Original Article

Gender-specific differences in aortic sinus curvature during aging: an anatomical and computational study

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Abstract

Introduction: Our goal was to investigate the potential impact of aortic sinus wall curvature on the risk for type A aortic dissection.

Methods: We measured the curvature and carried out histological tests of the aortic noncoronary sinus in 46 patients who did not die from cardiac disease. Based on observed curvature values, we investigated the mechanical stress in the aortic root using finite element analysis.

Results: Sinus curvature was found to experience a more than fourfold increase with age in males and reached the higher, age-independent values measured in females by age 65. The histological tests revealed that degenerative alterations did not significantly increase with aging in either gender, although fibrosis did in older women. Finite element analysis illustrated that the risk for a circumferential tear to occur was smallest when sinus curvature was highest.

Conclusions: We established significant gender-specific disparities in the aortic root during aging: while aortic sinus curvature was high in females throughout their lives, it experienced a more than fourfold increase in the lifetime of males, matching values in females only by age 65. Our mechanical analyses confirmed the overall potential protective role of higher sinus wall curvature with respect to type A aortic dissection, and geometry alone could not account for the known gender difference in aortic dissection prevalence. © 2009 Elsevier Inc. All rights reserved.

Keywords: Aortic dissection; Sinus curvature; Gender specific; Mechanical stress

1. Introduction

Most aortic dissections are proximal with a circumferentially oriented tear, which points to a longitudinal breakdown of the aortic tissue [1] and suggests an increase in longitudinal stress and/or a decrease in tissue strength as possible triggers [2]. Indeed, based on a mechanical analysis of the ascending aorta and supra-aortic vessels with simplified aortic root geometry, we previously showed that the aortic root movement was a source on par with hypertension for longitudinal stress in the ascending aorta [3].

Interestingly, proximal aortic dissections are observed predominantly in men aged 60 to 70. In fact, the prevalence of aortic dissection is two to five times lower in females than in males [1,4]. The underlying reasons for such different incidence rates have not been clarified. It was therefore timely to investigate possible gender-specific disparities in the aortic root at different ages. Aortic dilatation and increased aortic root size are well-recognized phenomena associated with aging in both sexes [5,6] and, thus, are nonspecific. Instead, we examined two previously unstudied parameters, namely, the curvature present in the aortic sinus and the amount of degenerative alterations at this location in patients who did not die from cardiac disease. We hypothesized that males would experience an age-dependent increase in curvature and fibrosis, whereas females would not experience a similar increase.

Methods

We performed a retrospective analysis of patients who underwent thoracic aorta surgery at the University of Ottawa Heart Institute (Ottawa, Canada) with a follow-up time greater than 1 year and who did not die of any cardiovascular event during this period. Patients were divided into two age groups: group 1: age ≤65 years, and group 2: age >65 years.

Results

Sinus curvature was found to experience a more than fourfold increase with age in males and reached the higher, age-independent values measured in females by age 65. The histological tests revealed that degenerative alterations did not significantly increase with aging in either gender, although fibrosis did in older women. Finite element analysis illustrated that the risk for a circumferential tear to occur was smallest when sinus curvature was highest.

Conclusions

We established significant gender-specific disparities in the aortic root during aging: while aortic sinus curvature was high in females throughout their lives, it experienced a more than fourfold increase in the lifetime of males, matching values in females only by age 65. Our mechanical analyses confirmed the overall potential protective role of higher sinus wall curvature with respect to type A aortic dissection, and geometry alone could not account for the known gender difference in aortic dissection prevalence. © 2009 Elsevier Inc. All rights reserved.
disease. Such location was chosen owing to its proximity to the sinotubular junction (STJ), a few centimeters above which most dissection tears are observed [1]. We used finite element modeling to further investigate how the aortic sinus wall curvature may influence the mechanics of the transmission of the pull exerted by the heart on the ascending aorta through the aortic root.

2. Methods

The study material consisted of 46 consecutive hearts with attached aortas from patients autopsied at the Ottawa Hospital Civic campus. All male (n=29) and female patients (n=17) died of noncardiac causes. The patients were 30 to 99 years old. The breakdown of patients in four age groups was as follows: 25 to 44 years (n=5), 45 to 64 years (n=13), 65 to 84 years (n=18), and 85 to 104 years (n=10). No patient had significant cardiac valve disease. There were no cases of congenitally bicuspid aortic valve, as well as of ascending aortic aneurysm or aortic dissection.

All materials were de-linked from patient identifiers, except patient age and gender. Histological sections were all taken by the same individual (J.P.V.) after the heart tissues had been fixed in 10% neutral buffered formalin for under a year. The longitudinal sections were cut through the noncoronary cusp, its adjacent left ventricular myocardium, the adjoining aortic sinus, and a short segment of the ascending aorta after the STJ. This location was chosen as it has been postulated that it might be where changes related to hemodynamics might be most marked [7]; furthermore, the coronary ostia might have an impact on wall curvature changes as vessel origins exhibit reinforced vessel wall architecture like other arterial bifurcation [8].

2.1. Histology

All the sections were processed and embedded in paraffin while minimizing handling that might affect wall curvature. One set of 4-μm slides was prepared and stained with hematoxylin, phloxine, and saffron (HPS; a trichrome stain) while another set was stained with Movat pentachrome for evaluation of elastic tissues and ground substance accumulation. All the samples and controls were done as a batch at the same time for consistency.

The sections were graded for degenerative changes in the sinus and ascending aorta in a graded scheme similar to that established by Schlatmann [9]. The aorta was evaluated for the following parameters: medial ground substance (glycosaminoglycan) accumulation, medial fibrosis, medial elastic fragmentation, and true medionecrosis (medial smooth muscle eosinophilia and loss of nuclei) (see the Appendix for details). An overall ranking was made for each sample by adding the four individual histology scores (ranging from 0 to 4), and a combined histology score was obtained from 0 to 16.

2.2. Wall curvature and thickness measurements

Forty-six individual sections (one per patient) such as those shown in Fig. 1 were scanned at high resolution (1200 pixels per 25.4 mm) into a computer and processed by the same individual (Ti.M.). Samples where the aortic wall was broken during preparation of the section were excluded from the analysis. By image processing using a program coded into MATLAB software (The MathWorks, Massachusetts, USA), 30 consecutive points were manually overlaid on the inner wall of the noncoronary sinus (Fig. 2). For consistency between the samples, the first point was chosen as the location where a prolongation of the inner wall of the left ventricular outflow tract would meet the aortic side of the leaflet. The last point reached into the ascending aorta, past the STJ. Since much less curvature was present above the STJ, the overall measure of curvature was not appreciably affected by where exactly the last point was drawn. Once the points were chosen, a cubic spline was fitted through them, and the ratio s/c of the spline curvilinear length s to the straight distance c between the first and last points was calculated. This ratio was used as a dimensionless descriptor of the aortic sinus wall curvature [10]. Two additional points were placed in the images to measure the sinus base wall thickness.

2.3. Finite element analysis

To investigate the mechanical relevance of sinus wall curvature, we used the following approach. Finite element models of the aortic root were constructed based on samples with various degrees of curvature and pressurized to physiological mean arterial pressure (MAP) levels. Since the diameters of the unpressurized aortic roots were not known (nor were their in vivo diameters), it was assumed, for comparison purposes, that the measured curvatures could have been found under physiological pressures. This also allowed for simplified linear material properties to be used. A longitudinal stretch corresponding to the physiological pull exerted by the heart on the aorta was applied, and the longitudinal and circumferential stresses were analyzed in the aortic sinus wall.

The modeling details were as follows. The contours of the sinus wall from three samples with low, medium, or high curvature levels [defined as log(s/c)=0.05, 0.10, and 0.15, respectively] were digitized over a 10-mm height and recreated in finite element program ANSYS 10.0 (ANSYS, Virginia, USA) without scaling. By rotating the contours along the assumed axis of the aortic root, simplified axisymmetric models of the aortic root were obtained, with a physiologically representative diameter of 24 mm at the base of the sinus (Models A-1 to A-3). Another diameter of 30 mm was also used for comparison purposes (Model B). The geometries were discretized into more than 10,000 quadrilateral (ANSYS element type...
Plane 42) axisymmetric elements. Fig. 3 shows a cross section of one model and the type of mesh used within the section. The material properties for the aortic tissue were idealized into an isotropic, linear elastic material, with an elastic modulus of 3 MPa and a Poisson’s ratio of 0.49 representing the near incompressibility of blood vessel tissue (Model A-2). These simple material properties have the capability to produce physiologically correct aortic wall deformations under systemic pressure [3]. Additional models were run with the elastic modulus taken as 1.5 MPa (typically younger, more compliant wall, Model A-1) and 6 MPa (typically older, less compliant wall, Model A-3) to contrast the respective roles of curvature and wall stiffness. Models A and B were subjected to a MAP of 100 mmHg (100 mmHg= 0.0133 MPa), while Model C, otherwise similar to Model A-2, was subjected to a MAP of 80 mmHg to illustrate the influence of blood pressure. The longitudinal stretch of 10% applied to all models was derived from our previous study [3] where an aortic root displacement of 8.9 mm was implemented as measured in healthy subjects [11]. Geometric nonlinear effects induced by noninfinite-simal displacements and deformations were included in the analyses.

2.4. Statistical analysis

The results from histology and wall measurements were analyzed for statistical comparisons between groups at the 0.05 confidence level using SPSS 12.0 (SPSS, Illinois, USA). The normality of the distributions was evaluated using the Lilliefors test. For normally distributed results, the t test, ANOVA, and Bonferroni post hoc test were used to delineate significant changes between groups; the
Kolmogorov–Smirnov two-sample test and the Kruskal–Wallis test were used for nonnormal distributions.

3. Results

3.1. Histology

Fig. 1 shows representative stained sections of the noncoronary site of the aortic root. The combined histology score is presented in the top panel of Fig. 4. The distributions of all histology scores, both individual and global, were not statistically normal. Overall, the absence of cardiovascular pathology in the patients considered was reflected by low combined histology scores, with a median and mean of 5.0 and a maximum value of 8 in one sample. There was no significant difference between groups within males and females and between males and females altogether.

Individually, ground substance accumulation, elastic fragmentation, and medionecrosis did not show significant changes between groups or between genders. However, while fibrosis in males did not exhibit any significant difference between age groups, fibrosis in females did, showing an increase with age (Fig. 4, bottom panel).

3.2. Wall curvature and thickness measurements

The ratio \( s/c \) describing the noncoronary sinus wall curvature did not have a normal distribution, but \( \log(s/c) \) did. Therefore, the latter definition of curvature was retained for this study.

Fig. 2. Screenshot illustrating the technique used for measurement of sinus wall curvature. Thirty points were manually positioned, and then a cubic spline was fitted through them to compute the curvilinear length and compare it to the straight distance between the first and last points.

Fig. 3. Cross-sectional details of the finite element model for one sample from a 38-year-old male. The total height of the axisymmetric model is 10 mm. For clarity, the mesh represented is four times bigger than that used for computation, in which the longest element side was equal to 0.025 mm. A mesh sensitivity analysis confirmed that the results did not change significantly if the mesh was further refined.
The top panel of Fig. 5 illustrates the overall more than fourfold increase in curvature with age in males, while curvature remained similar in females. Indeed, the four age groups in males did not have an equal curvature, while no significant difference was present between age groups in females. The curvature in females was higher than in males earlier in life (t test, \(P \approx .02\) between male and female age groups 25–44). However, males’ curvature caught up between ages 65 and 84 and increased even further afterwards, as reflected by significant mean differences between age groups 25–44 and 85–104 and between age groups 45–64 and 85–104 (Fig. 5, top panel). More evidence of changes in sinus wall curvature with age in males was found by regression analysis, which yielded a coefficient of correlation \(R^2 = .37\) between log\((s/c)\) and age (Fig. 6).

The bottom panel of Fig. 5 presents the measurements of the sinus base wall thickness, with an average of 0.8±0.2 mm. No statistically significant differences could be established between age groups, either in males or in females.

### 3.3. Finite element analysis

Upon loading, the sinus walls stretched and moved outward by a few millimeters, depending on the model parameters. Fig. 7 shows the results of the mechanical analysis for longitudinal and circumferential stresses within the sinus wall of the control model (Model A-2), for the different curvature levels. A global reduction in longitudinal stress (Fig. 7, top panel) is visible as curvature increases from left to right, and contour levels 0.23–0.45 MPa (light blue) occupy an increasingly smaller area in favor of contour levels 0–0.23 MPa (medium dark blue). By contrast, the circumferential stress (Fig. 7, bottom panel) globally decreased with higher curvature, as contour levels 0.02–0.16 MPa (medium dark blue) occupy a larger area as opposed to contour levels 0.16–0.29 MPa (light blue).

For easier comparison between the models, the stress values found in the elements in the mid-height region of the sinus models are reported in Table 1. Examination of this table reveals that a threefold increase in curvature (from 0.05 to 0.15) decreased the longitudinal and circumferential stresses by factors of 3–4 and 1.5–1.9, respectively. This was the case as the aortic root diameter, the blood pressure, and
the elastic properties of the aortic wall were individually varied. Overall, the stress values were lowest (longitudinal and circumferential stresses of 0.13 MPa and lower and 0.18 MPa and lower, respectively) and so was the expected risk of dissection, when sinus curvature was highest.

In females, as the average curvature measured was on the order of 0.10 irrespective of age (Fig. 5, top panel), the corresponding results in the middle column of Table 1 show that the aortic root experienced longitudinal and circumferential stresses in the ranges of 0.16–0.31 MPa and 0.08–0.20 MPa, respectively.

In males experiencing expected changes with aging, that is, whose sinus curvature and elastic modulus would be 0.05 and 1.5 MPa, respectively, when young, and then 0.15 and 6 MPa, respectively, when older, the longitudinal and circumferential stresses ranged from 0.13 to 0.20 MPa and from 0.09 to 0.28 MPa, respectively (Models A-1 to A-2 to A-3, diagonally upward, from left to right in Table 1). However, interestingly, some older males were found to have low sinus curvatures (Fig. 6) and may also have stiff aortic tissue. In such cases, the longitudinal stress may reach notably higher values (0.39 MPa in Model A-3 at a curvature of 0.05, Table 1).

4. Discussion

To our knowledge, this is the first study presenting gender and age differences in aortic sinus curvature. The study was based on aortic roots whose preservation process was identical; therefore, artifacts related to handling cannot account for the profound differences observed between males and females. Moreover, countless anatomical studies have relied on preserved hearts to bring better understanding of shape versus function [12–14]. Very importantly, a recent in vivo study based on a large population of patients established that dilatation of the sinuses of Valsalva during aging was independently related to male gender [15]. This directly supports the finding from our small-sized series that older males may reach high values of sinus wall curvature, because dilatation of the sinuses will induce increased wall curvature at the sinus base.

The mechanical influence of curvature, an otherwise purely geometric aspect, cannot be underestimated, as the finite element models built for this study demonstrated the

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Table 1
Wall stress at mid-height of the sinus in models with low, medium, and high curvature

<table>
<thead>
<tr>
<th>Model</th>
<th>D (mm)</th>
<th>MAP (mmHg)</th>
<th>E (MPa)</th>
<th>Curvature log(s/c) (-)</th>
<th>0.05</th>
<th>0.10</th>
<th>0.15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>σ_L (MPa)</td>
<td>σ_C (MPa)</td>
<td>σ_L (MPa)</td>
<td>σ_C (MPa)</td>
</tr>
<tr>
<td>A-3</td>
<td>24</td>
<td>100</td>
<td>6</td>
<td>.39±.04</td>
<td>.15±.04</td>
<td>.31±.05</td>
<td>.14±.03</td>
</tr>
<tr>
<td>A-2</td>
<td>24</td>
<td>100</td>
<td>3</td>
<td>.25±.04</td>
<td>.21±.02</td>
<td>.19±.03</td>
<td>.12±.03</td>
</tr>
<tr>
<td>A-1</td>
<td>24</td>
<td>100</td>
<td>1.5</td>
<td>.20±.02</td>
<td>.28±.02</td>
<td>.16±.03</td>
<td>.19±.02</td>
</tr>
<tr>
<td>B</td>
<td>30</td>
<td>100</td>
<td>3</td>
<td>.24±.04</td>
<td>.29±.02</td>
<td>.20±.02</td>
<td>.20±.02</td>
</tr>
<tr>
<td>C</td>
<td>24</td>
<td>80</td>
<td>3</td>
<td>.23±.04</td>
<td>.15±.02</td>
<td>.19±.04</td>
<td>.08±.02</td>
</tr>
</tbody>
</table>

All models were subjected to 10% longitudinal stretch. D is the aortic root diameter at the sinus base; E is the elastic modulus of the aortic wall; σ_L and σ_C are the longitudinal and circumferential stresses, respectively. Model A-2 is the control model. Known changes associated with aging are increased values for D, MAP, and E. In our measurements, females were found to have sinus curvature values close to 0.10 throughout their lives, while curvature in males ranged from 0.05 when young to 0.15 when older.
link between lower curvature and higher values of longitudinal and circumferential stresses. This suggests that, between two patients with similar aortic wall material properties, blood pressure, overall aortic diameter, and aortic root movement, it is the patient with less sinus wall curvature who is more at risk of aortic dissection. The mechanical analysis was not designed to show exactly where the dissection tear may occur but illustrated that a more curved aortic root will absorb the pull exerted by the heart more effectively than a straighter one, because it is geometrically more compliant.

Females tended to have a fairly constant and relatively high sinus wall curvature independently of age. This could grant women a mechanical protection from aortic dissection throughout their lives, as long as their aortic elasticity experiences little change. Yet, women after menopause are known to experience a drop in aortic elasticity [16]. In older women, this may offset the benefit from high aortic sinus curvature with regard to aortic dissection. Also, increased fibrosis in the blood vessel walls is known in older subjects [9] and was observed in our female patients. That fibrosis was not more present probably was due to the absence of cardiac disease and the low involvement of atherosclerosis in our patients.

By contrast, the curvature in males seemed to increase appreciably from younger to older ages. However, when the changes in curvature were combined with other known alterations associated with aging, such as decreased wall compliance and increased aortic diameter and blood pressure, the stress values in males were found to be comparable to those in women (Table 1). Since aortic dissections are significantly more prevalent in men [4], and although potential males combining low sinus curvature and stiff aortic wall were found to be at a greater risk of aortic dissection, we propose that other nongeometric factors must be at play in older males, whose impact is able to thwart the potential benefit of higher sinus curvature.

Among such factors, one can think of a weakening of the aortic material properties due to gender-specific differences in expression and activity of the matrix metalloproteinases and their inhibitors. From studies in abdominal aneurysms [17] and experimental aneurysms in rodents [18,19], it has been established that males are four times more prone to aneurysms than females. One may hypothesize that during aging in males, the aortic wall chemistry could be shifted toward more proteolytic activity [20,21], and this might be the case in the aortic root as well. In fact, the observed dilatation of the aortic sinuses in males [15] and the increased sinus curvature reported in this study may be secondary to a degradation of the aortic elastic properties. This possible explanation is consistent with the age-related wall strength diminution noted in dilated aortic roots [22].

It is also important to note that in patients with Marfan’s syndrome, higher rates of aortic dissections are observed in females than in males, despite lower aortic root diameters [23]. Therefore, further gender-specific studies of proteolytic activity in the ascending aorta and of the sinus wall curvature are needed in Marfan and non-Marfan patients alike.

Finally, simplifications designed to make the study tractable have to be acknowledged. The finite element models represented a simplified geometry of the aortic root. Precise quantification of geometric changes between unpressurized and pressurized aortic sinuses using advanced nonlinear material properties, as theoretically required, was beyond the scope of the study. Instead, focus was placed on the relative differences in mechanical stress levels brought about by changes in aortic sinus curvature. The potential role played by the coronary ostia as dampers of the mechanical stress exerted on the aortic root, as evidenced by fewer intimal tears observed there than at the noncoronary sinus, was not investigated. Possible localized sites of higher tissue stiffness, intimal atherosclerosis, and calcium deposits, which can increase the risk of intimal tear, were not considered either.

5. Conclusion

We established significant gender-specific disparities in the aortic root during aging: while aortic sinus curvature was high in females throughout their lives, it experienced a more than fourfold increase in the lifetime of males, matching values in females only by age 65. Our mechanical analyses confirmed the potential protective role of higher sinus wall curvature with respect to aortic dissection, and geometry alone could not account for the known gender difference in aortic dissection prevalence.

Appendix

Ground substance accumulation was graded from the Movat pentachrome slide as follows: Grade 0=none seen; Grade 1=tiny accumulation between the lamellae; Grade 2=larger accumulations in rare lamellae, single lamella involved; Grade 3=large accumulations involving several lamellae, some lamellae still relatively normal; Grade 4=marked accumulation with many lamellae involved; elastic fragmentation associated, relatively most of the section involved.

Elastic fragmentation was graded from the Movat pentachrome slide as follows: Grade 0=none seen; Grade 1=less than five small foci (two to four lamellae each) with fragmented lamellae in a 4× field; Grade 2=more than five small foci (two to four lamellae) with fragmented lamellae in a 4× field; Grade 3=several lamellae (greater than five lamellae) disrupted in a single focus; Grade 4=large areas (greater than five lamellae) of a lamellar loss and fragmentation.

Fibrosis was graded as follows: Grade 0=none seen; Grade 1=an increase of collagen on HPS or Movat stain involving less than 25% of the medial width; Grade 2=an increase of collagen on HPS or Movat stain involving 25% to
50% of the medial width; Grade 3=an increase of collagen on HPS or Movat stain involving 50% to 75% of the medial width; Grade 4=fibrosis increased in more than 75% of medial width.

Medioneerosis was graded as follows: Grade 0=none seen; Grade 1=loss of medial nuclei in an area on HPS or Movat stain involving less than 25% of the medial width; Grade 2=loss of medial nuclei in an area on HPS or Movat stain involving 25% to 50% of the medial width; Grade 3=loss of medial nuclei in an area on HPS or Movat stain involving 50% to 75% of the medial width; Grade 4=loss of medial nuclei in an area in more than 75% of medial width.

References