

Semi-Automated Software to Improve Stability and Reduce Operator Induced Variation in Vascular Ultrasound Speckle Tracking

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Short Running Title: Improving Stability in Vascular Ultrasound Speckle Tracking

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Abstract:

Objectives: Ultrasound is useful in predicting arteriovenous fistula (AVF) maturation, which is essential for hemodialysis in end-stage renal disease patients. We developed ultrasound software that measures circumferential vessel wall strain (distensibility) using conventional ultrasound Digital Imaging and Communications in Medicine (DICOM) data. We evaluated user-induced variability in measurement of arterial wall distensibility and upon finding considerable variation we developed and tested two methods for semi-automated measurement.

Methods: Ultrasound scanning of arteries of ten subjects scheduled for AVF surgery were performed. The top and bottom of the vessel wall were tracked using the Kanade-Lucas-Tomasi (KLT) feature-tracking algorithm over the stack of images in the DICOM cine loops. The wall distensibility was calculated from the change of vessel diameter over time. Two semi-automated methods were used for comparison.

Results: The location of points selected by users for the cine loops varied significantly, with a maximum spread of up to 120 pixels (7.8mm) for the top and up to 140 pixels (9.1mm) for the bottom of the vessel wall. This variation in users' point selection contributed to the variation in distensibility measurements (ranging from 5.63% – 41.04%). Both semi-automated methods substantially reduced variation and were highly correlated with the median distensibility values obtained by the 10 users.

Conclusions: Minimizing user-induced variation by standardizing point selection will increase reproducibility and reliability of distensibility measurements. Our recent semi-automated software may help expand use in clinical studies to better understand the role of vascular wall compliance in predicting the maturation of fistulas.

Key words: Kidney disease, Arteriovenous fistula, Vascular Distensibility, Ultrasound, Speckle Tracking, Semi-Automated

Introduction

Arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis treatment in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD).^{1,2} Unfortunately, about 20 to 60% of AVFs fail to mature sufficiently to sustain dialysis.^{3,4} Repeated surgical interventions or creation of a new fistula increases morbidity and medical costs and may adversely affect quality of life for patients.^{5,6}

Ultrasound imaging has been used to identify factors that may affect clinical AVF maturation. The efficacy of pre-operative and early post-operative studies involving duplex ultrasound scanning of vessels⁷ and the role of volume flow rate, vein distensibility, arterial and vein size⁸⁻¹¹ in predicting AVF maturation are being investigated. A post-operative evaluation up to six weeks after fistula creation reported that AVF blood flow, diameter, and depth may moderately predict unassisted and overall AVF clinical maturation.^{12,13} Diagnostic tools that can successfully predict functional AVF maturation are critical to improve the prognosis and treatment of CKD and ESRD patients.^{7,10,13}

We have developed novel ultrasound software which allows investigation of vascular mechanics clinically.¹⁴⁻¹⁸ This software uses standard ultrasound Digital Imaging and Communications in Medicine (DICOM) data to measure circumferential vascular wall strain (distensibility) based on speckle tracking techniques. The software

allows measurements of distensibility within single and multiple cardiac cycles and can be used to track changes in wall compliance as the AVF matures.^{14,15}

Ultrasound elastography has been widely used in the medical field to evaluate liver fibrosis and to differentiate between benign and malignant lesions in breast, thyroid, and prostate.¹⁹⁻²² There is also significant potential for ultrasound elastography to be useful in the vascular access and peripheral vascular setting.^{14,15,23-29} However, intra- and inter-operator variability in ultrasound measurements has always been a concern as indicated by studies in various organs.³⁰⁻³⁸ For example, operator dependent measurement and interpretation greatly influences the assessment of fetal growth, an essential component of prenatal care, facilitating the identification of fetuses at risk of perinatal morbidities or mortality.^{32,39} In the non-invasive assessment of endothelial function in cardiovascular disease using flow-mediated dilation (FMD) technique, operator based variability in ultrasound measurements of peripheral artery endothelium-dependent dilation significantly impairs its reproducibility and comparison between studies.²⁶ Therefore, it is imperative to identify user based errors and establish a standard data acquisition system and guidelines to enable accuracy and reproducibility of ultrasound imaging to have a positive clinical impact. To this end, we conducted an analysis of operator induced variation in the clinical setting and studied two potential solutions aimed at standardizing user input and measurement methods.

The two main operator-sourced factors that can affect the accuracy of our speckle tracking based software to measure vascular mechanical properties are: (1) proper and stable placement of the transducer on the subject's fistula for recording and (2) the software user interface calipers selected within the ultrasound image by the user

to obtain accurate measurements of the wall strain. In this study, we address the second potential source of variation. To do so, we evaluated the variability of the wall strain (distensibility) measurements as a function of user-induced variation in point selection of top and bottom edge of arterial vessel walls (using our previously developed method),¹⁴⁻¹⁷ as well as the physiologic variation in wall strain attributable to beat-to-beat variation in pulse pressure. Observing a significant degree in measurement variation arising from the users' variation in point selection, we devised software assisted measurement systems that implement semi-automated methods for vessel edge detection and strain peak and valley measurement. The purpose was to define and test algorithms and software for measurement standardization to increase the reproducibility and reliability of automated measurement of vessel wall distensibility in preparation for larger scale clinical testing.

Materials and Methods:

Subjects

We enrolled ten subjects (67 – 88years) with ESRD who were scheduled to undergo surgery to create an AVF. This study was approved by the local Veterans Affairs Ann Arbor Healthcare System's Institutional Research Board and a written informed consent was obtained from all participants.

Wall strain (distensibility):

Strain describes the deformation of an object. For instance, the normal Lagrangian strain can be defined as the ratio of the change in length to its original length. The circumferential vessel wall strain, given the cylindrically symmetric vessel

wall geometry, is the change in circumference of a vessel wall divided by the original circumference. Since the circumference is linearly related to the diameter of the vessel, this is equal to the ratio of the change in diameter divided by the original diameter.

As illustrated in Figure 1, following cardiac cycles, the blood pressure varies periodically with the peak and valley being the systolic pressure (P_s) and diastolic pressure (P_d), respectively. Given the linear relationship between blood pressure and the vessel circumference stress⁴⁰ the vessel circumference changes with the blood pressure and the vessel diameter varies between the systolic diameter (D_s) and diastolic diameter (D_d), accordingly. The vessel circumferential strain can be expressed as:

$$\varepsilon = \frac{(\pi D_s - \pi D_d)}{\pi D_d} = \frac{(D_s - D_d)}{D_d} \quad (1)$$

and we define Equation (1) as the distensibility of the vessel wall.

Ultrasound data acquisition

A GE LOGIQ E9 ultrasound system (LOGIQ E9 XD Clear 2.0, General Electric Healthcare, Waukesha, Wisconsin, USA) was used to scan the subject's inflow artery (brachial/radial); cine loop data were collected for a standard data capture time of 10 seconds at a frame rate of 33 Hz for nine subjects (with a 9L-D broad spectrum linear transducer; band width of 2 – 8 MHz) and 17 Hz for one subject (with a L-8-18i-D broad spectrum linear hockey stick transducer; band width of 4 – 15 MHz) from B-mode images in short-axis views of the artery; and DICOM data were exported for processing.

Post-processing and analysis

Our previously developed open source software^{14,15} was used to measure circumferential vascular wall strain or distensibility (tracking vessel wall diameter

changes over time) of brachial and radial arteries using standard ultrasound DICOM cine loop data.

To enable an optimal evaluation and reduce bias in the selection of points, these studies were performed by users that were not involved in the software design. The users were research personnel and included four clinicians. The users applied our open-source software based on ultrasound speckle tracking to obtain distensibility measurements for ultrasound cine loops of arteries from ten different subjects (Table-1A). Each user had individualized training with the first author of the manuscript to learn how to use the software. Once several sample cases were observed, and the users did not require any more trainer input, they were allowed to perform the study measurements on the test cases. The user interface of the software requires the user to select a position at the top and bottom of the vessel wall (the lumen-vessel wall interface) to measure distensibility as a function of time. To maintain consistency in the measurement of vessel distensibility, the ten users were instructed to choose two points along an imaginary vertical line in the center of the vessel in the first frame of the ultrasound cine loop. The two selected points were tracked using the Kanade-Lucas-Tomasi (KLT) feature tracking algorithm over the acquisition period. The point selection was repeated in case of loss of tracking.

The vessel diameter (distance between two points) was computed over the entire stack of images and a graph of the change in vessel wall diameter (cm) over time (secs) was plotted. To generate a more representative distensibility measurement, we asked each user to select six consecutive peaks (systolic/maximum diameters) and valleys (diastolic/minimum diameters) from the waveform and the mean of the vessel diameters

was used to determine the wall strain or distensibility of the vessel wall. After linear signal detrending (based on six selected peaks and valleys), the vessel distensibility (ϵ) was computed as in Equation (1).

The statistical analysis for this study mainly focused on subject-specific statistics computed across ten users. The median and mean distensibility were computed for each subject across all ten users, along with the standard deviation. We also reported relative distensibility variation (user-induced distensibility variation, %), via normalizing the standard deviation by mean distensibility.

The beat-to-beat variation (BBV) across all six peaks and valleys was defined as standard deviation of all the peaks (*systolic diameter*, D_s) minus the adjacent valleys (*diastolic diameter*, D_d) measurements (relative to that peak) normalized to the mean of diastolic diameters (\underline{D}_d):

$$BBV = \frac{1}{\underline{D}_d} \times Std\ Dev\{ \{(D_{si} - D_{di})\}_{i=1}^6, \{(D_{si+1} - D_{di})\}_{i=1}^5 \} \times 100\% \quad (2)$$

The relative BBV is derived by normalizing the BBV to distensibility (ϵ):

$$Relative\ BBV = \frac{BBV}{\epsilon} \quad (3)$$

Semi-automated methodology:

To reduce user input variation, we developed algorithms to standardize the areas requiring user input including vessel edge point selection and distensibility waveform peak and valley selection. We implemented and evaluated two methods of semi-automation for comparison with the baseline user input data. The automated methodology is flexible in its implementation, and we summarize the two different approaches tested in this study.

Method 1: Canny Edge Detection - Polynomial Detrending - Manual Thresholding

Method (CED-PD-MT):

For method 1, we implemented the CED-PD-MT that was developed in a previous study.¹⁸ This method starts with the user defined manual point selection and subsequently processes the vessel using filtering, segmentation, and automated edge detection prior to speckle tracking.¹⁸ To briefly summarize, coding for this method was implemented using MATLAB (MathWorks, Natick, MA, USA), and the threshold was adjusted manually to sharpen the lumen boundary in the CED-PD-MT method by the software operator. Then, the initial frame was extracted from the cine-loop DICOM data and binarized.^{41,42} Next, the user selected the center of the vessel of interest. A Canny edge detector identified the vessel contour by implementing smoothing, non-maximal suppression, and hysteresis.⁴³⁻⁴⁵ To adjust for factors that lead to fluctuations in peaks and valleys such as transducer motion, fluctuations in stroke volume and beat-to-beat blood pressure changes, we implemented a low order polynomial fit and subtracted this signal from the original displacement¹⁸ to detrend the signal. The consecutive peaks and valleys resulting from vessel distention were then approximated using penalized least squares and the direct and inverse discrete cosine transform to obtain a smoothed displacement signal defined as a low order polynomial.¹⁸

Method 2: Sobel Edge Detection - Linear Detrending - Fixed Thresholding Method

(SED-LD-FT):

For method 2, we implemented many of the steps as in method 1, with the primary differences being (1) using a Sobel edge detector instead of a Canny edge detector⁴⁶, (2) linear detrending instead of polynomial detrending, and (3) pre-set

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thresholding (no manual adjustment by the user). The coding environment was open-source Python Libraries (Python Software Foundation, Beaverton, OR, USA).

Additionally, the peak and valley determinations were performed by providing a pre-set parameter for the minimum peak and valley separation distance, which is dependent on the frame rate used to acquire the ultrasound data, and by providing a median filter window size for the distensibility signal waveform that resulted from speckle tracking. A modification of the KLT algorithm by Farneback⁴⁷ was implemented for speckle tracking for the SED-LD-FT data analysis. Standard Python libraries⁴⁸ were used for segmentation, signal processing, peak and valley selection.

Results:

Inter-user variation exists in point selection:

There was significant variation in the location of points selected by the users for the ten cine loops, with a maximum spread of up to 120 pixels (7.8mm) for the top and up to 140 pixels (9.1mm) for the bottom of the vessel wall as shown in Table-1A (first two rows). The cross-sectional view of the arteries in Figure 2 shows the spread of the locations of top and bottom points in the first frame of the ultrasound cine loop. There was minimum variation in user selection of the two points for subject #8 (top panel in Figure 2, Table-1A) and a maximum variation for subject #5 (bottom panel in Figure 2, Table-1A).

Inter-user variation in point selection affects distensibility measurements:

Table-1 shows the distensibility measurements done by the ten users for the ultrasound cine loops of arteries from ten subjects. The median distensibility of the ten arterial walls ranged from 2.07 to 6.09% (Table-1A). The variation in distensibility ranged from 5.63 – 41.04% for the ten arteries across users (Table-1A). Figure 3 shows a graph of the change in vessel wall diameter (cm) over time (secs). These wave plots of change in diameter vs time showed a maximum variation in distensibility of 41.04% for subject #1, and a minimum variation in distensibility measurement of 5.63% for subject #3 (Table-1A, Figure-3). The high variation in distensibility measurements of the arterial wall of subject #1 seemed to largely be due to a single outlier value (based on the selection of points on the lumen-vessel wall interface) by user #4 as shown in Figure- 3. Even if we exclude that value, subject #1 continues to show the most variation in distensibility.

The variation in point selection by users did not directly translate to the same extent in variation of the distensibility measurements of the arterial walls. However, subject #5 who had the maximum variation in location selection (Table-1A, Figure-2) by the ten users also showed a high variation in distensibility (15.07%; Table-1A). Subject #8 which showed minimum variation in location selection (Table-1A, Figure-2) showed a slightly lower variation in distensibility (11.64%; Table-1A).

Inter-user variation in point selection contributes to variation in beat-to-beat measurements:

The beat-to-beat variation in blood pressure (BP) is well described and attributable in part to respiratory modulation of intra-thoracic pressure, and accentuated

with irregular heart rhythms.^{49,50} As the driving force (BP) for distensibility varies, the effects (wall strain or distensibility) may be measured using this method. So, the effects of beat-to-beat variation in BP may be observed as beat-to-beat variation in distensibility.

The beat-to-beat measurements were obtained from different cycles (peaks and valleys; Figure 3) for all subjects across the different users (Table-1A). The relative beat-to-beat variation ranged from 6.41% (subject# 9) to 17.68% (subject# 5). Subject# 5 who showed a maximum variation in point selection by users (Figure-2, Table-1A) also exhibited a maximum beat-to-beat variation (17.68%, Table-1A) and a high variation in distensibility (15.07%, Table-1A). The inter-user variation in point selection contributed to variation in both beat-to-beat and distensibility (wall strain) measurements.

Semi-automated methods have potential to reduce user-induced variation:

Both semi-automated approaches (CED-PD-MT and SED-LD-FT) showed a strong correlation with the median user input-based results, with a correlation coefficient of 0.9758 for CED-PD-MT method and 0.8928 for SED-LD-FT method (Figure-4). Additionally, both methods were on average higher than the user input-based results (Tables -1B and -1C, Figure-4). It is important to note that the beat-to-beat variation in measurements was preserved in both semi-automated methods (Tables -1B and -1C), while showing the potential to reduce user-induced variation. Preserving the ability to detect this physiologic variation while reducing operator induced variation will allow additional future testing of pressure induced strain variation using semi-automated

methods. In addition to testing semi-automated methods that may help further testing, we developed a user-friendly browser-based user interface. Figure 5 shows the interface implementing the SED-LD-FT method.

Discussion:

The development of a vascular diagnostic system which can accurately measure parameters that can guide the creation of a successful AVF and its maturation will be beneficial to patients with CKD and ESRD undergoing maintenance hemodialysis.^{7,10,13} Our previous open-source ultrasound software based on speckle tracking algorithms has shown significant potential in detecting changes in vascular mechanics in the post-operative period following dialysis fistula creation.¹⁴⁻¹⁸ To evaluate and enhance the reliability and accuracy of the application of the software in a clinical setting, we conducted this study to understand the effect of user-induced and physiologic (beat-to-beat) variation on vascular distensibility. Upon finding significant user input induced variation, we sought to develop and evaluate methods that may standardize the measurement and allow more widespread testing.

An important initial finding which corroborates our earlier studies is that the software efficiently determined the circumferential vessel wall strain (distensibility) using the speckle tracking algorithm on standard DICOM images.^{14,15,17} The measurement of small changes in the motion of vessel walls with high resolution is encouraging since we

used conventional ultrasound scanners and open-source DICOM data available to any clinician.

For a successful application of the existing open-source software, it is important to carefully choose two points of interest at the top and bottom of the vessel wall which will be tracked to compute vessel diameter during speckle tracking. In the user input portion of the study, even though we set a basic rule for point selection, where the ten users were instructed to choose two points at the vessel edge and along the central axis of the vessel in the first frame of the ultrasound cine loop, there was variation in point selection across users which resulted in distensibility measurement variation. In an extreme case, the cine loop data collection for subject #5 had considerable motion intermittently throughout the data due to transducer instability at the time of ultrasound data collection. It is likely that this contributed to the very large variation in point selection by the users, who may have had to move away from the axis along the center of the vessel to choose the points to avoid loss of speckle tracking. The second possible source of variation by the user is in the selection of six sequential peaks and valleys in the distensibility waveform plot (diameter vs time) to compute distensibility values. To address these variations, we developed and tested two semi-automated methods, addressing both user point selection and peak/valley selection. Both automated methods replace individual user input with established but different thresholding and edge detection algorithms and automated algorithms for peak and valley selection. Interestingly, both semi-automated methods were highly correlated with the median user input results. Another interesting observation was that the results of both semi-automated methods averaged higher than the user input derived results. We speculate

that, in the user input study, the user may tend to select points that move less to improve the waveform and tracking, leading to lower distensibility measurements, a possible source of biasing in the user input method toward lower values. It is also possible that the semi-automated methods tended to select points closer to the vessel lumen which is the subject of an ongoing study. These points may move more than points further away from the vessel edge, increasing the semi-automated distensibility measurements. In addition, these points will have a smaller baseline diameter that will tend to increase the distensibility measurement. In either case, the diagnostic thresholds for distensibility have not been established, and having a reliably repeatable measurement is crucial for clinical study, even at the expense of a measurement bias. Nevertheless, these potential sources of measurement bias require additional investigation and we have plans for laboratory studies to evaluate them further.

Based on our analysis, variation in distensibility measurement is not only influenced by variation in user point selection but also by physiologic beat-to-beat variation. Interestingly, both beat-to-beat variation and variation in point selection by users contribute to the variation in distensibility with a similar degree. This raises the possibility of implementing protocols or algorithms that can standardize point selection, minimizing user introduced variation, while allowing for physiologic beat-to-beat variation in distensibility, which could have diagnostic utility. Distensibility may be a dynamic variable, related to the underlying BP, heart rate, and pulse pressure, as well as the mechanical properties of the vessel wall. Both semi-automated methods preserved the beat-to-beat variation in measurements, while showing the potential to reduce user-induced variation. Further study is in progress to understand which

components of these automation strategies, edge detection, detrending, and/or thresholding most influence the performance differences.

Also, the arterial waveform plots (change of diameter of vessel wall over time) in our study indicates that variation observed in raw distances is less than variation in distensibility measurements. This too is an important observation and results from the diameter (baseline distance) varying more than the vessel wall excursion. Even though the transducer was placed gently, the surface transducer pressure may subtly compress the vessel, changing baseline diameter and influencing the denominator of the distensibility measurement. While transducer effects were not evaluated in this study, this is another variable that must be standardized. Given the non-linear vascular wall elasticity,^{24,27} the same pulse pressure may result in a greater distance excursion (numerator) when the vessel is compressed. Given that the excursion (numerator) was comparatively stable, this suggests little change in the underlying elastic modulus of the vessel wall with this mild degree of surface pressure. If this is the case, the excursion may be a more reliable measure, and the excursion divided by the pulse pressure may provide a parameter that can be used as a surrogate for vessel wall elastic modulus.⁵¹

Our initial motivation for performing this study came from recognizing that human factors may influence measurement during development of this software. While the study is relatively small in number (10 datasets using 10 trained users), the lessons learned have been important. It is clear from this detailed study on user-induced variation and potential solutions which may address variation that there is a need to define rules and algorithms to increase uniformity in point selection and hence increase accuracy and reproducibility of the automated measurement of vessel distensibility. Our

first steps in semi-automated measurement were able to do this. Our results are also influencing plans for future clinical studies, reinforcing the need to study the impact of these measurement algorithms. We now have ongoing studies aimed to further develop and test these automated methods to support larger clinical studies. A recognized limitation is that all our subjects had ESRD, and we plan future studies with controls and other disease groups to further evaluate these distensibility measurements.

Conclusions:

We present our continuing effort to develop and optimize non-invasive, reproducible, and accurate technology to help predict factors influencing the creation and maturation of a functional mature AVF. The overarching goal is to enhance vascular access and hemodialysis maintenance/care for CKD and ESRD patients. This study identifies user-based point selection as a significant source of variation. There is also an observable beat-to-beat physiologic variation in the circumferential vessel wall strain (distensibility). We have developed semi-automated methods to reduce user-induced variation that preserve physiologic measurement variation. These methods also increase the ease of use by simplifying user input. Additional work has resulted in a user interface that will also simplify use. The two methods show differences in their correlation level and bias when compared with reference (median) measurements. Studies are in progress to understand the impact of differences between methods. Our research plans include data and software sharing agreements with additional investigators in other institutions to expand clinical testing and further develop the methods. We also plan to expand testing the applications in peripheral vascular disease

(carotid and lower extremities). Further investigation will determine where vascular strain measurements may be helpful in the diagnosis of stenotic (diseased) and non-stenotic (healthy) vessels, along with studies to evaluate the potential role of vascular strain in predicting and improving clinical outcomes.

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Table 1: Distensibility and Relative Beat-to-Beat (BTB) variation.

Table -1A: Effect of variation in point selection by users: Maximum spread of selected points in top and bottom position (pixels); Median Distensibility (%) of the arterial walls of the ten subjects; Mean Distensibility (%) \pm Standard Deviation (SD); User-induced Distensibility Variation (Relative Distensibility Variation, %); Relative beat-to-beat (BTB) variation (%)

Tables – 1B and 1C: Use of semi-automated methods #1 (Canny Edge Detector – Polynomial Detrending – Manual Thresholding; CED-PD-MT) and #2 (Sobel Edge Detector – Polynomial Detrending – Fixed Thresholding; SED-LD-FT) to measure Distensibility (%) and Relative BTB variations (%).

Table 1: Distensibility and Relative Beat-to-Beat (BTB) variation**Table 1A: Effect of variation in point selection by users**

Subject #	1	2	3	4	5	6	7	8	9	10
Maximum spread in Top position										
(pixels)	14	10	15	12	120	20	20	10	12	7
Maximum spread in Bottom position										
(pixels)	20	7	14	7	140	16	30	5	8	10
Median Distensibility (%)	2.07	2.16	2.83	2.32	2.43	2.49	4.87	5.77	2.5	6.09
	2.39 ±	2.152	2.84 ±	2.312	2.46 ±	2.53 ±	5.04 ±	5.929	2.583	6.061
Mean Distensibility (%) ± SD	0.98	± 0.21	0.16	± 0.19	0.37	0.27	0.55	± 0.69	± 0.31	± 0.38
User-induced Distensibility Variation										
%	41.04	9.76	5.63	8.22	15.07	10.66	10.91	11.64	12.00	6.27
Relative BTB Variation %	15.81	11.9	17.55	12.26	17.68	7.16	15.89	10.23	6.41	14.38

Table 1B: Use of CED-PD-MT semi-automated method

Subject #	1	2	3	4	5	6	7	8	9	10
Distensibility (%)	2.55	2.75	3.74	2.60	3.44	2.89	5.81	6.59	3.59	7.50

Relative BTB Variation (%)	13.88	13.90	17.58	26.28	13.11	7.52	12.19	15.04	4.55	14.96
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Table 1C: Use of SED-LD-FT semi-automated method

Subject #	1	2	3	4	5	6	7	8	9	10
Distensibility (%)	3.10	2.49	3.65	3.02	2.64	2.85	7.97	6.77	4.47	8.60
Relative BTB Variation (%)	18.38	16.15	12.37	16.85	19.58	7.07	23.64	14.77	6.34	23.77

Figure Legends:

Figure 1: Circumferential vascular wall strain (distensibility, \mathcal{E}): Defined as the ratio of the change in vessel diameter, the difference between diastolic diameter (D_d) and systolic diameter (D_s), during a cardiac cycle, to the original diastolic diameter

Figure 2: Cross-sectional view of arteries in the left panels with a magnified view (3.5X) of arteries in the right panels: The location of points chosen by ten users (represented by different colors) at the top and bottom of the arterial wall on the first frame of the ultrasound cine loop of subject #8 (top panel; minimum variation) and of subject #5 (bottom panel; maximum variation).

Figure 3: Minimum (subject #3) and Maximum (subject #1) variation in Distensibility: Wave plots (change in diameter of vessel wall over time) based on locations of points chosen by ten users (#1 - #10). Six sequential peaks and valleys marked by the users are shown in red.

Figure 4: Regression analysis comparing the distensibility obtained by the two semi-automated methods Canny Edge Detector – Polynomial Detrending – Manual Thresholding (CED-PD-MT, blue) and Sobel Edge Detector – Polynomial Detrending-Fixed Thresholding (SED-LD-FT; red) with the median distensibility obtained by the ten users.

Figure 5: User Interface (UI) under development allows users to identify the ultrasound data to be analyzed [upper left] with automated edge detection [upper right] and motion tracking to determine maxima (peaks) and minima (valleys) [lower graph] and results [upper right corner].

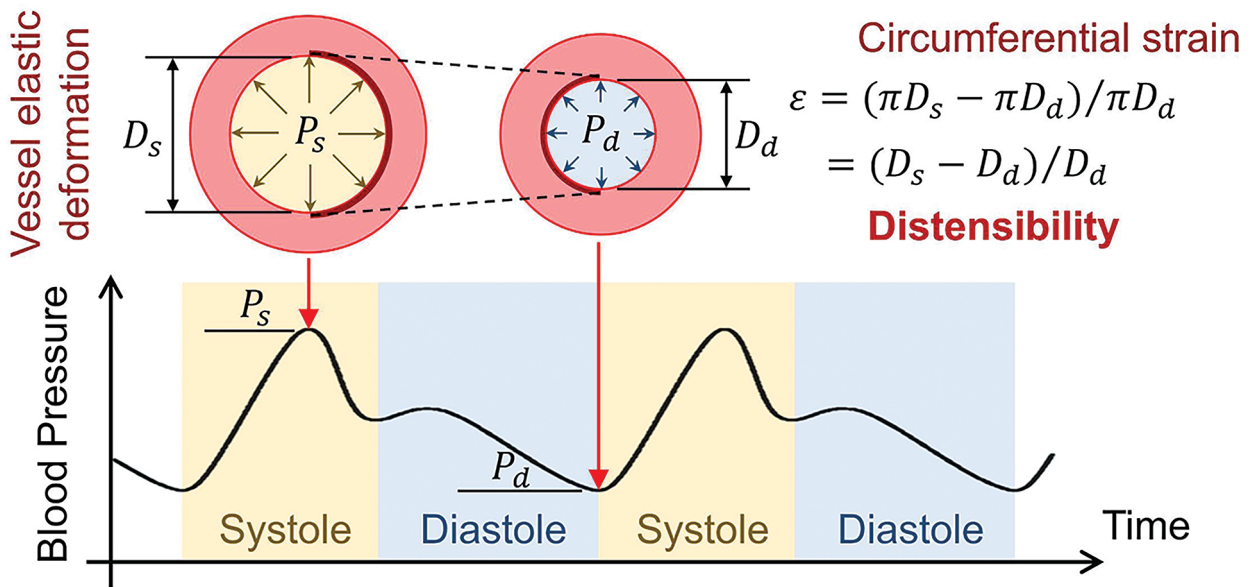
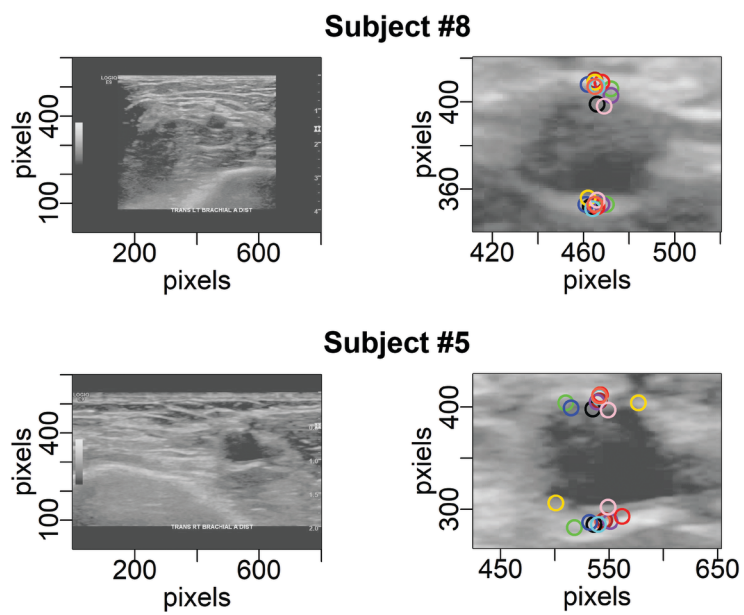
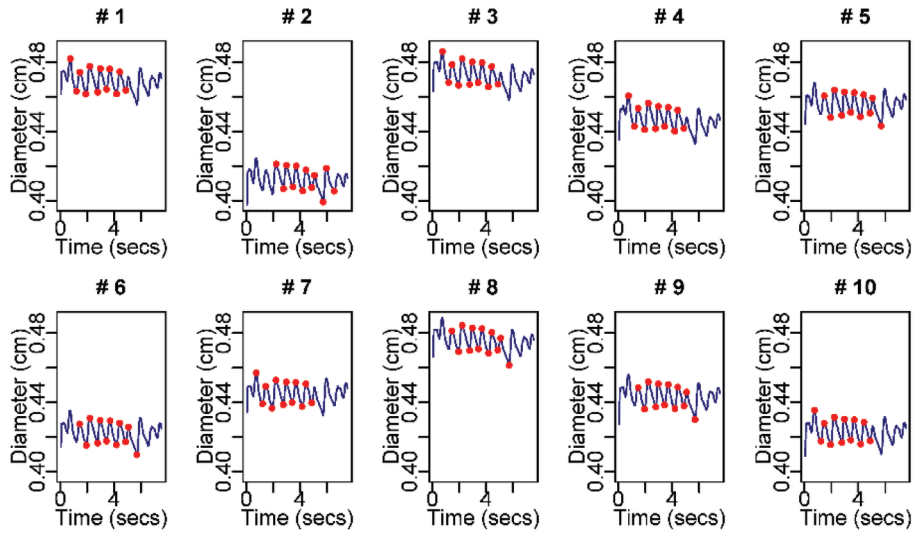


Figure-1.tif

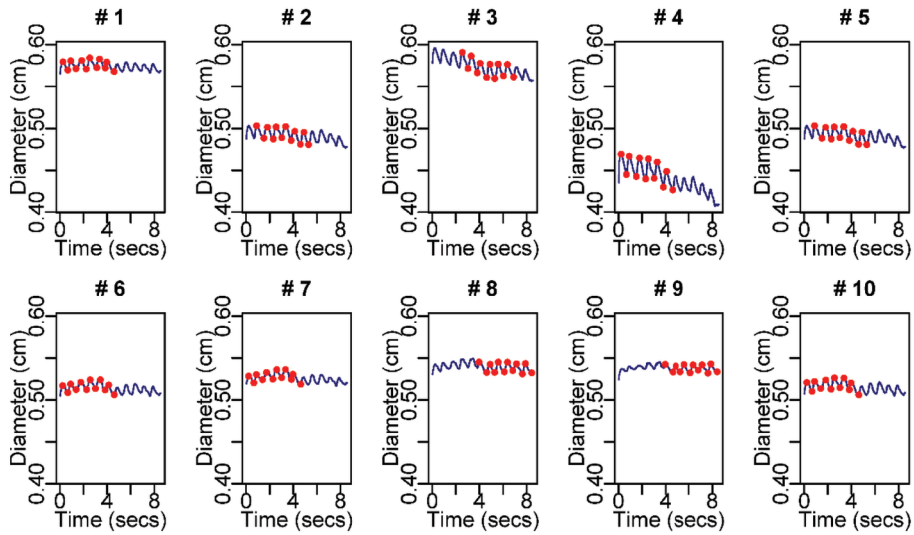


Figure_2.tif

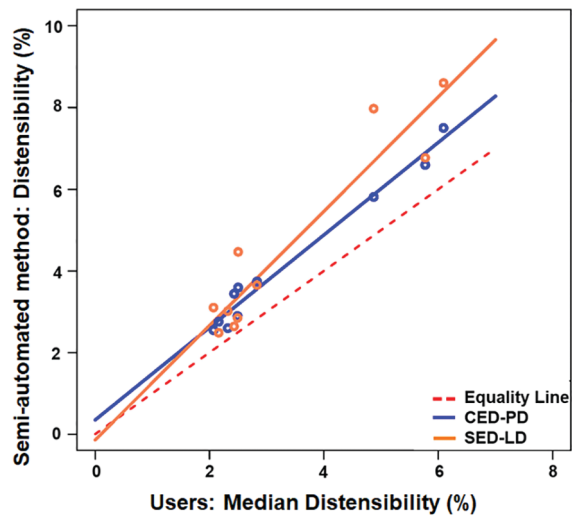
Subject #3



Subject #1



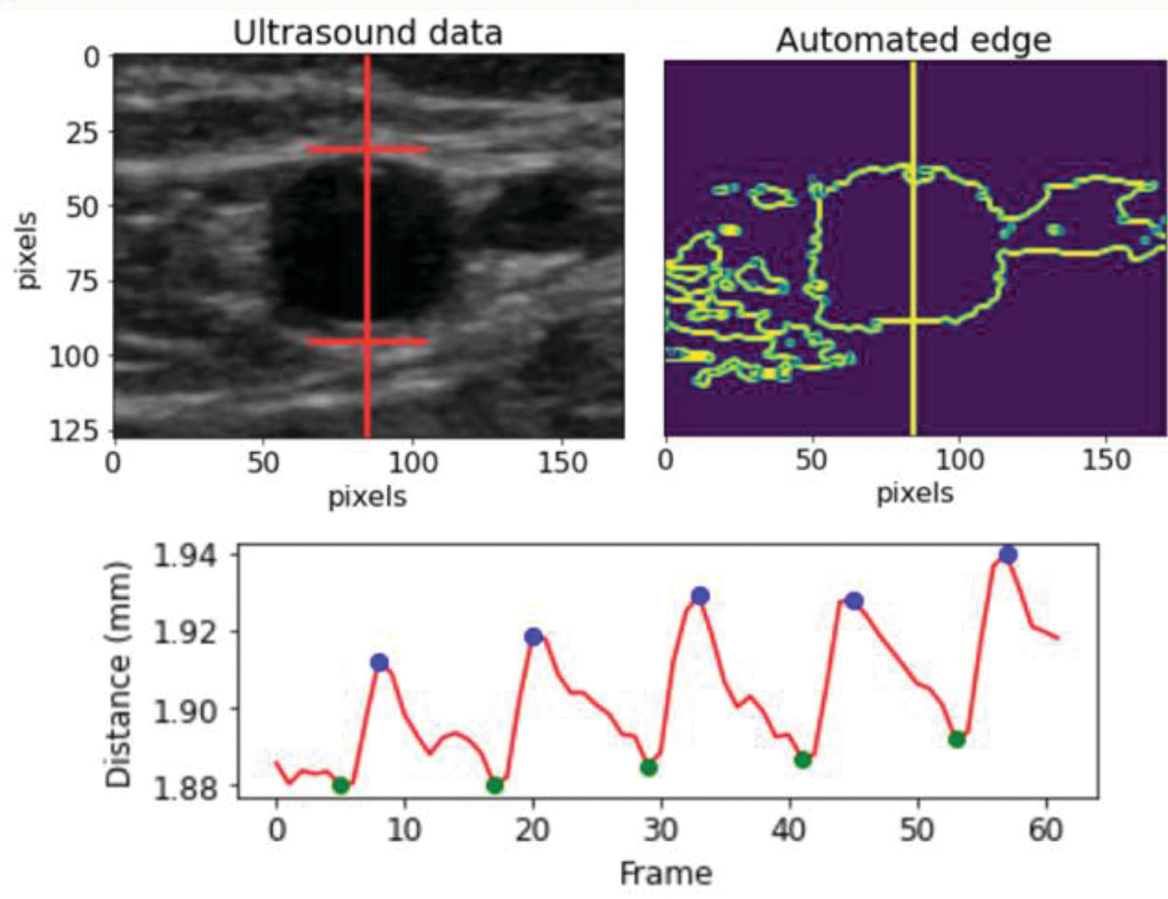
Figure_3.tif



Figure_4.tif

Control Panel

Distensibility: 2.14%
Peak diameter: 1.92 mm
Valley diameter: 1.88 mm



Figure_5.tif

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Date: 11/24/2021

Your Name: Nirmala Rajaram

Manuscript Title: Semi-Automated Software to Improve Stability and Reduce Operator Induced Variation in Vascular Ultrasound Speckle Tracking

Manuscript Number (if known): JUM-2021-10-1272

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Date: 11/23/2021

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Manuscript Number (if known): JUM-2021-10-1272

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Date: 11/24/2021

Your Name: Miguel Angel Funes Lora

Manuscript Title: Semi-Automated Software to Improve Stability and Reduce Operator Induced Variation in Vascular Ultrasound Speckle Tracking

Manuscript Number (if known): JUM-2021-10-1272

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Date: 11/24/2021

Your Name: James Hamilton

Manuscript Title: Semi-Automated Software to Improve Stability and Reduce Operator Induced Variation in Vascular Ultrasound Speckle Tracking

Manuscript Number (if known): JUM-2021-10-1272

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Date: 12/6/2021

Your Name: Peter Henke

Manuscript Title: Semi-Automated Software to Improve Stability and Reduce Operator Induced Variation in Vascular Ultrasound Speckle Tracking

Manuscript Number (if known): JUM-2021-10-1272

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Date: 11/23/2021

Your Name: Venkataramu Krishnamurthy

Manuscript Title: Semi-Automated Software to Improve Stability and Reduce Operator Induced Variation in Vascular Ultrasound Speckle Tracking

Manuscript Number (if known): JUM-2021-10-1272

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Please place an "X" next to the following statement to indicate your agreement:

I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Author Manuscript

ICMJE DISCLOSURE FORM

Date: 12/15/2021

Your Name: Timothy G Morgan

Manuscript Title: Semi-Automated Software to Improve Stability and Reduce Operator Induced Variation in Vascular Ultrasound Speckle Tracking

Manuscript Number (if known): JUM-2021-10-1272

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

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Author Manuscript

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Author Manuscript

ICMJE DISCLOSURE FORM

Date: 12/16/2021

Your Name: Nicholas Osborne

Manuscript Title: Semi-Automated Software to Improve Stability and Reduce Operator Induced Variation in Vascular Ultrasound Speckle Tracking

Manuscript Number (if known): JUM-2021-10-1272

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4	Consulting fees	<input type="checkbox"/> None	
		Medtronic aortic	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	<input checked="" type="checkbox"/> None	
6	Payment for expert testimony	<input checked="" type="checkbox"/> None	
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Author Manuscript

ICMJE DISCLOSURE FORM

Date: 12/16/2021

Your Name: Albert Shih

Manuscript Title: Semi-Automated Software to Improve Stability and Reduce Operator Induced Variation in Vascular Ultrasound Speckle Tracking

Manuscript Number (if known): JUM-2021-10-1272

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Author Manuscript

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Author Manuscript

ICMJE DISCLOSURE FORM

Date: 11/24/201

Your Name: Brian Thelen

Manuscript Title: Semi-Automated Software to Improve Stability and Reduce Operator Induced Variation in Vascular Ultrasound Speckle Tracking

Manuscript Number (if known): JUM-2021-10-1272

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Author Manuscript

ICMJE DISCLOSURE FORM

Date: 11/22/2021

Your Name: William Weitzel

Manuscript Title: Semi-Automated Software to Improve Stability and Reduce Operator Induced Variation in Vascular Ultrasound Speckle Tracking

Manuscript Number (if known): JUM-2021-10-1272

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Date: 11/28/2021

Your Name: Lenar Yessayan

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Date: 11/23/2021

Your Name: Yihao Zheng

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