Title: Vascular Deformation Mapping as a Method for 3D Growth Mapping During CT Surveillance of Thoracic Aortic Aneurysm

Authors: Nicholas S. Burris, MD[1,2,4]; Zhangxing Bian[1,3]; Jeffrey Dominic, MS[1,3], Jianyang Zhong[1,3], Ignas B. Houben, MD[5], MS; Diederik Van Bakel MD[5]; Himanshu J. Patel, MD[5]; Brian D. Ross[1,4,6], Gary E. Christensen[7], Charles R. Hatt[1,8], PhD

1. Department of Radiology, University of Michigan
2. Department of Biomedical Engineering, University of Michigan
3. Department of Electrical Engineering and Computer Science, University of Michigan
4. Center for Molecular Imaging, University of Michigan
5. Department of Cardiac Surgery, University of Michigan
6. Department of Biological Chemistry
7. Department of Electrical and Computer Engineering, University of Iowa
8. Imbio, LLC

Word Count: 3019

Article Type: Original Research

Correspondence Information:

Nicholas S. Burris, M.D.

Department of Radiology

University of Michigan

1500 E. Medical Center Drive

CVC 5588, SPC-5030

Ann Arbor, MI 48109-5030

Additional Contact Information:

Cell: (410) 925-4200

Office: (734) 768-7169

e-mail: nburris@med.umich.edu

Keywords: thoracic aortic aneurysm; vascular deformation mapping; aortic growth; aortic dissection; deformable registration

Summary Statement: XXX

Key Results:

- One
- Two
- Three

Abstract:

Background:

Purpose:

Materials & Methods:

Results:

Conclusion:

Introduction

Thoracic aortic aneurysm (TAA) is a common disease that is increasing in prevalence worldwide, with approximately 3% of patients over the age of 50 having a dilated thoracic aorta (1-3) and recommended to undergo imaging surveillance (4). The majority of patients with TAA have an indolent disease course, with aortic growth occurring either slowly or not at all over a period of years to decades (5). However, life-threatening complications such as rapid growth, aortic dissection and rupture can occur in otherwise asymptomatic patients at pre-surgical aneurysm sizes (6, 7), emphasizing the need for better techniques to more accurately assess disease progression, inform surgical candidacy and predict complications. A fundamental limitation to improved management of TAA is the lack of imaging techniques to accurately assess aortic growth. Current medical imaging assessment techniques are based on measurements of maximal aortic diameter; however, the degree of variability associated with

aortic diameter measurements – on the order of ± 1-5 mm despite optimal measurement technique – frequently prevent confident assessment of disease progression at average TAA growth rates (<1 mm/year)(8-11). Furthermore, diameter measurements are inherently 2-dimensional and are performed in fixed anatomic locations and are unable to capture the 3-dimensional (3D) nature of TAA growth.

To overcome this limitation, prior research has described the feasibility of a medical image analysis technique, termed Vascular Deformation Mapping (VDM), for three-dimensional (3D) assessment of aortic growth using deformable image registration techniques (12, 13). This approach utilizes high-resolution, volumetric computed tomography angiography (CTA) data, and allows for comprehensive quantification of aortic growth at any point aortic wall, avoiding the limitations of manual definition of analysis planes and caliper measurements. Despite these advantages, image analysis techniques based on deformable image registration are not without potential errors and pitfalls, and thus an evaluation of the VDM in a clinical population with TAA is needed to understand the clinical and reliability and utility of this technique.

The objectives of this study were two-fold: 1) determine performance of the VDM algorithms in a clinical cohort of TAA patients undergoing imaging surveillance including assessment of reproducibility and identification of sources of error in the analysis workflow, 2) describe unique patterns of 3D aortic growth observed in TAA patients and investigate the agreement of VDM analysis with standard clinical assessments.

Methods

Patient Identification and Clinical Data Abstraction

All procedures were approved by the local institutional review board (HUM00133798) and informed consent was waived given the retrospective design. Using electronic medical records search software, we identified 50 patients at our institution with serial ($n \geq 2$) CTA examinations covering the thoracic aorta between 2006-2020 undergoing imaging surveillance

of TAA in either the pre- or post-operative setting. Patients were excluded from analysis for: non-ECG gated acquisition (n=5), lack of thin slice (≤3mm) reconstructions (n=1), poor aortic opacification (<200 HU at ascending aorta, n=2), interval surgical aortic repair (n=2) or severe motion artifact (n=3) (**Figure 1**). Patients with mild motion-related blurring affecting only the aortic root were included as long as the proximal coronary arteries could be clearly visualized. A total of 38 unique patients encompassing 105 CTA examinations and 68 surveillance intervals were selected for analysis. Clinical and demographic information was collected by chat review. Maximal diameter measurements of the thoracic aorta were recorded from clinical CT reports for comparison with VDM assessment. Of note, all aortic measurements at our center are performed in a dedicated 3D lab by trained technologists using standardized measurement protocols and centerline measurement technique.

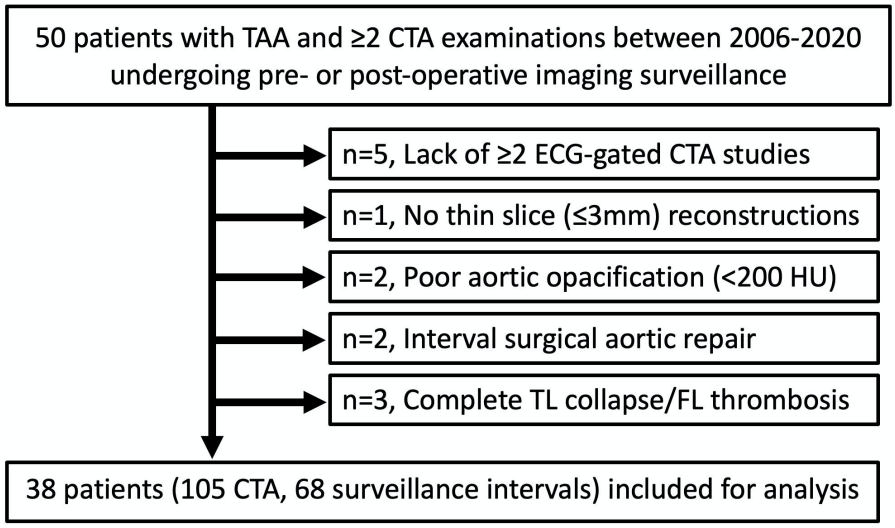


Figure 1: Flow diagram depicting inclusion and exclusion criteria.

Vascular Deformation Mapping

The VDM analysis pipeline for measurement of three-dimensional aortic growth uses diffeomorphic image registration to quantify the local deformation of the aortic wall between two CTA examinations and results are visualized by superimposing a colorized scale of deformation values on the three-dimensional surface of the aortic geometry. The steps involved in VDM analysis include: 1) segmentation of the thoracic aorta on CTA images from scans acquired at

two different time points with the first time point considered the fixed image and the second time point considered the moving image, 2) image pre-processing steps including cropping and clamping voxels with negative Hounsfield values at 0 to avoid adjacent lung influencing the registration and dilation of aortic masks by 3 voxels to ensure inclusion of the wall, 3) rigid registration (Euler) to approximately align the two CTA images (Elastix, Utrecht, Netherlands), 4) alignment of the aortic centerline using a highly regularized multi-image, multi-metric deformable registration which applies a penalty term to enforce rigid movement of voxels within the aortic segmentation but allows deformation of the peri-aortic voxels optimized rigid aortic registration (14), 5) multi-resolution, multi-metric b-spline deformable image registration using mutual information with 10 mm grid spacing and a bending energy penalty of 100, 6) generate a polygonal mesh of the aortic surface (approximately 100,000 - 400,00 unique surface elements) at baseline (fixed) geometry, 7) translate mesh vertices of baseline model using the deformation field calculated in Step 5 and 8) quantify deformation as the ratio of surface area change at each triangular mesh element (termed Area Ratio) with colorized visualized in Paraview (Kitware Inc., Clifton Park, NY, USA).

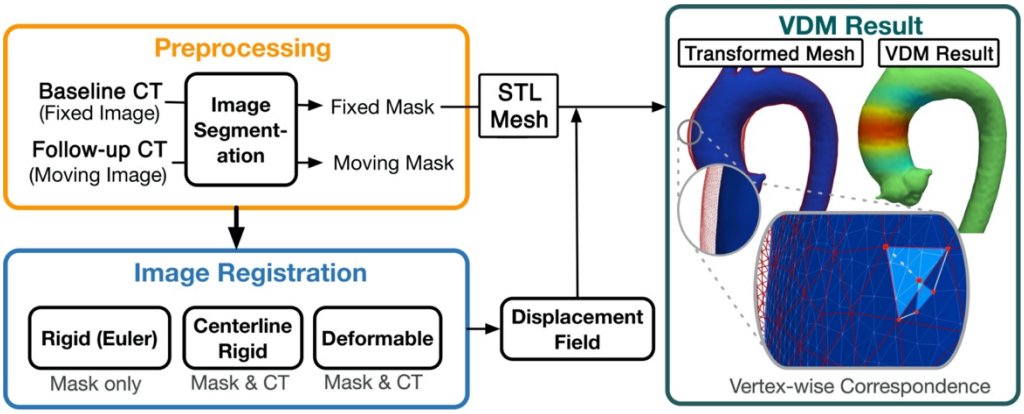


Figure 2: Simplified schematic overview of the steps involved in the VDM analysis pipeline. ECG-gated aortic CTA DICOM data is retrieved for baseline and follow-up examinations and CTA data undergoes aortic segmentation (orange box), followed by rigid and deformable registration (blue box). The displacement field calculated from registration steps is used to translate the mesh vertices of the baseline model, and the ratio of change in the surface area of each mesh element (Area Ratio) is plotted on the aortic surface using a colorized scale.

Image Segmentation Technique, Inter-Rater Reproducibility Analysis

Manual aortic segmentation is used in the VDM workflow to create aortic masks and is thus a potential source of variability. While all CTAs were segmented by a rater with four years of experience with aortic image analysis (I.H.), we had an additional rater with 5 years of experience (D.V) perform segmentations on 45 randomly selected CTA intervals to investigate the influence of manual segmentation variability on VDM output. Raters segmented the thoracic aortic from the root to just beyond the celiac axis, including the proximal arch vessels, using state-of-the-art segmentation tools (Mimics v22.0, Materialise, Leuven, Belgium).

Quality Assurance Process and Registration Accuracy Assessment

Considering the potential for accumulated error in the VDM output due to the multistep nature of the analytic pipeline, we adopted a multistep quality assurance (QA) protocol to evaluate the validity of each VDM output, with QA steps performed by a senior researcher with 15 years of experience with cardiovascular imaging. The QA protocol involved visual confirmation of segmentation and registration accuracy using dual color/channel plots of to ensure overlap of the aortic luminal boundary after the final deformable registrations step; specific steps in the QA protocol are described in the **Supplementary Material**. The identified case of registration failures/errors was recorded.

To assess registration accuracy, landmarks were manually placed along the aortic wall by a senior researcher with 15 years cardiovascular image analysis experience (N.B), and landmark registration error was determined by calculating the Euclidean distance between homologues points after the final deformable transformation. Conserved anatomic landmarks such as branch points (coronary, arch vessels and intercostal arteries) and discrete intimal calcifications were used to place landmarks on the aortic surfaces across serial CTAs within each patient. Deformable registration was performed using VDM parameters, in both the forward and reverse directions, and using all possible combinations of CT intervals for each patient.

Statistics

Patient characteristics were reported as mean ± SD for normally distributed continuous variables, median and interquartile range (IQR) for non-normal continuous variables, and frequencies for categorical variables. Normality was assessed using the Shapiro-Wilk test. Pearson's correlation coefficient was used to assess correlation between continuous variables. Agreement of growth assessment (binary yes/no) between clinical measurements and VDM was determined using Cohen's kappa statistic (κ). Inter-rater agreement of aortic segmentations was assessed using Dice Similarity Coefficient (DSC) to determine the overall degree of segmentation overlap, and Average Hausdorff Distance (AVD) to assess the average distance between segmentations at the aortic boundry. To assess inter-rater agreement of surface Area Ratio values from VDM, displacement fields calculated from each rater's registration were used to translate mesh vertices of a common aortic geometry to allow point-to-point correspondence for direct comparison. A p-value of < 0.05 was considered significant for all statistical tests. Statistical analyses were performed using Stata 14.0 (StataCorp LP, College Station, TX).

Results

Patient Characteristics and VDM Analysis Failures

Among the 37 patients who were included for analysis, the 3D growth mapping with VDM was completed without error in 34 (91%). VDM analysis was deemed successful after QA steps in 58 of 68 intervals (85%). The reasons for registration failure we identified included: irregular slice intervals in source DICOM images (n=3), excessive motion/stair-step artifact (n=2), streak artifact from dense superior vena cava (SVC) contrast (n=2), and streak artifact related to SVC cardiac implantable electronic device (CIED) leads. Examples of error cases are shown in **Supplemental Figure 1**.

The average patient age was 69.0 ± 9.3 years (range: 46-85 years) and the majority were female (n=21, 55%). The majority of TAAs involved the ascending aorta (n=26, 69%) and were considered degenerative in etiology by clinical notes (n=23, 60%). Approximately one-third of patients (11/38) had a history of prior aortic repair and were undergoing post-surgical imaging surveillance. Complete patient characteristics are shown in **Table 1**. CTA examinations were performed between November 2005 and January 2020, with the median number of CTAs per patient of 2 (IQR: 2, 3; range: 2-7) with median surveillance interval of 1.1 years (IQR: 1.0, 2.0; range: 0.4-11.8).

Characteristics (n=38)	**Mean ± SD (range)**
Age (years)	69.0 ± 9.3 (range: 46-85)
Sex (male/female), n	17/21
Hypertension, n (%)	27 (73%)
Hyperlipidemia, n (%)	19 (50%)
Smoking history, n (%)	22 (58%)
History of connective tissue disease, n (%)	2 (5%)
Body mass index (kg/m^2)	28.2 ± 5.5 (range: 14.2-40.5)
Aneurysm Location	
Ascending, n (%)	26 (69%)
Descending, n (%)	10 (26%)
Both, n (%)	2 (5%)
Aneurysm Etiology	---
Degenerative, n (%)	23 (60%)
Atherosclerotic, n (%)	9 (24%)
Genetic, n (%)	2 (5%)

Inflammatory, n (%)	1 (3%)
Bicuspid aortic valve, n (%)	3 (8%)
Baseline Maximal Aortic Diameter (mm)	45.8 ± 5.6 (range: 33-58)
Prior Aortic Surgery, n (%)	11 (29%)

Table 1: Patient characteristics and demographics.

Registration Accuracy and Inter-rater Reproducibility Analysis

A total of 199 unique landmarks were manually placed at discrete anatomic locations along the aortic wall in 79 CTAs with an average of 7.2 landmarks per patient. Considering all registration combinations, a total of 1,021 point-pairs were used to assess landmark registration error. The median registration error was 0.77 mm (IQR: 0.54-1.10 mm, range: 0.07-4.57 mm).

Inter-rater agreement for aortic segmentation was high with average Dice similarity coefficient of 0.97 ± 0.02 (range: 0.93-0.99) and an Average Hausdorff Distance of 0.12 ± 0.20 mm (range: 0.01-1.20 mm). When comparing the inter-rater agreement of Area Ratio values between approximately 5.4 million homologous surface elements, we found no bias (bias= 0.0) narrow limits of agreement (-0.03 to 0.03 Area Ratio; Bland-Altman plot in **Figure 3A**), and excellent inter-rater correlation of Area Ratio values (r=0.95, **Figure 3B**).

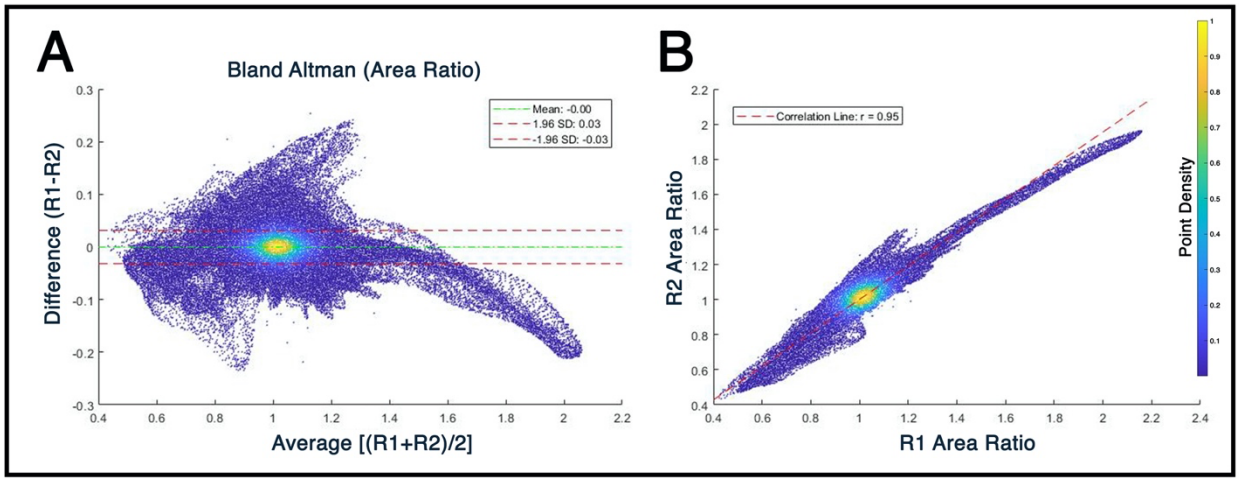


Figure 3: Bland-Altman plot with bias (dashed green line) limits of agreement (dashed red lines) depicting interrater agreement of Area Ratio values at homologous surface mesh elements (~5.4 million) generated from VDM analysis.

Three-Dimensional Growth Assessment

Overall, the median Area Ratio by VDM was 1.13 (IQR: 1.10, 1.19, range: 1.05 - 1.78). VDM analysis was able to clearly depict aortic growth in common TAA locations including ascending (**Figure 4A**), descending (**Figure 4B**), aortic root (**Figure 4C**) and perianastomotic (**Figure 4E**). Growth was localized the segment of maximal aortic dilation in 9 out of 14 intervals (64%) with growth by VDM analysis; however, in 6 VDM intervals (36%) growth was identified in an aortic segment outside of the primary aneurysmal segment. Longitudinal changes in aortic growth were also able to be clearly visualized by VDM (**Figure 5**). Among the 14 patients that had more than one surveillance interval, 11 patients demonstrated stable aortic dimensions by VDM at all surveillance intervals (**Figure 5A**), 2 demonstrated progressive growth at every interval, and 1 patient demonstrated stability at the initial surveillance interval and growth at subsequent intervals (**Figure 5B**).

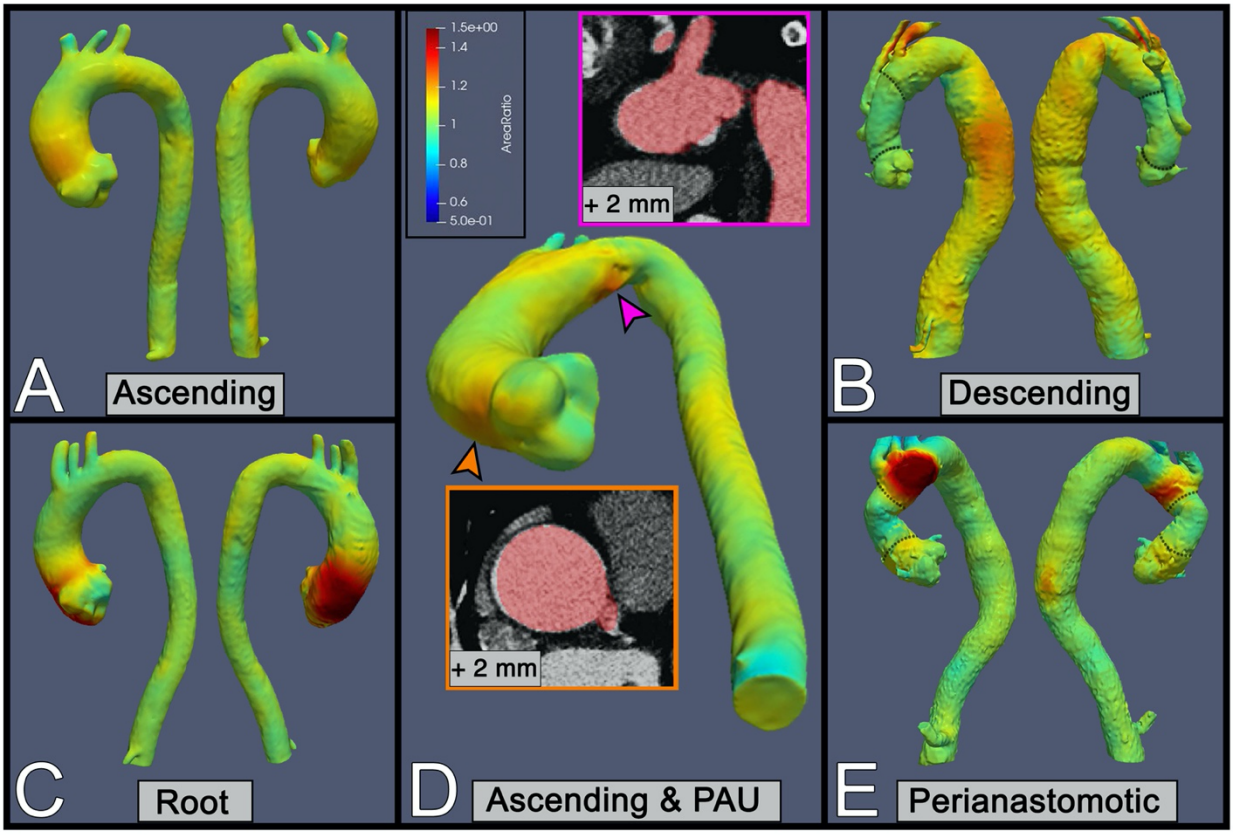


Figure 4: Examples of TAA growth patterns identified by VDM in a clinical cohort of patients undergoing CTA imaging surveillance. Representative examples of ascending aortic growth involving the tubular segment (A) and root (B), as well as post-surgical growth involving the descending aorta (B) and perianastomotic region in the arch (E); black dotted lines depict surgical graft anastomoses. Six intervals demonstrated growth in locations other than the primary aneurysmal segment, for example an enlarging penetrating ulcer was noted in the arch of a patient with a growing ascending aneurysm (D). Red masks depicting the baseline anatomy are overlaid on follow-up CT scans after rigid registration to allow for visual depiction of growth.

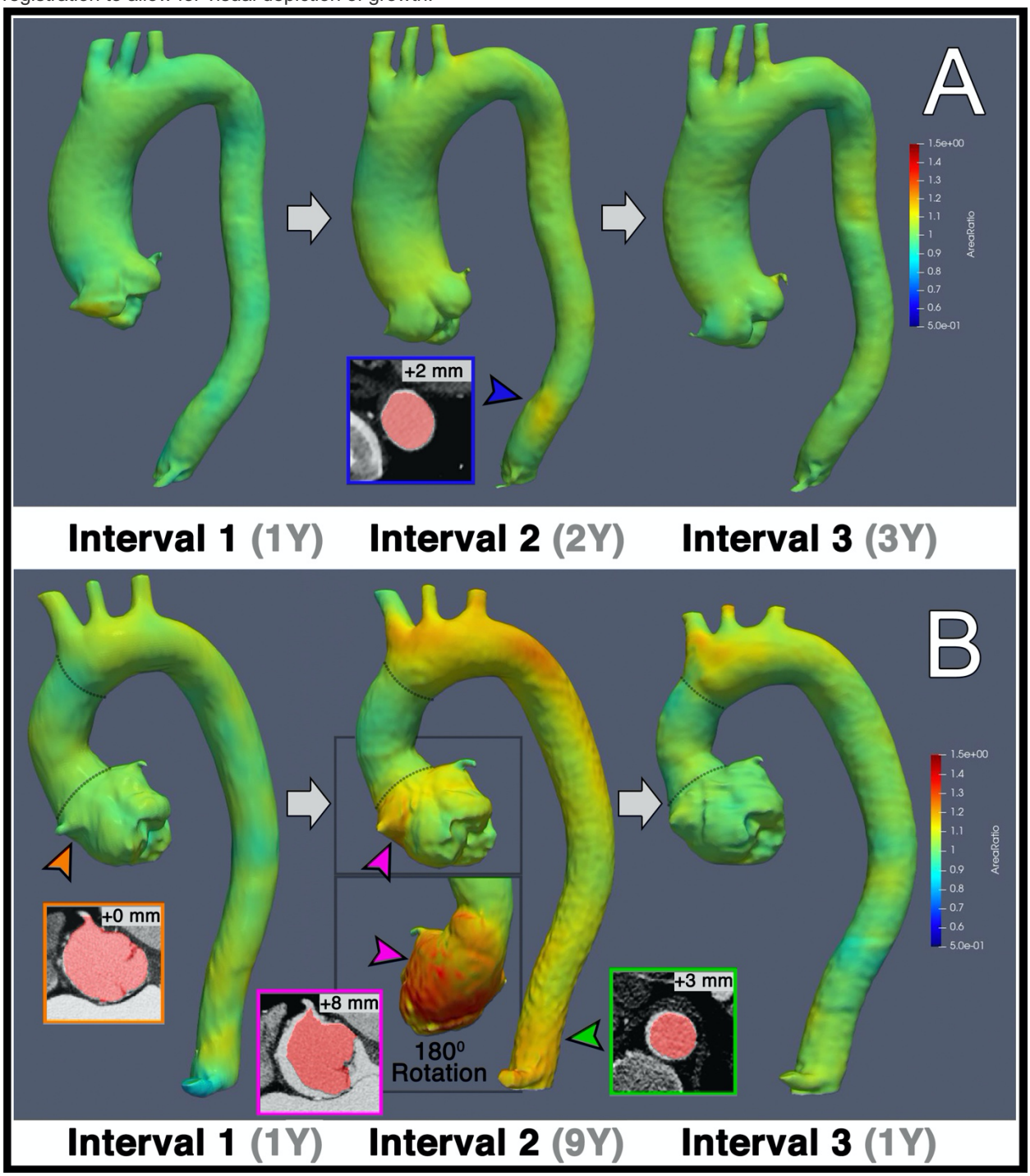


Figure 4: Representative cases depicting longitudinal VDM growth assessments. The majority (~80%) of patients with multiple surveillance intervals demonstrated stability of the aneurysmal segment (A), whereas the remaining

patients demonstrated progressive growth during longitudinal surveillance (B). Outside of the aneurysmal segment, VDM identified additional regions of growth in the descending thoracic aorta (blue and green arrowheads) and the arch (B, Interval 2).

Agreement with Clinical

There was strong agreement ($r=0.85$, $p<0.001$) between peak Area Ratio values and the change in maximal aortic diameter as measured by clinical CT (**Figure 6**). For further analysis we created binary growth categories based on published data on reducibility of clinical diameter measurements (8-10) and the observed inter-rater variability of VDM Area Ratio values (**Figure 6**), with "growth" defined as diameter change in the aneurysmal segment of ≥3 mm based on clinical measurements and ≥1.2 Area Ratio change by VDM (i.e., 20% increase in surface area). When analyzing growth as a binary outcome, there was agreement between VDM and clinical diameter growth categorizations in 89% (49/55) of surveillance intervals with (kappa= 0.70, 95% CI: 0.42-0.86). Of note, clinical diameter change was not able to be determined in 3 surveillance intervals as baseline diameter was not reported clinically. Among the 6 cases where growth assessments were discordant between VDM and clinical diameter measurements, there were 4 cases where VDM detected growth while diameter measurements did not, and 2 cases where diameter measurements detected growth but VDM did not. In 3 of the 4 discrepant cases with growth by VDM the location of peak Area Ratio was at the sinotubular junction, while the location of the clinically reported maximal diameter was at the mid-ascending level. In 6 surveillance intervals VDM analysis detected an additional region of growth (≥1.2 Aera Ratio) outside of the maximally dilated segment, of which 5/6 were located in the arch (3 arch penetrating atherosclerotic ulcers, 1 proximal left subclavian artery, and 1 fusiform dilation of mid arch) and 1 was at the location of a small descending TAA PAU.

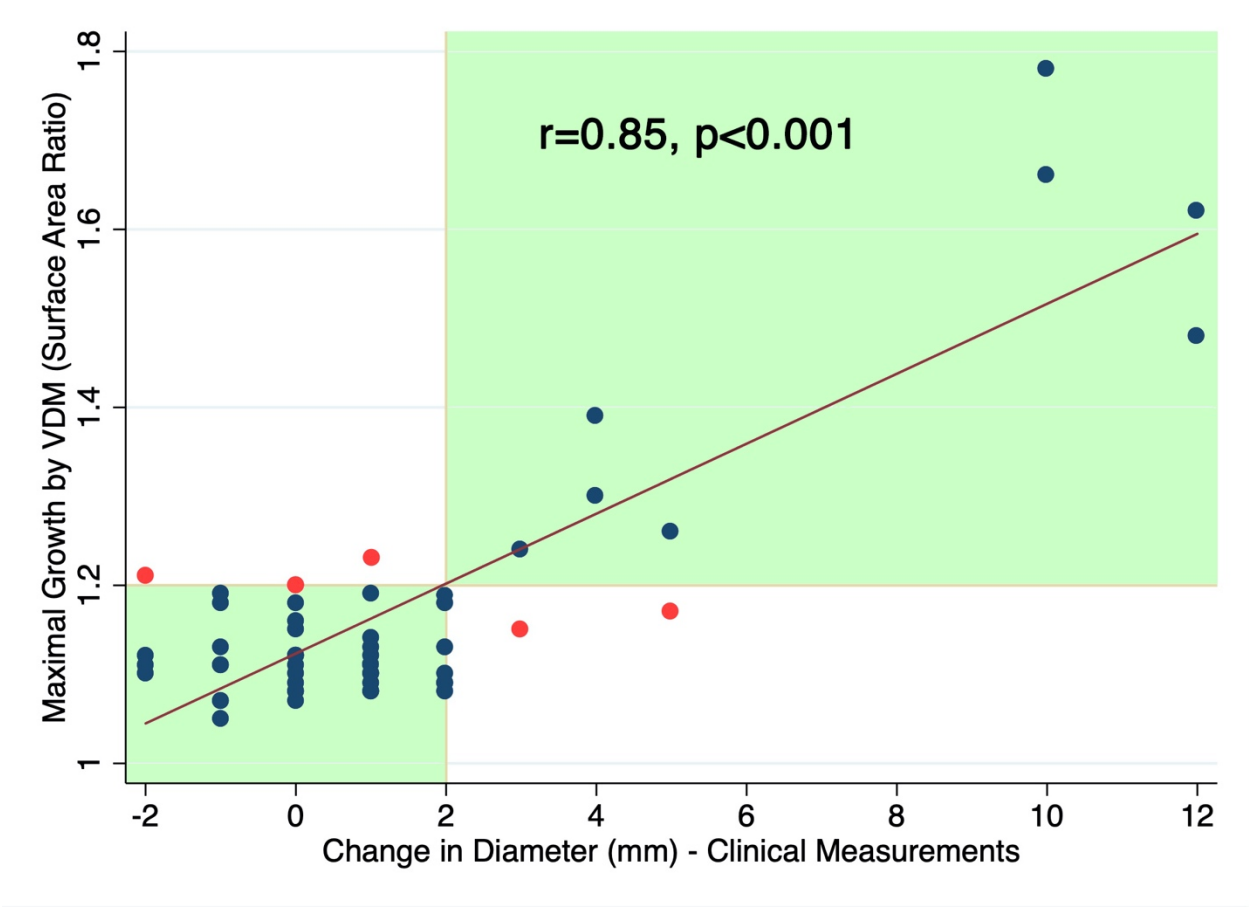


Figure 6: Scatterplot depicting the agreement between maximal aortic growth quantification by clinical diameter measurements and VDM (Area Ratio) at the aneurysmal segment. Green shaded regions depict regions of concordant growth assessments, while red points depict cases with discrepant growth assessments.

Discussion:

In this work we present results to support validation of a novel method for three-dimensional thoracic aortic aneurysm growth quantification using Vascular Deformation Mapping (VDM) in a clinical cohort of patients with various manifestations of thoracic aortic aneurysm (e.g., ascending, descending and postsurgical). In summary, we found that VDM analysis was technically successful in 85% of the evaluated intervals, and that the most common reasons for failure of the VDM analysis were related to streak artifact degrading the luminal boundary of the ascending aorta and artifacts related to ECG-gating (e.g., stairstep). Despite minor inter-rater variability in aortic segmentations (<1 mm), the measured surface Area Ratio changes plotted as the final output of VDM demonstrated excellent interrater agreement.

In addition to demonstrating the feasibility for analyzing aortic growth in the maximally dilated segment, VDM identified additional areas of sub-maximal growth in other regions of the aorta in one third of patients with growing TAA. Lastly, VDM analysis yielded a comprehensive three-dimensional analysis of growth patterns and 3D growth assessments demonstrated agreement with standard clinical assessments in the majority of cases.

Aortic diameter is the current metric used to assess growth and determine candidacy for surgical repair. However, diameter measurements suffer from significant measurement variability and are limited in their ability to predict rapid growth and risk acute complications such as aortic dissection (6). Assessment of aortic growth/growth rate over time is a primary objective of imaging surveillance and provides useful information about the aortic wall integrity, trajectory of disease progression and need for surgical intervention (4, 15). Unfortunately, confident assessment of disease progression by aortic diameter is often difficult and measurement variability alone can result in growth rates that suggest the need for surgical repair (5). The Vascular Deformation Mapping technique represents an attempt to overcome such limitations by harnessing the high-resolution and volumetric (plane-independent) nature of CTA data in combination with deformable image registration techniques that can align medical images with submillimeter accuracy (16). Inter-rater agreement of VDM derived Area Ratio values was excellent despite small variations in manual segmentation. Furthermore, the degree of inter-rater variability of Area Ratio relative its range in this clinical population (± 0.03 with range of 1.05 – 1.78) was proportionally smaller than the typical degree of diameter measurement variability relative to its range (± 2 mm with range of diameter change of -2 – 12 mm), suggesting that VDM is a more precise measurement technique.

Beyond simply yielding a more precise growth assessment, VDM technique allows for a more comprehensive evaluation of aortic growth than is possible with aortic diameter measurements including the ability to evaluate the eccentricity and longitudinal extent of growth. Similar image analysis techniques using deformable image registration have been employed to

yield quantitative imaging biomarkers for more comprehensive disease monitoring and phenotyping in the lungs (e.g., COPD, pulmonary fibrosis)(17, 18), brain (e.g., glioma)(19-21), and bones (22, 23), but to our knowledge VDM represents the first application of such a quantitative mapping technique to aortic disease. While aortic diameter has a known relationship with tensile wall stress (e.g., law of Laplace), this relationship assumes a circular shape, uniformly distributed and unidirectional stresses, and homogenous composition of the aortic wall, assumptions which are not accurate in TAA. Thus, a kinematic assessment of aortic surface area changes by VDM may more accurately reflect underlying wall stresses due to the localized and multi-directional nature of the assessment. The development of such quantitative methods to assess TAA disease progression have potential to improve risk stratification by better delineating surveillance intervals with slow growth versus no growth and may serve as a quantitative outcome to better assess the effects of pharmacologic and surgical interventions. Preliminary investigations have suggested that VDM analysis may be able to help with surgical planning by better depicting the full extent of aortic growth (13), and in combination with computational modeling techniques may be a useful tool to investigate the mechanisms underlying development of regional phenomena such as rupture and aortic dissection (24, 25).

Our study has several limitations. First, we did not systematically investigate patient outcomes in this study given that our objectives were focused on evaluating the technical performance, reproducibility and clinical validity of VDM. As such, the localized changes in aortic surface area measured by VDM require further investigation to define their prognostic significance, although such studies will require significantly larger patient cohorts with long-term follow-up given the slow nature of TAA growth and low rates of complications. Secondly, the VDM technique is susceptible to errors in the presence of streak and motion artifact, and thus the performance of VDM may be suboptimal at centers that do not routinely utilize ECG-gating and/or have older generation CT scanners with narrower detector arrays. Modern CT scanners that use high-pitch acquisition (e.g., FLASH) to generate motion free aortic images without the

need for ECG gating may help overcome this limitation, however, we have nonetheless developed QA procedures to easily identify regions of registration failure indicating an erroneous VDM outputs. Thirdly, given the need for aortic segmentation and registration, VDM analysis does currently require more analysis time than diameter measurement, however, with the addition of deep learning techniques for automated aortic segmentation, the burden of analysis time can be shifted from human analysts to computational time with only minimal human interaction for QA analysis. Lastly, given that we analyzed clinical CTA data, there is no available ground truth by which to adjudicate discrepant growth assessments between VDM and clinical diameter assessments. However, given the well-known variability of diameter measurements, the well-validated nature of b-spline deformable registration algorithms, VDM's high degree of inter-rater reproducibility and our rigorous QA procedures, we believe that VDM analyses included in our analysis accurately depict changes in aortic wall morphology.

Conclusion:

Vascular Deformation Mapping (VDM) is a feasible method for three-dimensional quantification of longitudinal aortic growth in heterogeneous clinical population of patients with thoracic aortic aneurysm. VDM analysis yielded reliable growth assessments in 85% of evaluated surveillance intervals with excellent inter-rater reproducibility, with failure events related to streak and motion image artifacts. Accurate, quantitative assessments of aortic growth may provide a more nuanced assessment of patient risk to inform treatment decisions, uncover unique disease phenotypes and greatly advance our understanding of the long-term growth trajectories and outcomes for patients with TAA.

Acknowledgments:

Sources of Funding:

NSB- Radiologic Society of North America Research Scholar Grant (RSCH1801); NIH SBIRR44 HL145953

BDR- XXX

HJP- David Hamilton Fund and the Phil Jenkins Breakthrough Fund, as well as the Joe D. Morris Collegiate Professorship in Cardiac Surgery.

Disclosures:

NSB- Entitled to royalties related to licensure of intellectual property related to the VDM technique.

CRH- Employee of Imbio LLC, a company which has financial interests in VDM technology.

BDR- Entitled to royalties related to licensure of intellectual property related to the VDM technique.

References:

1. Benedetti N, Hope MD. Prevalence and significance of incidentally noted dilation of the ascending aorta on routine chest computed tomography in older patients. Journal of computer assisted tomography 2015;39(1):109-111. doi: 10.1097/RCT.0000000000000167
2. Mori M, Bin Mahmood SU, Yousef S, Shioda K, Faggion Vinholo T, Mangi AA, Elefteriades JA, Geirsson A. Prevalence of Incidentally Identified Thoracic Aortic Dilations: Insights for Screening Criteria. The Canadian journal of cardiology 2019;35(7):892-898. doi: 10.1016/j.cjca.2019.03.023
3. McClure RS, Brogly SB, Lajkosz K, Payne D, Hall SF, Johnson AP. Epidemiology and management of thoracic aortic dissections and thoracic aortic aneurysms in Ontario, Canada: A population-based study. J Thorac Cardiovasc Surg 2018. doi: 10.1016/j.jtcvs.2017.11.105
4. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE, Jr., Eagle KA, Hermann LK, Isselbacher EM, Kazerooni EA, Kouchoukos NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation 2010;121(13):e266-369. doi: 10.1161/CIR.0b013e3181d4739e
5. Elefteriades JA, Farkas EA. Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. J Am Coll Cardiol 2010;55(9):841-857. doi: 10.1016/j.jacc.2009.08.084

6. Pape LA, Tsai TT, Isselbacher EM, Oh JK, O'Gara P T, Evangelista A, Fattori R, Meinhardt G, Trimarchi S, Bossone E, Suzuki T, Cooper JV, Froehlich JB, Nienaber CA, Eagle KA. Aortic diameter >or = 5.5 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). Circulation 2007;116(10):1120-1127. doi: 10.1161/circulationaha.107.702720
7. Rylski B, Branchetti E, Bavaria JE, Vallabhajosyula P, Szeto WY, Milewski RK, Desai ND. Modeling of predissection aortic size in acute type A dissection: More than 90% fail to meet the guidelines for elective ascending replacement. J Thorac Cardiovasc Surg 2014;148(3):944-948 e941. doi: 10.1016/j.jtcvs.2014.05.050
8. Quint LE, Liu PS, Booher AM, Watcharotone K, Myles JD. Proximal thoracic aortic diameter measurements at CT: repeatability and reproducibility according to measurement method. Int J Cardiovas Imag 2013;29(2):479-488. doi: 10.1007/s10554-012-0102-9
9. Rudarakanchana N, Bicknell CD, Cheshire NJ, Burfitt N, Chapman A, Hamady M, Powell JT. Variation in maximum diameter measurements of descending thoracic aortic aneurysms using unformatted planes versus images corrected to aortic centerline. Eur J Vasc Endovasc Surg 2014;47(1):19-26. doi: 10.1016/j.ejvs.2013.09.026
10. Lu TLC, Rizzo E, Marques-Vidal PM, von Segesser LK, Dehmeshki J, Qanadli SD. Variability of ascending aorta diameter measurements as assessed with electrocardiography-gated multidetector computerized tomography and computer assisted diagnosis software. Interactive cardiovascular and thoracic surgery 2010;10(2):217-221. doi: 10.1510/icvts.2009.216275
11. Asch FM, Yuriditsky E, Prakash SK, Roman MJ, Weinsaft JW, Weissman G, Weigold WG, Morris SA, Ravekes WJ, Holmes KW, Silberbach M, Milewski RK, Kroner BL, Whitworth R, Eagle KA, Devereux RB, Weissman NJ, Gen TACI. The Need for Standardized Methods for Measuring the Aorta: Multimodality Core Lab Experience From the GenTAC Registry. JACC Cardiovasc Imaging 2016;9(3):219-226. doi: 10.1016/j.jcmg.2015.06.023
12. Burris NS, Hoff BA, Kazerooni EA, Ross BD. Vascular Deformation Mapping (VDM) of Thoracic Aortic Enlargement in Aneurysmal Disease and Dissection. Tomography 2017;3(3):163-173. doi: 10.18383/j.tom.2017.00015
13. Burris NS, Hoff BA, Patel HJ, Kazerooni EA, Ross BD. Three-Dimensional Growth Analysis of Thoracic Aortic Aneurysm With Vascular Deformation Mapping. Circ Cardiovasc Imaging 2018;11(8):e008045. doi: 10.1161/CIRCIMAGING.118.008045
14. Staring M, Klein S, Pluim JP. A rigidity penalty term for nonrigid registration. Med Phys 2007;34(11):4098-4108. doi: 10.1118/1.2776236
15. McLarty AJ, Bishawi M, Yelika SB, Shroyer AL, Romeiser J. Surveillance of moderate-size aneurysms of the thoracic aorta. Journal of cardiothoracic surgery 2015;10:17. doi: 10.1186/s13019-015-0220-2
16. Klein S, Staring M, Pluim JP. Evaluation of optimization methods for nonrigid medical image registration using mutual information and B-splines. IEEE Trans Image Process 2007;16(12):2879-2890.
17. Hoff BA, Pompe E, Galban S, Postma DS, Lammers JJ, Ten Hacken NHT, Koenderman L, Johnson TD, Verleden SE, de Jong PA, Mohamed Hoesein FAA, van den Berge M, Ross BD, Galban CJ. CT-Based Local Distribution Metric Improves Characterization of COPD. Sci Rep 2017;7(1):2999. doi: 10.1038/s41598-017-02871-1
18. Galban CJ, Han MK, Boes JL, Chughtai KA, Meyer CR, Johnson TD, Galban S, Rehemtulla A, Kazerooni EA, Martinez FJ, Ross BD. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. Nat Med 2012;18(11):1711-1715. doi: 10.1038/nm.2971
19. Moffat BA, Chenevert TL, Lawrence TS, Meyer CR, Johnson TD, Dong Q, Tsien C, Mukherji S, Quint DJ, Gebarski SS, Robertson PL, Junck LR, Rehemtulla A, Ross BD. Functional

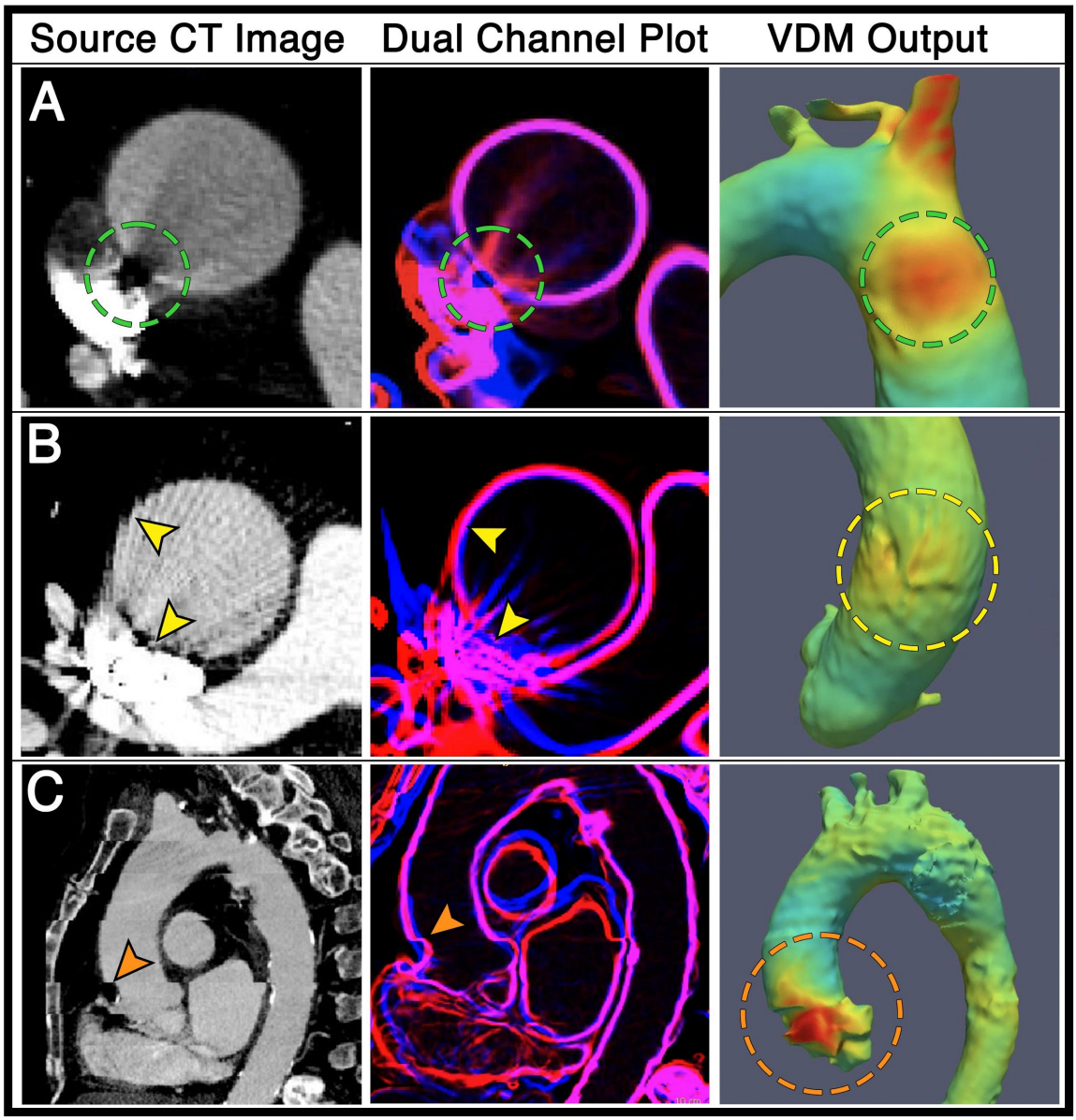
diffusion map: a noninvasive MRI biomarker for early stratification of clinical brain tumor response. Proc Natl Acad Sci U S A 2005;102(15):5524-5529. doi: 10.1073/pnas.0501532102
20. Tsien C, Galban CJ, Chenevert TL, Johnson TD, Hamstra DA, Sundgren PC, Junck L, Meyer CR, Rehemtulla A, Lawrence T, Ross BD. Parametric response map as an imaging biomarker to distinguish progression from pseudoprogression in high-grade glioma. J Clin Oncol 2010;28(13):2293-2299. doi: 10.1200/JCO.2009.25.3971
21. Hoff BA, Lemasson B, Chenevert TL, Luker GD, Tsien CI, Amouzandeh G, Johnson TD, Ross BD. Parametric Response Mapping of FLAIR MRI Provides an Early Indication of Progression Risk in Glioblastoma. Acad Radiol 2020. doi: 10.1016/j.acra.2020.08.015
22. Hoff BA, Kozloff KM, Boes JL, Brisset JC, Galban S, Van Poznak CH, Jacobson JA, Johnson TD, Meyer CR, Rehemtulla A, Ross BD, Galban CJ. Parametric response mapping of CT images provides early detection of local bone loss in a rat model of osteoporosis. Bone 2012;51(1):78-84. doi: 10.1016/j.bone.2012.04.005
23. Hoff BA, Toole M, Yablon C, Ross BD, Luker GD, VanPoznak C, Galban CJ. Potential for Early Fracture Risk Assessment in Patients with Metastatic Bone Disease using Parametric Response Mapping of CT Images. Tomography 2015;1(2):98-104. doi: 10.18383/j.tom.2015.00154
24. van Bakel TMJ, Burris NS, Patel HJ, Figueroa CA. Ascending aortic rupture after zone 2 endovascular repair: a multiparametric computational analysis. Eur J Cardiothorac Surg 2019;56(3):618-621. doi: 10.1093/ejcts/ezy458
25. Houben IB, Nama N, Moll FL, van Herwaarden JA, Nordsletten DA, Williams DM, Patel HJ, Figueroa CA, Burris NS. Mapping pre-dissection aortic wall abnormalities: a multiparametric assessment. Eur J Cardiothorac Surg 2020;57(6):1061-1067. doi: 10.1093/ejcts/ezz381

Supplementary Material:

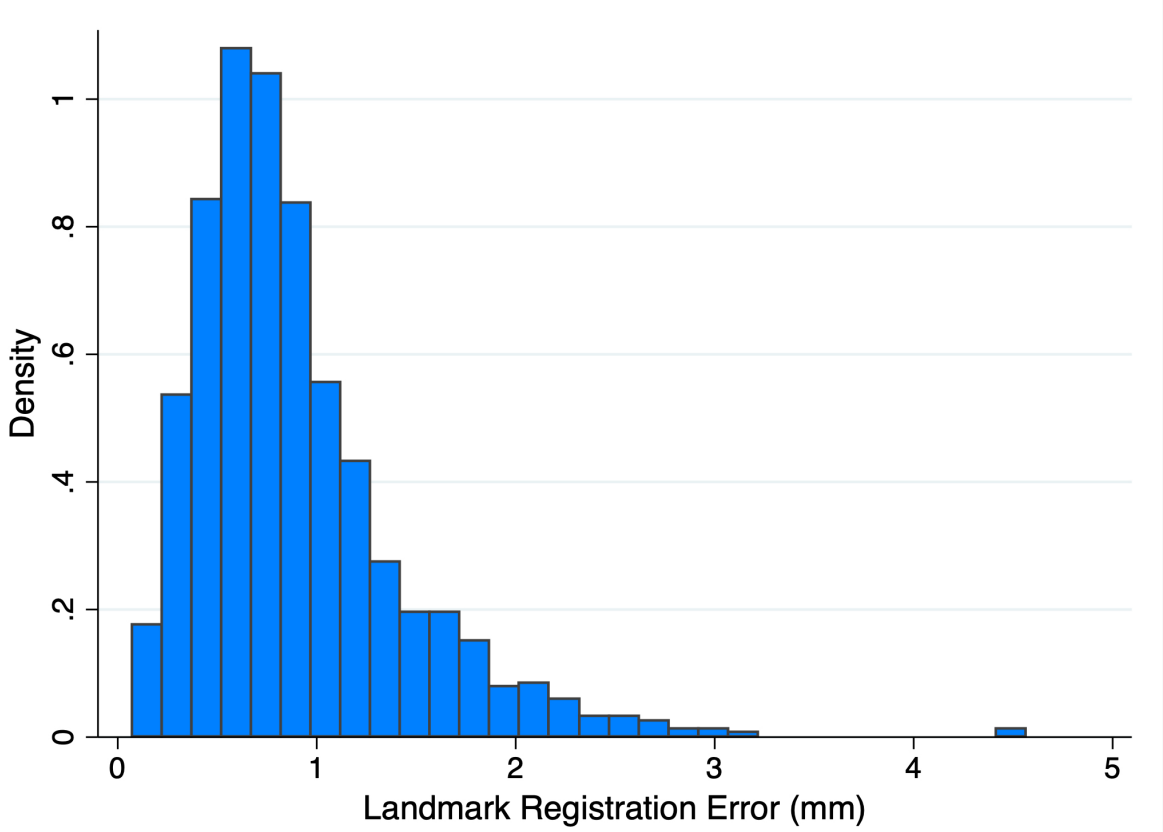
Quality Assurance (QA) Protocol

The steps included in our QA protocol included: 1) visual inspection of the fixed and moving image masks to confirm absence of segmentation errors, 2) inspection of the warped moving image after each sequential registration step using open-source transformix/elastix software (Utretch, Netherlands) to ensure appropriate transformation of the moving image towards to the fixed image target, 3) inspection of a dual-channel image created using a gradient magnitude filter to enhance the aortic boundary, with fixed and warped moving images colored red and blue respectively (i.e., area of image overlap display as purple), and lastly 4) confirmation that areas deformation on the colorized VDM surface plot correspond to areas of offset between the fixed image and warped moving image after rigid transformations before deformable transformation. All QA issues were resolved when possible (e.g.,

segmentation/copping errors), but if remediation was not possible then the analysis interval was considered failed, and the cause of failure was recorded.



Supplemental Figure 1: Representative examples of error cases identified by our quality assurance steps. Streak artifacts related to dense contrast material in the superior vena cava (SVC) results in distortion of the luminal boundary, misregistration on dual channel image and artifactual growth along the posterolateral ascending aorta on VDM (A). Similarly, streak artifact from metallic lead in the SVC results in mild but more diffuse distortion of the aortic boundary, with corresponding misregistration on dual channel images and mild intensity artifactual deformation on VDM (B). Stair-step artifact can be visualized on source CT image (orange arrowhead), which results in misregistration and erroneous deformation on VDM analysis (C).



Supplemental Figure 2: Histogram displaying the distribution of registration errors measured by manual placement of 199 unique landmarks (1,021 point-pairs). Median registration error was 0.77 mm (IQR: 0.54-1.10 mm, range: 0.07-4.57 mm).

The VDM technique Furthermore, considering that diameter measurements are performed in standard anatomical locations to minimize measurement variability, the extent and heterogeneity of aortic growth is not well assessed by current techniques.

The Vascular Deformation Mapping technique represents an attempt to overcome such limitations by harnessing the high-resolution and volumetric nature of CTA data sets in combination with deformable image registration techniques that can align medical images with submillimeter accuracy. Inter-rater agreement of Area Ratio values was high with limits of agreement for Area Ratio measurements found to be ±3% compared with the 5-78% range of Area Ratio changes measured by VDM in this clinical cohort.