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Research article

Longitudinal analysis of thoracic aortic expansion in non-syndromic real-world patients

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ABSTRACT

Remodeling of the thoracic aorta is commonly seen and viewed as a precursor to an aortic aneurysm. However, while aneurysms have been shown to expand at a rate of approximately 1 mm annually, the expansion of the pre-aneurysmal aorta is poorly characterized, especially in relation to age, gender, and aortic size *per se*. We identified patients that had undergone echocardiography at least twice at a large university medical center. Diagnosis codes, medications, and blood test results were obtained from hospital records. Syndromic patients were excluded (e.g., Marfan's syndrome, bicuspid aortic valve). Final population comprised n = 24,928 patients (median age 61.2 years (inter-quartile range (IQR): 50.6–71.5); 55.8% males) that had undergone a median of 3 echocardiograms (2–4; range 2–27) during a median of 4.0 years (IQR: 2.3–6.2). Hypertension was present in 39.6% of patients and diabetes in 20.7%, median LV ejection fraction was 56.0% (IQR: 41.0–62.0). Aortic size measurements were analyzed in mixed models while clustering on individual patients. Mean expansion was determined for sinus of Valsalva as 1.93 (95% confidence interval; CI_{95}: 1.87–1.99) mm per decade, and for ascending aorta as 1.76 (CI_{95}: 1.70–1.82) mm per decade. Faster expansion was found in males, with larger aortic size, and younger age (p for interaction <0.05 for all). In conclusion, expansion of the thoracic aorta, in real world, non-syndromic patients, is slow and averages <2 mm per decade. This will help to inform management of this large patient group.

1. Introduction

Remodeling of the thoracic aorta is commonly seen in clinical echocardiography, partly due to demographic changes and an ageing population [1]. In a large majority of cases, degenerative changes occur secondary to replacement of elastin fibers with collagen, necrosis of smooth muscle cells and medial fibrosis. A smaller subgroup have congenital aortopathy due to e.g. Marfan's disease or bicuspid aortic valve, leading to early accumulation of mucoid extracellular matrix in the aortic media [2]. While the more common, degenerative form of aortic remodeling is typically slower than the syndromic form, changes that occur over time are irreversible and progressive. The risk of an acute aortic syndrome begins to rise once the aorta reaches an inflexion point at 6.0 cm [3]. This leads to the

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important question of how often patients need to undergo repeat imaging, which in turn depends on the expected rate of expansion. Registry data have shown that an aneurysmal aorta grows by an average of 1 mm/year [4]. Some authors have therefore suggested that surveillance scans should be performed as frequently as annually once the diameter reaches 4.0 cm [5,6]. However, the rate of expansion of the commonly encountered remodeled, but "pre-aneurysmal", thoracic aorta is poorly characterized in real-world patients. This is an important question as frequent imaging can be a driver of healthcare costs. We wished to understand better how rapidly the thoracic aorta enlarges in clinical practice and studied this question using longitudinal data from a population of patients followed at a large university medical center.

2. Methods

Subjects were identified through interrogation of the clinical echocardiography database at the Department of Adult Cardiology at National Heart Centre Singapore. Patients were considered for inclusion if they had undergone echocardiograms on at least 2 occasions during the period July 2, 2007–April 4, 2018, with an entry on both occasions for aortic size. This time frame was chosen as a single reporting system had been in operation in the clinical lab during this time, which enabled a standardized data export to be performed. We excluded patients with observation period <12 months (defined as time between first and last recorded aortic diameter) or any documented syndrome known to directly alter aortic size (including Marfan, Loeys-Dietz, Turner, William, and bicuspid aortic valve). While recruitment was agnostic as to the indication for the scan, co-morbidity data were obtained through exports of diagnosis codes entered in hospital records available from clinic visits and hospitalizations (ICD-10 codes recorded by hospital clinical coding unit), and all blood test results and medications prescribed both during clinic visits and hospitalizations were extracted. While this project was initiated as a departmental audit, institutional ethics guidance was sought prior to commencement. As per SingHealth Centralised Institutional Review Board recommendation, it did not require informed consent.

All echocardiograms were performed in strict accordance with the American Society of Echocardiography chamber quantification guidelines [7,8] including assessment of the diameter of the aorta which was made in end-diastole in a perpendicular plane to the aortic long axis, using the leading edge-to-leading edge convention. Intra- and interobserver variability for aortic diameters at our echocardiography lab, defined as coefficient of variability (standard deviation of differences divided by the mean; tested in 50 consecutive scans), is 3.6 and 4.3%, respectively [9].

Data were analyzed in mixed models, regressing aortic size on follow-up time while clustering on individual patients. Models related expansion rate to gender, age (at the time of the first scan), and aortic size. As the latter was measured repeatedly during the observation time of the study, it was characterized by regression to the mean. This was mitigated by using the *mean* of the available

Table 1
Characteristics of final study population.

Variable		Value
Demographics		
	Age, years	61.6 (50.6–71.5)
	Male sex, n (%)	13,901 (55.8)
	Height, cm	161.3 (11.5)
	Weight, kg	64.7 (15.2)
	BMI, kg/m^2	24.2 (21.4–27.4)
	BSA, m^2	1.7 (0.3)
Follow-up		
	Observation period, years	4.0 (2.3–6.2)
	Echocardiograms, n	3.0 (2.0–4.0)
Hemodynamic assessment		
	Systolic blood pressure, mmHg	132.3 (22.6)
	Diastolic blood pressure, mmHg	71.8 (12.1)
	Heart rate, beats per minute	73.0 (64.0–84.0)
Rhythm		
	Atrial fibrillation/flutter, n (%)	2391 (9.6)
Co-morbidities		
	Hypertension, n (%)	9876 (39.6)
	Diabetes mellitus, n (%)	5161 (20.7)
	Ischemic heart disease, n (%)	3241 (13.0)
Medications		
	ACEi/ARB, n (%)	6217 (24.9)
	Betablocker, n (%)	7793 (31.3)
	Calcium antagonist, n (%)	3671 (14.7)
	Thiazide diuretic, n (%)	592 (2.4)
	Loop diuretic, n (%)	3813 (15.3)
	Spironolactone, n (%)	1243 (5.0)
	Statin, n (%)	7425 (29.8)
	Aspirin, n (%)	5614 (22.5)
	Oral anticoagulant, n (%)	1733 (7.0)

Population data are tabulated for final study sample (n = 24,928). ACEi denotes angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area.

aortic size measurements for each patient when creating subgroups (instead of the *first* recorded size). Subgroups were formed such that continuous variables could be presented and interpreted in a clinically meaningful manner, while also maintaining similar power in individual subgroups. Age was therefore divided into 4 categories: <50 years, 50–59 years, 60–69 years, and ≥70 years. Similarly, aortic size was entered as covariate after dividing into 3 subgroups: <3.0 cm, 3.1–3.4 cm, and ≥3.5 cm. Exploratory analyses were performed to understand the role of age for cardiovascular risk factors by regressing these variables (e.g., diabetes mellitus and hypertension) on age in logistic regression. All data in this article are shown as mean (standard deviation) or median (inter-quartile range) as appropriate, unless otherwise indicated. All analyses were performed in R version 3.6.3.

3. Results

We identified a total of n = 78,462 patients who had undergone n = 186,672 scans during the selected time interval. There were n = 25,515 patients with observation time >365 days, of which n = 587 had been diagnosed with a syndrome (bicuspid aortic valve in n = 344, other syndromes in n = 247) leading to exclusion. Final study population therefore comprised n = 24,928 patients, who had undergone a median of 3 scans per patient (range: 2–27) over an observation period of 4.0 (2.3–6.2) years (Table 1). Subgroups created based on patient age were of similar size: age <50 years: n = 5933; 50–59 years: n = 5424; 60–69 years: n = 6386; ≥70 years: n = 7062. Investigations (shown in Table 2) showed that depressed LV ejection fraction (LVEF; <40%) was found in 23% of patients, a group characterized by a higher prevalence of diabetes (33.5% vs. 21.1% in patients with normal LVEF) and hypertension (46.3% vs. 43.0% in patients with normal LVEF). Female patients (44%) were characterized by higher age (61 vs. 58 years), less hypertension (36.6 vs. 42.0%) and less diabetes (18.4 vs. 22.5%). Cardiovascular risk factors including diabetes and hypertension were more commonly diagnosed in higher age groups: prevalence of diabetes was 9.5% in patients aged <50 years vs. 20.2% in patients aged >65 years, and prevalence of hypertension was similarly 16.8% in patients aged <50 years vs. 48.6% in patients aged >65 years. Each 1-decade increment in patient age was associated with an increase in the odds of diabetes of 1.26 (95% confidence interval; CI_{95}: 1.24–1.29) and an increase in the odds of hypertension of 1.44 (CI_{95}: 1.42–1.47).

Aortic size was larger with higher age throughout middle-age but appeared to stabilize in the elderly. Sinus of Valsalva (SoV) size in patients aged <50 years was 3.0 (0.4) cm vs. 3.1 (0.4) cm in patients aged 50–59 years vs. 3.2 (0.4) cm in patients aged 60–69 years, but size was stationary in patients aged ≥70 years: 3.2 (0.4) cm. Ascending aortic size followed the same pattern: size was 2.9 (0.4) cm in patients aged <50 years vs. 3.2 (0.4) cm in patients aged 50–59 years vs. 3.4 (0.4) cm in patients aged 60–69 years, but remained stationary in the highest age strata: age ≥70 years: 3.4 (0.4) cm ($p < 0.001$). Estimates of the rate of expansion is presented for subgroups in a forest plot shown in Fig. 1 and are also cross-tabulated in Supplemental Tables 1–2.

Rate of SoV expansion was 1.93 mm/decade (CI_{95}: 1.87–1.99). Males expanded faster than females: 2.12 mm/decade (CI_{95}: 2.04–2.21) vs. 1.66 mm/decade (CI_{95}: 1.58–1.74; p for interaction <0.001). Patients with large SoV diameters progressed faster: 1.76 mm/decade at diameter <3.0 cm (CI_{95}: 1.66–1.86) vs. 1.88 mm/decade at diameter 3.0–3.4 cm (CI_{95}: 1.79–1.97) vs. 2.11 mm/decade at diameter ≥3.5 cm (CI_{95}: 1.98–2.24; p for interaction <0.001). Rate of expansion was slower with higher age: 2.02 mm/decade at age <50 years (CI_{95}: 1.91–2.14) vs. 2.01 mm/decade at age 50–59 years (CI_{95}: 1.89–2.13) vs. 1.89 mm/decade at age 60–69 years (CI_{95}:

Table 2
Clinical investigations.

Variable		Value
Echocardiography		
	Inter-ventricular septal diameter, cm	1.0 (0.9–1.1)
	Left ventricular end-diastolic diameter, cm	4.8 (4.3–5.2)
	Left ventricular posterior wall thickness, cm	1.0 (0.8–1.1)
	Left ventricular mass, g	164.5 (130.1–209.2)
	Left ventricular ejection fraction, %	56.0 (41.0–62.0)
	Trans-mitral E-wave, m/s	0.9 (0.3)
	Trans-mitral A-wave, m/s	0.8 (0.3)
	Tricuspid annular plane systolic excursion, cm	2.2 (0.5)
	Sinus of Valsalva, cm	3.1 (2.8–3.3)
	Size <3.0, n	10,470
	Size 3.0–3.4, n	10,355
	Size ≥3.5, n	4103
	Sino-tubular junction, cm	2.4 (2.2–2.7)
	Ascending aortic diameter, cm	3.2 (2.9–3.5)
	Size <3.0, n	8208
	Size 3.0–3.4, n	10,609
	Size ≥3.5, n	6111
Blood test results		
	Hemoglobin, g/dL	13.1 (2.1)
	Creatinine, μmol/L	85.0 (68.0–107.0)
	Glucose, mmol/L	5.8 (5.1–7.6)
	HbA1c, %	6.1 (5.6–7.2)
	Total cholesterol, mmol/L	4.8 (1.2)
	LDL-cholesterol, mmol/L	2.9 (1.0)

Clinical investigations including echocardiography and blood test results are tabulated. LDL denotes low density lipoprotein.

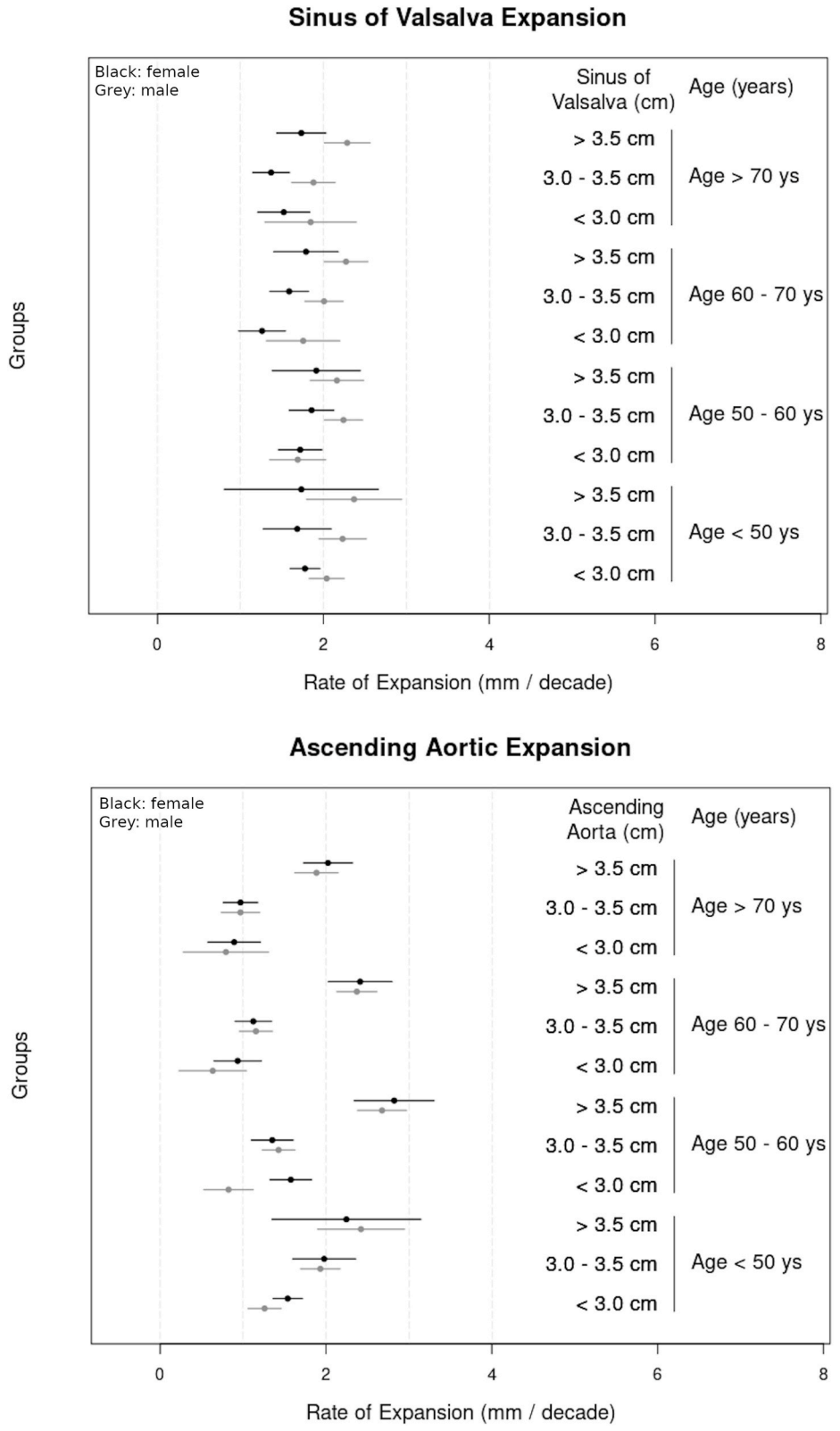

Fig. 1. Estimated thoracic aortic expansion in patient subgroups. Upper panel shows sinus of Valsalva, lower panel shows ascending aorta. Females are shown in black and males in grey.

1.77–2.00) and 1.81 mm/decade at age ≥70 years (CI_{95}: 1.69–1.93; *p* for interaction <0.001).

Rate of expansion for the ascending aorta in the entire population was 1.76 mm/decade (CI_{95}: 1.70–1.82). Males expanded faster than females: 1.82 mm/decade (CI_{95}: 1.73–1.90) vs. 1.68 mm/decade (CI_{95}: 1.60–1.77; *p* for interaction = 0.02). Groups characterized by larger ascending aortic diameter progressed faster: 1.26 mm/decade at diameter <3.0 cm (CI_{95}: 1.16–1.36) vs. 1.29 mm/decade at diameter 3.0–3.4 cm (CI_{95}: 1.21–1.37) vs. 2.29 mm/decade at diameter ≥3.5 cm (CI_{95}: 2.18–2.41; *p* for interaction <0.001). Ascending aorta also exhibited a slower rate of expansion at higher age: 1.84 mm/decade at age <50 years (CI_{95}: 1.72–1.95) vs. 1.89 mm/decade at age 50–59 years (CI_{95}: 1.77–2.01) vs. 1.72 mm/decade at age 60–69 years (CI_{95}: 1.60–1.84) and 1.56 mm/decade at age ≥70 years (CI_{95}: 1.43–1.68; *p* for interaction <0.001).

4. Discussion

The present study was designed to evaluate thoracic aortic expansion in a longitudinal dataset comprising a relatively unselected population of non-syndromic all-comers at a large university hospital cardiology department. Mean rate of expansion was more rapid at the level of the SoV at 1.9 mm per decade vs. 1.8 mm at the level of the ascending aorta. Expansion was more rapid in patients with larger aortic size, and fastest in younger patients.

The present analysis was based on longitudinal data, in contrast to earlier studies which have predominantly been cross-sectional in design: patients have typically been studied once and the rate of expansion has been inferred from estimates obtained by regressing aortic size on patient age. Daimon et al. studied n = 700 healthy Japanese volunteers in the JAMP cohort, which was recruited to establish normal limits for echocardiography in Asians, and described a 1–2 mm larger SoV for each 1-decade difference in age especially in males (e.g. mean SoV diameter in subjects aged 60–69 years vs. 70–79 years was 3.3 vs. 3.5 cm, respectively) [10]. Son et al. studied a small population of n = 112 self-reportedly healthy individuals of an average age of 44 years, and found a difference of up to 1.6 and 3.1 mm per 10-year increment in age for SoV and ascending aorta, respectively (e.g. age groups 40–49 vs. 50–59 years: 2.59 vs. 2.90 cm) [11]. Mirea et al. described aortic diameters of a population of n = 500 patients referred for clinical echocardiography. Each 1-decade change in age was associated with a difference in diameter of 0.7 mm and 1.1 mm of the SoV and ascending aorta, respectively [12]. Vriz et al. studied n = 422 healthy volunteers and found that higher age groups (divided into bins approximately 10 years wide) exhibited progressively larger aortic size: 1.3 mm and 1.6 mm increments for SoV and ascending aorta, respectively [13]. Data from the NORRE cohort, where healthy subjects were enrolled to establish normal ranges for echocardiographic measurements (n = 704) exhibited differences for a 10-year increment in age of approximately 0.7 mm and 1.2 mm for SoV and ascending aorta, respectively [14]. Lastly, a population of n = 575 healthy middle-aged adults studied by Bossone et al. exhibited a difference of 1.6 mm for each 10-year increment in age [15].

At a rate of expansion of 1.8–1.9 mm per decade (ascending aorta and SoV, respectively) the expansion that occurred in the present population is more rapid than several of the afore-mentioned cross-sectional estimates. However, while cross-sectional analyses are relatively less difficult to perform and analyze, there are several reasons why these may not compare directly to longitudinal data. Concretely, as cross-sectional analysis typically only includes the first scan for each patient, subsequent expansion is hidden from the observer, and rapid changes may not be well represented. This can be especially problematic if the case-mix is heterogenous and differs e.g. between younger and older subjects (as seen in the present study: diabetes and hypertension were both more common at higher age), as this will distort estimates when regressing aortic size on age in aggregate. Moreover, cross-sectional analyses of real-world data may be dominated by patients who are scanned only once and thus inherently less likely to expand rapidly.

In methodological terms, a key consideration when comparing longitudinal and cross-sectional analyses is also the assumption that the expansion process is linear [16]. Interestingly, non-linearities were noted in the present dataset most prominent of which was a deceleration of expansion at higher age. This phenomenon would invalidate attempts at regressing size on patient age in a linear manner during the full, multi-decade age range of the population, raising important questions as to the validity of some earlier, cross-sectional growth estimates. As for the present study, a mixed model was used which arguably also does involve an assumption of linearity of growth trajectory. However, at a median observation period of 4 years, the inflexion point in the elderly is unlikely to invalidate the key findings of this report. The deceleration with higher age is an interesting finding *per se* which has been described in some earlier studies where size was progressively larger throughout middle-age, but higher age groups were characterized by stabilization [17] or even seemingly smaller aortic diameters [18]. Analyses of the biomechanics of the thoracic aorta have shown the importance of the arrangement and mechanical properties of collagen fibers when these stretch within the wall of the enlarging aorta: altered alignment of collagen fibers and gradual uncrimping from their original wavy phenotype are both believed to lead to a greater proportion of the load being borne by collagen in the aortic wall, limiting its further distensibility [19].

Few published reports exist where the size of the thoracic aorta has been evaluated longitudinally over time. Nwabuo reported data from a total of n = 2933 individuals enrolled in the CARDIA cohort who were scanned twice, 20 years apart. Expansion of the ascending aorta occurred during these 2 decades of follow-up in males and females from 29.9 to 33.3 cm (males), and from 26.1 to 28.7 cm (females). This corresponds to an ascending aortic expansion rate of 1.7 vs. 1.3 mm/decade in males and females, respectively, which is relatively close to the expansion found in the present population (1.8 vs. 1.7 mm/decade in males and females, respectively) [20]. In contrast, Lam et al. studied n = 4542 community-dwellers in the Framingham Offspring Study over a 16-year period. The mean rate of expansion of the ascending aorta during follow-up was found to be only 0.7 and 0.9 mm/decade, in females and males, respectively [21]. While the results of the present study were thus closer to the estimates reported in CARDIA, the present study is not directly comparable to either. Firstly, there were large differences in age (Framingham Offspring Study: mean age 45.5 years, CARDIA: median age 30 years, whereas mean age in the present study was 61.1 years). Secondly, both earlier studies were performed in populations with a lower frequency of key co-morbidities (Framingham Offspring Study: 3.6% diabetics, CARDIA: 0.4% diabetics,

whereas present study comprised 19.6% diabetics). As such, while the analyses of relatively healthier subjects in Framingham Offspring Study and CARDIA do provide a useful characterization of the thoracic aortic of a relatively healthy population, it may be argued that the expected rate of expansion in clinical practice needs to be defined based on longitudinal real-world data. As earlier reports have not clearly answered the important question of how rapidly the aorta expands in the real world, the purpose of the present project was to fill that gap. The results of the present report do not support the notion that patients at the pre-aneurysmal stage should be brought back annually for follow-up scans, but instead suggest that repeat imaging can be performed considerably less frequently than that.

As with any real-world analysis, the present study has its limitations. Firstly, descriptive statistics can be incompletely known in real-world datasets. However, data shown in tables are provided primarily to provide readers with an understanding of the characteristics of the study population and only variables deemed to be robust to e.g. misclassification error were used to create subgroups in models (age, gender, and aortic size). Owing to regression to the mean of aortic size measurements, the relationship between size and expansion rate was analyzed using the mean of all available measurements for each case, which can influence allocation of patients to subgroups. However, at a median observation period of approximately 4 years, the expected change in aortic size during the study is less than 1 mm. As the bin width of size categories was 5 mm, the impact of erroneous categorization is therefore likely to be limited: any noise introduced by this methodology would have been addressed by the power afforded by the population size, which was substantially larger than other, similar studies published earlier.

5. Conclusion

We conducted a large, longitudinal study of thoracic aortic growth in out-patients followed at a university medical center. Mean expansion was 1.9 mm/decade at the level of the SoV, and 1.8 mm/decade at the level of the ascending aorta. More rapid expansion was noted in males, younger patients, and those with larger aortic size.

Author contribution statement

Josiah Ng: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

See Hooi Ewe and Anders Sahlén: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Ju Le Tan and Zee Pin Ding: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Victor Chao, Lieng-Hsi Ling and Kenny YK Sin: Analyzed and interpreted the data; Wrote the paper.

Terrance SJ Chua: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

The authors do not have permission to share data.

Additional information

Supplementary content related to this article has been published online at [URL].

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15823.

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