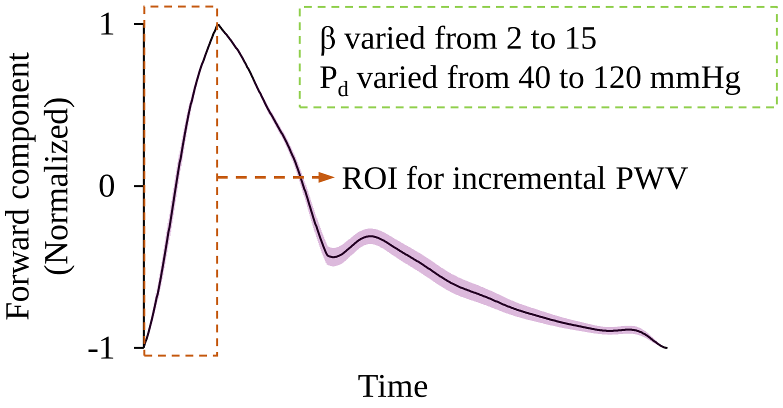
$$P = P_d\, e^{\beta\left(\frac{D(t)}{D_d} - 1\right)}$$

$\beta = 5$ and $P_d = 90$ mmHg

3.3.2 Incremental local PWV after wave separation analysis







- ✓ Unaffected by choice of β and P_d
- ✓ Worst case error in PWV limited to 2%

- ✓ Separated waves devoid of ambiguous region
- ✓ Repeatability for normotensive and hypertensive subjects.