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Temporal evolution of ascending aortic aneurysm wall stress predicts all-cause mortality

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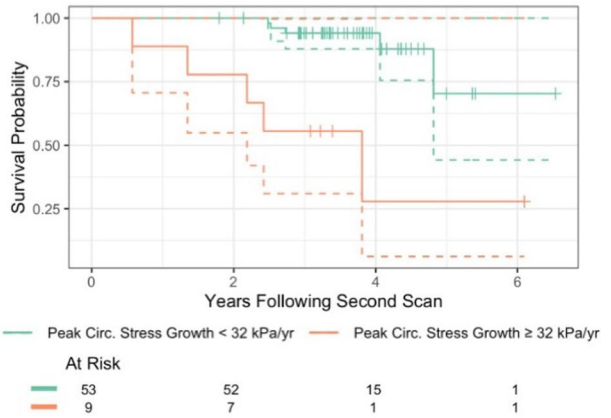
Temporal Evolution of Ascending Aortic Aneurysm Wall Stress Predicts All-Cause Mortality

Summary

The utility of temporal changes in geometric and biomechanical risk metrics for aTAA is unknown. We found that large increases in FEA-derived, *in vivo* peak circumferential stress over time, but not aortic diameter or length, was associated with increased all-cause mortality. These findings suggest a role for sequential surveillance of aneurysm biomechanics.

Evolution of peak circumferential wall stresses over time and subsequent mortality.



Legend: FEA, finite element analysis; aTAA, ascending thoracic aortic aneurysm

Abstract

OBJECTIVES: Diameter-based risk stratification for elective repair of ascending aortic aneurysm fails to prevent type A dissection in many patients. Aneurysm wall stresses may contribute to risk prediction; however, rates of wall stress change over time are poorly understood. Our objective was to examine aneurysm wall stress changes over 3–5 years and subsequent all-cause mortality.

†The first two authors contributed equally to this work.
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METHODS: Male veterans with <5.5 cm ascending aortic aneurysms and computed tomography at baseline and 3- to 5-year follow-up underwent three-dimensional aneurysm model construction. Peak circumferential and longitudinal wall stresses at systole were calculated using finite element analysis. Temporal trends were assessed by mixed-effects modelling. Changes in aortic wall stresses, diameter and length over time were evaluated as predictors of subsequent 3-year all-cause mortality by Cox proportional hazards modelling.

RESULTS: Sixty-two male veterans were included in the study. Yearly changes in geometric and biomechanical measures were 0.12 mm/year (95% confidence interval, 0.04–0.20) for aortic diameter, 0.41 mm/year (0.12–0.71) for aortic length, 1.19 kPa/year −5.94 to 8.33) for peak circumferential stress, and 0.48 kPa/year (−3.89 to 4.84) for peak longitudinal stress. Yearly change in peak circumferential stress was significantly associated with hazard of death—hazard ratio for peak circumferential stress growth per 10 kPa/year, 1.27 (95% CI, 1.02–1.60; $P = 0.037$); hazard ratio for peak circumferential stress growth $\geq$ 32 kPa/year, 8.47 (95% CI, 2.42–30; $P < 0.001$).

CONCLUSIONS: In this population of nonsurgical aneurysm patients, large temporal changes in peak circumferential stress, but not aortic diameter or length, was associated with all-cause mortality. Biomechanical stress and stress changes over time may be beneficial as additional risk factors for elective surgery in small aneurysms.

Keywords: Ascending thoracic aortic aneurysm • Type A dissection • Wall stress

ABBREVIATIONS

3D	Three-dimensional
ATAD	Acute type A dissection
aTAA	Ascending thoracic aortic aneurysm
CTA	Computed tomography angiography
DTA	Descending thoracic aorta
FEA	Finite element analysis

INTRODUCTION

Ascending thoracic aortic aneurysm (aTAA) is a well-established risk factor for acute type A dissection (ATAD), a highly fatal cardiovascular catastrophe with in-hospital mortality of 11–23% [1, 2]. The primary strategy to prevent ATAD in aTAA patients is elective surgical repair at a diameter $\geq$5.5 cm at most centres for patients without rapid growth, symptoms or a family history of connective tissue disorder or sudden death [3, 4]. The adequacy of the 5.5 cm absolute size threshold is controversial, with additional recommendations for intervention at 4.5–5.0 cm based on concomitant procedures and center experience, as well as alternative measures of relative aortic size.

ATAD is a complex haemodynamic and biomechanical phenomenon with associations beyond aortic diameter [4]. It has been estimated that up to 90% of aTAA patients fail to meet elective surgical repair guidelines prior to dissection [5, 6], reflecting the need to study aTAA dissection risk in a patient-specific and mechanistic manner. Finite element analysis (FEA) is a validated computational method which can assess failure modes and determine wall stresses using patient-specific geometry, material properties, and haemodynamic loading conditions. We previously showed that there is a significant overlap in wall stresses across different aortic diameters [7–9]. Moreover, prior FEA studies have implicated peak wall stresses at specific points in time as a biomechanical risk factor in aTAA [10–12]. However, little data exist on the evolution of aTAA biomechanics over time. The aim of this study was to investigate wall stress changes over a several-year period and subsequent clinical events in patients with <5.5 cm aTAA considered to be at low risk of dissection.

MATERIALS AND METHODS

Ethical statement

This study was approved by the Institutional Review Board (IRB) at the University of California San Francisco and San Francisco Veterans Affairs Healthcare System (IRB 13–10932, approved 8/19/2010). Written consent was waived for this retrospective study.

Data acquisition

Patients were identified from a cardiac surgery aortic clinic spanning July 2011 to September 2019 based on the following inclusion criteria: patients with aTAA $\geq$4.0 cm and <5.5 cm without rapid growth or connective tissue disorder, who had electrocardiogram-gated computed tomography angiography (CTA) scans at baseline and at a follow-up period of 3–5 years. For patients with more than 1 follow-up CT scan, the most recent available scan was used. Patient records were reviewed to obtain baseline demographic and clinical data, as well as the primary outcomes of incidence of surgical aTAA repair and all-cause mortality for up to 3 years following the 2nd scan. Patients were excluded if they had primarily aortic root or arch dilatation, prior surgical aortic valve replacement, or poor CTA image quality. De-identified images were used to reconstruct three-dimensional (3D) geometries of left ventricular outflow tract, aortic annulus, sinuses, sinotubular junction, ascending aorta, arch, and a portion of descending thoracic aorta (DTA). Maximum diameter in the diastolic phase was measured from CTA scans using centerline 3D reconstruction by a single radiologist blinded to stress results. Aortic length was measured as the sum of 50 straight centerline measurements from the aortic annulus to the innominate artery centerline as described previously [13].

Development of model for finite element analysis

FEA is a validated computational method for *in vivo* determination of aneurysm wall stress [14] which is the force per unit area applied to the aortic wall. Stress is defined by 6 directional components; of these, we focused on the circumferential and

longitudinal directions as they are likely implicated in the intimal tear that initiates aortic dissection. As previously described, we conducted FEA while taking into account the zero-pressure geometry [14]. To create a model for FEA of each aorta, CTA images were imported into MeVisLab (http://www.mevislab.de/home/about-mevislab). Aortic lumen segmentation was performed on planes reconstructed orthogonal to the long axis of the aorta, from left ventricular outflow tract to DTA. Segmented data were imported into GeoMagic (3D Systems, Morrisville, NC) for 3D surface reconstruction. Reconstructed surfaces were then imported into TrueGrid (XYZ Scientific Applications Inc., Pleasant Hill, CA) for FE mesh generation. Convergence studies were performed to determine optimal mesh density. The mesh was refined until the stress results varied $<1\%$ for 2 subsequent mesh refinements. Ultimately, 3 elements were used across the vessel wall thickness for each model, with $\sim$11 000 elements. These meshes were imported into LS-DYNA (LSTC Inc., Livermore, CA) for pressure-loading simulations.

Zero-pressure correction

ATAA geometry under *in vivo* physiologic blood pressure conditions was considered prestressed, which must be accounted for to accurately determine *in vivo* wall stress [14, 15]. We used a modified updated Lagrangian method to calculate a geometric configuration that when loaded to physiological stresses would match the prestressed aortic geometry [16].

Collagen-embedded hyperelastic material model

The aTAA wall was modelled as an incompressible hyperelastic material, comprised of non-collagen matrix reinforced with dispersed collagen fibres [17]. Details of the equations of the strain energy density function for the aTAA model have been described previously [7, 14, 18]. ATAA material properties were obtained from our previous aTAA biaxial stretch testing and specified separately for bicuspid and tricuspid aortic valve aneurysms [7, 12, 18, 19].

Finite element simulation

LS-DYNA was used to perform FE simulations with the specified collagen-embedded hyperelastic material model. Three-dimensional brick elements were used to reconstruct the aTAA wall. Wall thickness, derived from our prior aneurysm experimental studies [7, 8, 12, 18, 19]. was set at 1.75 mm. Translational motion was fixed proximally at left ventricular outflow tract, 20 mm below the annulus, to allow aortic root motion during the cardiac cycle and fixed distally at DTA to account for the physiologic effect of the ligamentum arteriosum, without constraints to rotational motion. Simulations were then performed by applying time-dependent arterial pressure to the aortic lumen, mimicking normal cardiac cycles. Physiologic blood pressure was assumed to be 120/80 mmHg for all patients to consistently compare wall stress magnitudes at the same pressure. Cardiac cycles had a duration of 800 ms, including a 300 ms increase from diastolic to systolic pressure followed by a 500 ms decrease to diastolic pressure.

Data analysis

Mechanical stresses on the aortic wall due to pressure loading were calculated. Analyses were performed at systole utilizing 99th-percentile wall stresses (hereafter referred to as peak stresses) to avoid artefacts arising from inhomogeneities in the mesh, as previously described. Peak stresses in the circumferential and longitudinal direction were calculated at the ascending aorta using LS-DYNA post-processing software. Reproducibility of wall stresses was tested with 2 independently reconstructing aTAA models and performing FEA as described above in a 20% subset of patients.

Statistical analyses were performed using R version 4.1.1 (http://www.r-project.org). Temporal changes in aortic diameter, length, and peak wall stresses were assessed using mixed-effects modelling using the lme4 package with a fixed effect for the number of years from the initial scan and a random intercept at the patient level to account for baseline differences and differences in the length of follow-up among patients.

Annual growth rates in aortic diameter, length, and peak wall stresses were assessed as continuous covariates in separate univariate Cox proportional hazards models of all-cause mortality in the 3 years following the 2nd scan using the survival and ggsurvplot packages. Normality of covariates was assessed with the Shapiro–Wilks test. As a sensitivity analysis, models were refit after winsorizing any non-normal covariates as follows: values below the 5th percentile were replaced with the 5th percentile value, and values above the 95th percentile were replaced with the 95th percentile value. For any covariates meeting the significance threshold in the preceding step, binary breakpoints were assessed by minimizing the *P*-value on the coefficient across a range of candidate thresholds. Cox proportional hazards models were fit for binary breakpoints from the 10th percentile (e.g. change in peak circumferential stress ≥ -48 kPa/year) to the 90th percentile (e.g. change in peak circumferential stress ≥ 40 kPa/year). The chosen breakpoint resulted in the Cox model with the minimum *P*-value. Linearized risks were calculated using the summary function. The proportional hazards assumption was assessed by plotting the Schoenfeld residuals against time. As there were no surgical aTAA repairs during the follow-up period, there was no need to account for the competing risk of repair. Median follow-up following the 2nd scan was estimated by applying the Kaplan–Meier method to the censored times.

Pearson's *r* was calculated for the correlations among annual growth rates in aortic diameter, length, and peak wall stresses. Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Clinical profiles

Sixty-two male patients had a mean (SD) age of 67 (7.7) years (Table 1). Common comorbidities at baseline were obesity (mean body mass index 30.0 [5.6]), former smoking history (35/62, 56%), hypertension (44/62, 71%) and hyperlipidemia (44/62, 71%). Rates of antihypertensive medication use ranged from 15/62 (27%) for diuretics to 22/62 (35%) for beta-blockers. Common haemodynamic risk factors at baseline were aortic

Table 1: Characteristics of the study population at baseline.

Characteristic	Overall
N	62
Age, mean (SD)	67 (7.7)
Male, *n* (%)	62 (100)
Race, *n* (%)	
Caucasian	47 (76)
African American	7 (11)
Alaska Native or Native American	2 (3.2)
Asian	1 (1.6)
Multiracial	1 (1.6)
Unknown	4 (6.5)
Comorbidities	
Body mass index, mean (SD), kg/m^2	30.0 (5.6)
Smoking history, *n* (%)	
Active	14 (23)
Former	33 (53)
Never	15 (24)
Hypertension, *n* (%)	44 (71)
Hyperlipidaemia, *n* (%)	44 (71)
Diabetes mellitus, *n* (%)	8 (13)
Chronic obstructive pulmonary disease, *n* (%)	15 (24)
Antihypertensive medications, *n* (%)	
ACEi/ARB	21 (34)
Beta-blocker	22 (35)
Diuretic	15 (24)
Calcium channel blocker	17 (27)
Haemodynamic factors	
Bicuspid aortic valve, *n* (%)	5 (8.1)
Aortic insufficiency, *n* (%)	17 (35)
Aortic stenosis, *n* (%)	3 (4.8)
Left ventricular ejection fraction, mean (SD), %	61 (8)
Mitral insufficiency, *n* (%)	6 (13)
Mitral stenosis, *n* (%)	0 (0)

Missing data were 2 (3.2%) for body mass index, 14 (23%) for valvulopathies and 20 (32%) for ejection fraction.

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

Table 2: Characteristics of the baseline and follow-up scans used for finite element analysis.

Characteristic	Overall
N	62
Time between 1st and 2nd scan (years), mean (SD)	4.0 (0.85)
Time between 1st and 2nd scan, *n* (%)	
3 years	21 (34)
4 years	24 (39)
5 years	17 (27)
Blood pressure at 1st scan (mmHg), mean (SD)	125 (14)/77 (10)
Blood pressure at 1st scan, *n* (%)	
≥130/80	32 (55)
≥140/90	8 (14)
Blood pressure at 2nd scan (mmHg), mean (SD)	125 (14)/75 (10)
Blood pressure at 2nd scan, *n* (%)	
≥130/80	21 (37)
≥140/90	10 (18)

Missing data were 4 (6%) for blood pressure measurements at the 1st scan and 5 (8%) for blood pressure measurements at the 2nd scan.

Table 3: Baseline values and annual growth rates for geometric and biomechanical features of ascending thoracic aortic aneurysms, as estimated by linear mixed-effects modelling.

Characteristic	Baseline (95% CI)	Annual growth rate (95% CI)
Aortic diameter (mm)	42.7 (41.6 to 43.7)	0.12 (0.04 to 0.20)
Aortic length (mm)	119 (116 to 122)	0.41 (0.12 to 0.71)
Peak circumferential stress (kPa)	428 (408 to 449)	1.19 (−5.94 to 8.33)
Peak longitudinal stress (kPa)	234 (221 to 246)	0.48 (−3.89 to 4.84)

insufficiency (17/48, 35%), mitral insufficiency (6/48, 13%) and bicuspid aortic valve (5/62, 8.1%).

Median follow-up between the 1st and 2nd scans was 4.0 (interquartile range, 3.2–4.6) years (Table 2). At the 1st scan, mean blood pressure was 125 (14)/77 (10) mmHg, with 32/58 (55%) exceeding 130/80 mmHg. At the 2nd scan, mean blood pressure was 125 (14)/75 (10) mmHg, with 21/57 (37%) exceeding 130/80 mmHg.

On reproducibility analyses in a 20% subset of patients ($n = 12$), the difference in results between 2 independent investigators was 3±(2)% in the circumferential direction and 1±(2)% in the longitudinal direction.

Annual growth rates

Based on linear mixed-effects models (Table 3), baseline values were 42.7 mm (95% confidence interval [CI], 41.6–43.7) for aortic diameter, 119 mm (116–122) for aortic length, 428 kPa (408–449) for peak circumferential stress, and 234 kPa (221–246) for peak longitudinal stress. Growth rates were 0.12 mm/year (0.04–0.20) for diameter, 0.41 mm/year (0.12–0.71) for length, 1.19 kPa/year (−5.94 to 8.33) for peak circumferential stress, and 0.48 kPa/year (−3.89 to 4.84) for peak longitudinal stress.

All-cause mortality

There was a median follow-up of 3.55 years (interquartile range, 3.11–4.31) following the 2nd scan. During this time, 10 patients died, of which 1 death was specifically attributed to a non-cardiac cause (pneumonia), while cardiac or aortic causes could not be ruled out in the other cases in the absence of autopsy. No patients underwent aortic repair.

Annual growth rates in aortic diameter, length, and peak wall stresses were initially assessed as continuous variables in Cox proportional hazards models of all-cause mortality following the 2nd scan (Table 4). Of these variables, only peak circumferential stress growth rate had a significant association with all-cause mortality (hazard ratio, 1.27 per 10 kPa/year; 95% CI, 1.02–1.60; $P = 0.037$). Peak longitudinal stress growth rate was not significantly associated with all-cause mortality (hazard ratio, 1.02 per 10 kPa/year; 95% CI, 0.74–1.42; $P = 0.88$). Annual growth rates in aortic diameter and peak longitudinal stress met statistical significance for non-normality. Winsorizing these covariates did not alter the significance of their respective Cox models.

The binary breakpoint minimizing the *P*-value for this association was 32 kPa/year, representing the 85th percentile peak circumferential stress growth rate in the study population (Fig. 1). The hazard ratio for peak circumferential stress growth ≥32 kPa/year was 8.47 (95% CI, 2.42–30; $P < 0.001$). Probabilities of death

Table 4: Univariate associations between annual growth rates in geometric and biomechanical aneurysm features and subsequent all-cause mortality, as estimated by Cox proportional hazards modelling.

Univariate model	Hazard ratio (95% CI)	*P*-value
Aortic diameter growth rate (continuous increment of 1 mm/year)	0.37 (0.04–3.86)	0.41
Aortic length growth rate (continuous increment of 1 mm/year)	1.23 (0.72–2.10)	0.45
Peak circumferential stress growth rate (continuous increment of 10 kPa/year)	1.27 (1.02–1.60)	0.037
Peak longitudinal stress growth rate (continuous increment of 10 kPa/year)	1.02 (0.74–1.42)	0.88
Peak circumferential + longitudinal stress growth rate (continuous increment of 20 kPa/year)	1.43 (0.98–2.09)	0.051
Peak circumferential stress growth rate ≥32 kPa/year (binary classification)	8.47 (2.42–30)	0.0008

The binary breakpoint for peak circumferential stress growth rate was found by minimizing the *P*-value across candidate thresholds (−48 to 39 kPa/year in 1-kPa/year increments). 32 kPa/year represents the 85th percentile peak circumferential stress growth rate in the study population.

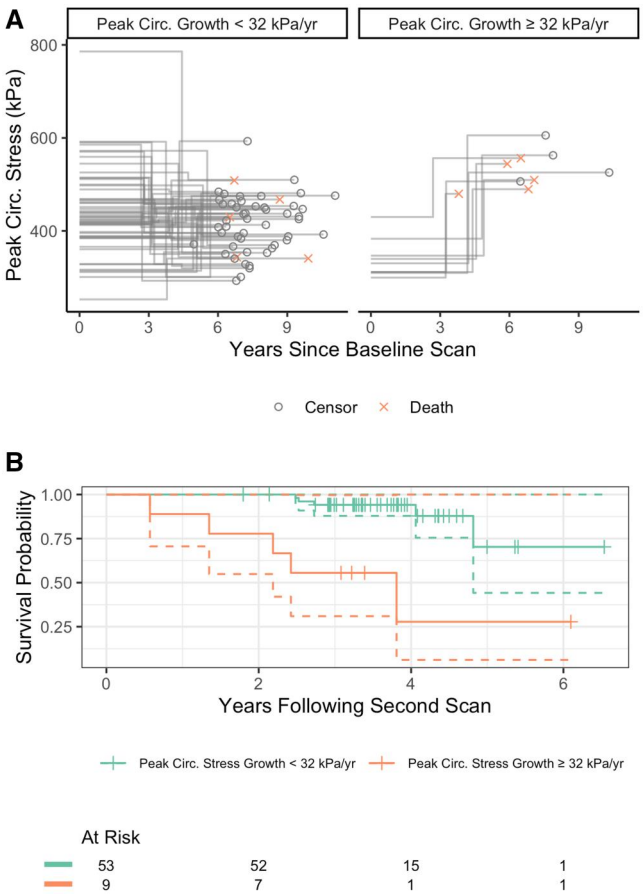

Figure 1: (**A**) Evolution of peak circumferential wall stresses over time and subsequent mortality. Vertical step-offs demonstrate the timing and magnitude of changes in peak circumferential wall stress during follow-up. Terminal points demonstrate the clinical event at the latest follow-up. (**B**) Kaplan–Meier curves showing freedom from all-cause mortality following the 2nd scan, stratified by change in peak circumferential stress between the 1st and 2nd scans. Dashed lines indicate the 95% confidence interval.

for patients with an increase in peak circumferential stress ≥32kPa/year were 0.66, 1.36 and 5.72% at 1, 2 and 3 years, respectively.

Correlations among annual growth rates

Among annual growth rates in aneurysm features (Fig. 2), peak circumferential stress growth rate had the highest correlation with peak longitudinal stress growth rate($r = 0.56$, $P < 0.001$), followed by aortic length growth rate ($r = 0.36$, $P = 0.004$). There was no significant correlation between peak circumferential stress growth rate and aortic diameter growth rate ($r = -0.04$, $P = 0.76$).

DISCUSSION

Current guidelines for prophylactic repair of aTAA are based on absolute diameter, diameter indexed to body surface area or height, cross-sectional area indexed to height, or large temporal increase in diameter [3]. Little prior work has examined temporal changes in other geometric and biomechanical features of aTAAs. In this study, we found that while growth rates in diameter, length, and peak wall stresses were modest overall, there was an association between elevated growth rates in peak circumferential stress and risk of subsequent mortality. Moreover, there was a poor correlation between peak circumferential stress growth rate and aortic diameter growth rate. Given that wall stresses are a complex function of local aortic geometry, these findings suggest that local aortic geometry may change independently of global aortic radius. These results are important for future ATAD risk stratification in nonsurgical aTAA patients and indicate that a population of patients may be at higher risk of mortality despite aneurysm size stability, although the relationship of this finding with dissection risk specifically must be explored further.

These findings are supported by a recent FEA study of patients with aortic diameters <50 mm who experienced ATAD, finding that areas of peak stress correlated with the initial location of the intimal tear and not the area of greatest aortic diameter [20]. Prior studies have reported that aortic wall strength tends to be greater in the circumferential rather than longitudinal direction and have implicated peak longitudinal stresses at a single time point in risk of dissection or death [10–12, 21–23]. Interestingly in this study, interval change in peak circumferential rather than longitudinal stress was associated with all-cause mortality. These findings are not necessarily in conflict, given the complex interplay among variations in local aneurysm geometry and changes in peak wall stress, as well as our finding that annual growth rates in peak circumferential and longitudinal stresses were strongly correlated. Future work may explore whether a combination of peak circumferential and longitudinal stresses at a particular point in time, as well as their recent temporal evolution, improves risk prediction for dissection or death.

To date, no studies have directly compared aTAA wall stresses within the same patient over multiple time points. One prior study of DTA aneurysms found that the need for surgery corresponded more strongly with increased peak stresses than with aortic diameter, although it was limited by a mean follow-up time of 17.5 months [24]. Our results further suggest that in patients with similar diameters, peak wall stress changes over a

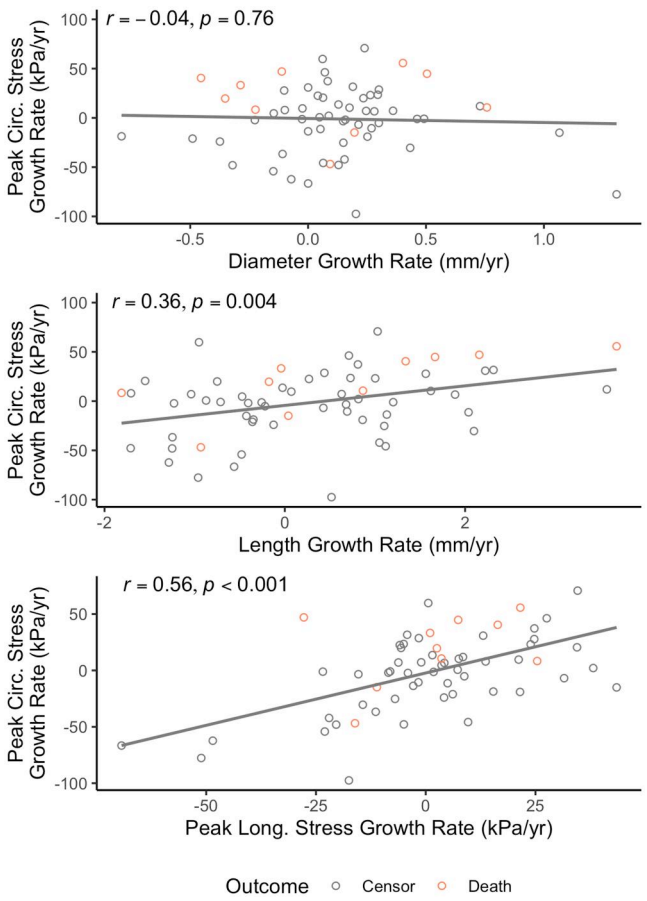

Figure 2: Correlation between annual peak circumferential stress growth rate and annual growth rates in aortic diameter, length and peak longitudinal stress. Pearson's *r* and its respective *P*-value are shown, as is the linear best-fit line. Outcomes refer to events following the 2nd scan.

period of 3–5 years may be associated with subsequent aTAA risk.

Understanding the temporal evolution of patient-specific aneurysm wall stresses is important to not only inform appropriate patient-specific intervals for aneurysm surveillance but also provide guidance in medical optimization and surgical decision-making. Uncontrolled hypertension is 1 modifiable risk factor strongly associated with aneurysm formation and dissection [25, 26]. One FEA study demonstrated that increases in applied blood pressure from 120 to 160 mmHg caused increases in wall stress across the whole aTAA surface, with the largest increases at areas with peak stress [27]. Furthermore, 1 prospective study using echocardiogram data from chronically hypertensive patients found that aTAA wall stresses decreased 33.0 (1.2)% when systolic pressure decreased from 160 to 110 mmHg, and 21.0 (0.7)% when systolic pressure decreased from 140 to 110 mmHg [28]. While that study did not use FEA, it suggests that wall stress change over time may help evaluate the effectiveness of antihypertensive treatment in aTAA patients.

Study limitations

One study limitation is the inclusion of only male and primarily Caucasian patients, reflective of patient demographics of the VA Healthcare system where we practice. Previous literature suggests male sex is a protective factor for aortic dissection risk [29]. However, male veterans have a high prevalence of aneurysm risk factors including hypertension, hyperlipidemia, obesity and smoking [25]. Accordingly, our results may reflect mixed effects and may not apply to more diverse populations or to women. Moreover, while this observational, retrospective study suggests an association between temporal changes in peak wall stresses and subsequent risk of mortality, causal interpretation should be avoided.

Notably, we did not directly observe aortic dissection or the need for urgent aneurysm repair during the study period, as we lacked reliable postmortem data. While some percentage of unspecified cardiac deaths in an aneurysm population is likely attributable to aortic events, there are few robust estimates of this trend. Future studies specifically designed for prospective aortic event adjudication are needed to assess whether patients with increasing wall stress despite stable aortic diameter may benefit from increased surveillance or earlier operative intervention. It is important to note the assumptions underlying FE modelling. In order to make wall stress a clinically translatable method of risk determination, we were limited by available clinical information (i.e. CTA imaging). Therefore, we could not account for inhomogeneities along the aortic wall and used averaged material properties as there are currently no means to determine material properties *in vivo*. Nevertheless, we have previously demonstrated that there is no significant difference in FEA-calculated stresses when using population-averaged material properties compared to patient-specific material properties [30]. As in other FEA studies, we did not account for the viscous effect in our model. While prior work has demonstrated that the hysteresis per cycle is stable and small [31], the viscous effect on the aorta may still be of importance in determining the true stress and strain during dynamic loading and unloading phases within the cardiac cycle.

While we investigated wall stresses via FEA, reductions in wall strength can influence dissection events. Fluid–structure interaction investigations to determine wall shear stress may be important to understand the role of wall strength in aTAA development and growth.

CONCLUSION

Patients with aTAA diameters under the threshold for surgical intervention are managed with clinical surveillance. In this study population, changes in aortic diameter, length, and peak wall stresses were modest over 3–5 years. However, death in the years following these changes was significantly associated with a large peak circumferential stress growth rate but not a diameter or length growth rate. Changes in local aortic geometry could explain the association between stress changes over time and the risk of mortality despite a stable global diameter. This finding warrants further prospective investigation to follow aortic geometry and stress over time with careful adjudication of adverse aortic events.

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Conflict of interest: None declared.

DATA AVAILABILITY

The data underlying this article cannot be shared publicly for the privacy of individuals who participated in the study. De-identified data will be shared on reasonable request to the corresponding author.

Author contributions

Siavash Zamirpour: Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing—original draft; Writing—review & editing. **Arushi Gulati:** Data curation; Formal analysis; Investigation; Methodology; Software; Visualization; Writing—original draft; Writing—review & editing. **Yue Xuan:** Data curation; Investigation; Methodology; Writing—review & editing. **Joseph R. Leach:** Conceptualization; Writing—review & editing. **David A. Saloner:** Conceptualization; Methodology; Resources; Writing—review & editing. **Julius M. Guccione:** Conceptualization; Methodology; Resources; Writing—review & editing. **Marko T. Boskovski:** Formal analysis; Visualization; Writing—review & editing. **Liang Ge:** Conceptualization; Formal analysis; Funding acquisition; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing—review & editing. **Elaine E. Tseng:** Conceptualization; Formal analysis; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing—review & editing.

Reviewer information

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