Original Research

Segmental Differences of Aortic Function and Composition: Clinical Implications

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Key words:
Aorta, elastic properties, morphology.

Introduction: Aortic function is an important determinant of pressure and flow in the entire cardiovascular system. This study aimed at evaluating segmental differences of aortic function and composition, in order to understand their clinical implications.

Methods: The thoracic aorta from each of 20 healthy pigs was divided into four and the abdominal into three segments. From the stress-strain curves, relationships between elastic modulus and stress were obtained for low (part I), physiologic (part II) and high (part III) stresses. Linear regression analysis was performed.

Results: No differences were found in the intercepts and slopes for part I. Significant differences were found in the intercepts and slopes between the thoracic and abdominal segments for part II, and in the slopes for part III, suggesting that the distal segments became progressively stiffer. Histologic examination disclosed higher concentrations of elastin in the proximal and collagen in the distal aortic wall. Aortic wall thickness reduced from proximal to distal aorta. Multiple regression analysis showed good correlations between elastic moduli and either elastin in part I ($r=0.640$) or collagen in part III ($r=0.803$).

Conclusions: The elastic properties and composition vary in different aortic segments. These differences should be taken into consideration when aortic function is determined in clinical practice.

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It is well appreciated today that the aorta not only serves a conduit function but also plays important roles in modulating left ventricular function, myocardial perfusion, and arterial function throughout the entire cardiovascular system. The aorta expands during left ventricular systole and recoils during diastole. A large proportion of the left ventricular stroke volume is stored in the aorta during left ventricular systole under normal conditions, while during diastole the stored blood flows into the periphery. This function of the aorta is important for maintaining blood flow and pressure throughout the cardiac cycle. Aortic storage capacity is directly related to the elastic properties of the aorta and is diminished or lost in different disease states and in the elderly.[1,2]

The ejection of blood from the ventricle during systole generates pressure and pulse waves that are perceived in the periphery as arterial pressure and arterial pulse, respectively. The pulse wave velocity, defined as the speed with which the pulse wave travels in the aorta, is directly related to the elastic properties of the aortic wall. A decrease in the elastic properties of the aorta causes an increase in pulse wave velocity. Increased pulse wave velocity in the stiff aorta will result in an increase in diastolic-systolic expansion of the peripheral arteries and an increase in maximal blood velocity in the arteries during systole; this increased pulsatile stress will promote the development of vascular damage. When the pulse wave reaches the periphery it reflects back to the ascending aorta. Normally the reflecting waves reach the ascending aorta early in diastole; this results in the formation of the diastolic wave. Reflecting waves which reach the aortic valve early in

diastole facilitate coronary blood flow. When the elastic properties of the aorta are diminished and the pulse wave velocity increases, the reflecting waves from the periphery return into the ascending aorta earlier, fuse with the systolic part of the pulse and result in an increase in late systolic peak of pulse pressure and the disappearance of the diastolic wave, leading to an increase of left ventricular work and a decrease of the coronary blood flow.[1,2]

Contemporary technology allows assessment of function in all segments of the aorta under physiologic pressures. Differences in regional aortic function, however, under low and high stresses, in particular as they relate to elastin and collagen content,[3,4] have not been studied. The goal of this investigation was to determine the elastic properties of different segments of the aortic wall under a wide range of stresses, including low, physiologic and very high stresses, in relation to elastin and collagen content.

Methods

Animals and specimen preparation

Twenty healthy female Landrace pigs, 3 months old and weighing from 21 to 27 kg, were used in the present study. Animal housing and handling was conducted in compliance with the guiding principles of the American Physiological Society and the Greek Presidential Decree 160/1991, issued after the 609/1986 Directive of the European Union. The experimental protocol was approved by the institutional ethics committee. Euthanasia was induced with a bolus dose of sodium thiopental. The chest was opened through a left thoracotomy at the level of the fourth intercostal space, and the entire aorta, from the aortic valve to its bifurcation in the iliac arteries, was resected and gently cleaned of surrounding connective tissues. Upon later histologic examination, the tunica intima, media and adventitia were seen on stained sections, indicating that they were intact. The thoracic aorta was divided into four and the abdominal into three segments (Figure 1). Strips of fixed dimensions were taken from each segment in the longitudinal direction for stress-strain analysis.

Stress-strain analysis

Mechanical testing of the aortic strips was carried out on an automatic uniaxial tensile-testing device (Vitrodyne V1000 Universal Tester, Liveco Inc, Burlington, VT, USA), specifically suited for biological tissues, as described previously from our laboratory.[5,6] The strips were held vertically in the grips of the apparatus with small pieces of non-slip paper. The lower grip was connected to a fixed support, while the upper one was attached to an actuator that was elevated and lowered at a rate of 10 $\mu m.s^{-1}$. To sustain normal tissue hydration, the strips were submerged in a normal saline solution at a temperature of 37° C, regulated by means of a heater coil (1130A, PolyScience, Niles, IL, USA).

To stabilize the aortic specimens and minimize viscoelastic phenomena, preconditioning consisting of ten successive cycles with constant final levels of extension was performed in all strips. Preconditioning was accomplished when reproducible force-extension hysteresis loops were obtained.[5-10] After preconditioning, the stress-strain relationship was obtained. Measurements were recorded with a sampling frequency of 50 Hz. The final data were used for analysis.

The initial dimensions of the strips were recorded

SCHEMATIC PRESENTATION OF AORTIC SEGMENTS

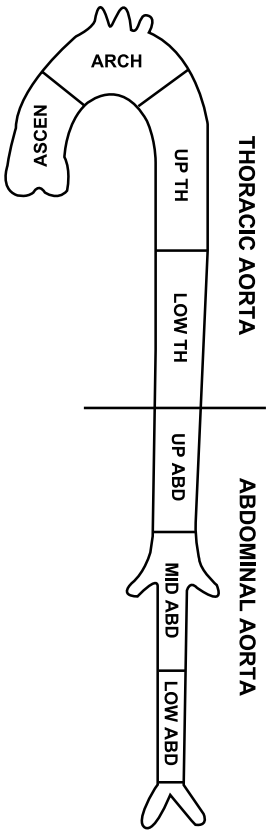


Figure 1. Schematic representation of aortic segments: Ascen – ascending, Arch – aortic arch, Up Th – upper thoracic, Low Th – lower thoracic; Up Abd – upper abdominal, Mid Abd – middle abdominal, Low Abd – lower abdominal aorta.

in the state of no-load. Their length and width were measured with a ruler with 1 mm divisions, while their initial thickness was determined via a laser beam micrometer (LS-3100, Keyence Corp, Osaka, Japan) with 1 μm resolution.[5,6,11] Owing to the non-uniform width and thickness of the specimens, four measurements were taken and the average value was used for analysis. The Vitrodyne device used a 5 kg load cell for the evaluation of force and a rotary encoder providing feedback on the deformed length with 10 μm accuracy.

Stress (σ) was calculated using the formula: $\sigma=F\lambda/w_o t_o$, where F is the tensile force exerted on the aortic strips, w_o and t_o are the initial width and thickness, and λ is the longitudinal stretch ratio (ratio of the deformed to the initial length). Strain (E) was calculated using the formula: $E = 1/2 (\lambda^2-1)$. Elastic modulus (M) was obtained using the formula: $M = d\sigma/dE$ (first derivative of stress with respect to strain).[5,6]

A typical relationship between stress and strain of a strip from the aortic arch is shown in Figure 2a. Figure 2b shows the relationship between elastic modulus and stress of the same data. A bilinear curve was observed after an initial non-linear region, as previously reported.[6,11] Briefly, each curve consisted of three parts, corresponding to low (part I), physiologic (part II) and high stresses (part III). The three distinct parts of the curve were defined as follows. The correlation coefficient of the linear regression between elastic modulus and stress (beginning from the highest stress) was increased by raising the number of data up to a critical point, beyond which it was decreased substantially. This point was considered to be the transition stress, separating parts II and III. A similar procedure was used to define the transition to parts II and I of the curve. Together with the determination of the three parts, their intercepts and slopes were computed. Physiologically, the intercepts for parts I, II and III may be considered in turn as indices of the inherent stiffness of aortic wall at low, physiologic and high stresses, independent of the applied stress level, while the slopes are indicative of progressive aortic stiffening under low, physiologic, and high stressing.

Histologic studies

Five samples from each aortic wall segment were ob-

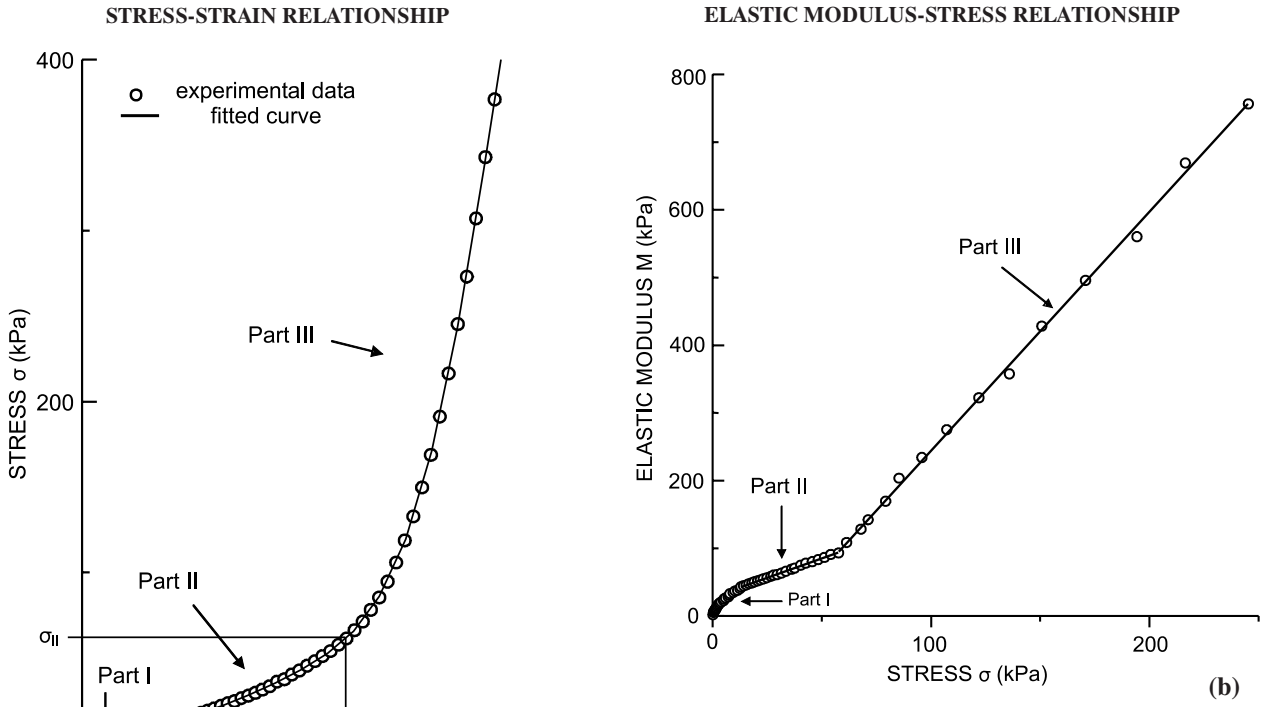


Figure 2. (a) Stress-strain relationship of the aortic wall. The transition points (σ_I, E_I and σ_{II}, E_{II}) defining the limits of the three parts are shown. (b) The same data are presented as an elastic modulus-stress curve. Note the bilinear relationship in parts II and III after a short non-linear part I.

tained and immersed in 10% neutral formalin for a minimum of 24 hours. They were embedded in paraffin using standard techniques, sliced in 5 μm sections, and stained with orcein and Masson's trichrome. Elastin and collagen contents, as well as thickness of the aortic wall were measured in appropriately stained sections by a computer-assisted image analysis technique, as described previously from our laboratory.[5,11,12] The apparatus comprised a Sony-iris CCD video-camera system (Sony Corp, Japan), fitted to an Olympus BX40 light microscope (Olympus Optical Co Ltd, Tokyo, Japan), a host computer and SigmaScan v2.0 image analysis software (Jandel Scientific, Erkrath, Germany).

Statistical evaluation

Statistical evaluation[13] was performed using linear regression (least-squares fitting procedure according to Marquardt) and multiple regression analysis, using the SPSS v8.0 for Windows application (SPSS Inc, Chicago, IL, USA). Intercepts and slopes of the regression lines between elastic modulus and stress for parts I, II and III were determined. The Bonferroni test for multiple comparisons among the aortic segments was also performed. Analysis of variance (ANOVA) was used when appropriate. A p-value <0.05 was considered statistically significant.

Results

Elastic modulus-stress curves

The relationships between elastic modulus and stress for the seven segments of the aorta are illustrated in Figure 3. A linear relationship was obtained in part I when the data were transformed onto a logarithmic scale on both axes, while linear relationships were present in all segments for parts II and III.

Intercepts and slopes for the three parts of the relationship between elastic modulus and stress were evaluated. As indicated in Table 1, statistically significant differences were not found in the intercepts (inherent stiffness) and slopes (rate of change of stiffness with stress) in part I. Significant differences were found in part II in certain slopes and intercepts. Statistically significant differences were found in part III only for the slopes, but not for the intercepts. The data suggest that, at physiologic and high stress, the aortic wall becomes progressively stiffer from the aortic root to the distal aorta.

Histologic studies

Representative cross-sections of the aortic wall (aortic arch) are shown in Figure 4. Elastin fibers were stained orange with orcein and collagen fibers were stained green with Masson's trichrome. Image analysis showed that elastin comprised approximately 35% and collagen 22% of the aortic wall in the ascending, while in the lower abdominal aorta the ratio of these contents was reversed (Figure 5a). The wall of the aortic arch and the upper descending thoracic aorta had the highest elastin content, whereas the wall of the lower abdominal aorta had the lowest. Collagen content increased steadily from the aortic root to the distal aorta (Figure 5a).

Aortic wall thickness decreased from the central aorta to the periphery (Figure 5b). The thickness of the aortic wall was 2.054 ± 0.071 mm in the ascending, 1.476 ± 0.058 mm in the lower thoracic, and 1.172 ± 0.026 mm in the lower abdominal aorta.

Correlations of elastic modulus with elastin and collagen content, and aortic thickness

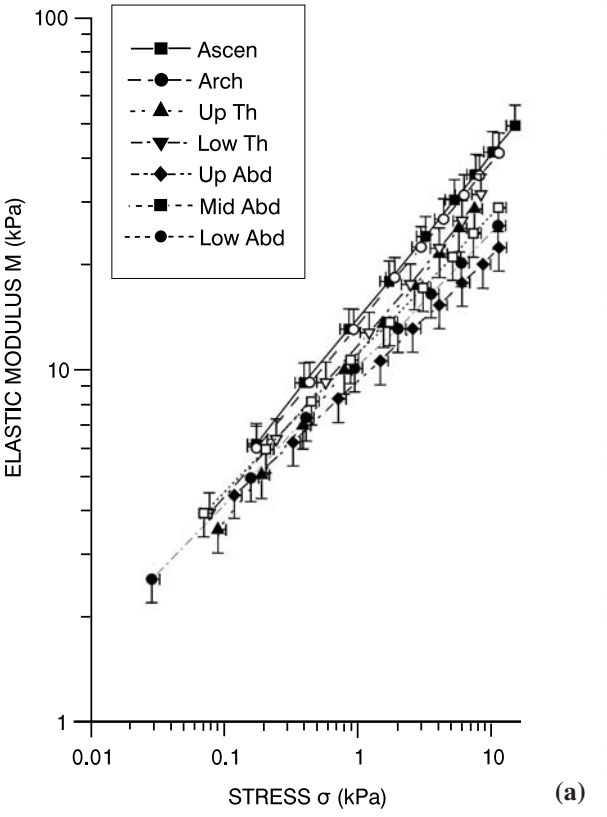
Correlations of elastin and collagen content with the elastic moduli of parts I, II and III of the curves are shown in Table 2. A good correlation was found between elastin content and the elastic moduli in part I ($r=0.639$); inverse and weak correlations were found between elastin content and the elastic moduli in parts II and III. A good correlation was found between the elastic moduli and collagen content in part III ($r=0.763$). Correlations between the elastic moduli and collagen content in parts I and II were poor. Multiple regression analysis, using elastin and collagen as predictors, accounted for only slightly better correlation compared to elastin alone for part I, collagen alone for part III, and either elastin or collagen for part II.

A good correlation was found between the elastic moduli and aortic thickness for part I ($r=0.609$). Inverse correlations were found between the elastic moduli and aortic thickness for parts II ($r=-0.240$) and III ($r=-0.809$).

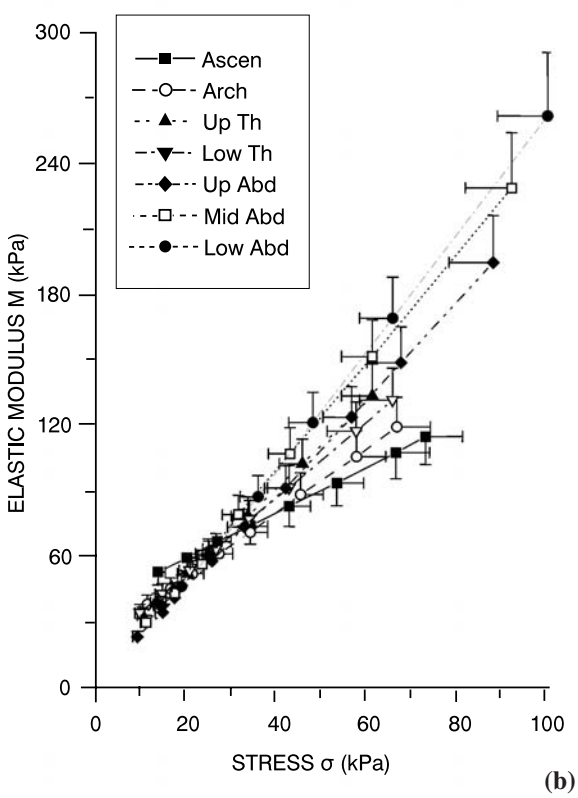
Discussion

The main finding of the present study is that the function and composition of the aortic wall are nonhomogeneous. The distal segments of the aortic wall were significantly stiffer compared to the proximal

PART I OF ELASTIC MODULUS-STRESS RELATIONSHIP



PART II OF ELASTIC MODULUS-STRESS RELATIONSHIP



PART III OF ELASTIC MODULUS-STRESS RELATIONSHIP

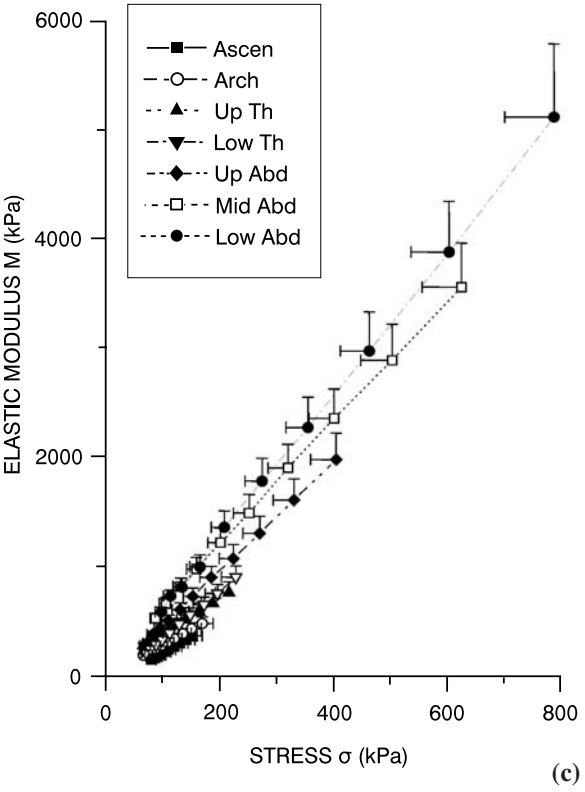


Figure 3. Relation between elastic modulus and stress in the seven segments of the aorta for part I (a), part II (b) and part III (c). Values are expressed as mean ± standard error of the mean. Definition of aortic segments as in Figure 1. See Table 1 for p-values.

Table 1. Relationships between elastic modulus and stress for parts I, II and III of the curve.

Aortic segment	Linear regression parameters					
	Part I		Part II		Part III	
	Int (kPa)	Slope	Int (kPa)	Slope	Int (kPa)	Slope
Ascen (n=20)	1.138 ± .163	0.486 ± .078	34.915 ± 5.623	1.037 ± .155	-80.356 ± 20.598	2.823 ± .092
Arch (n=20)	1.125 ± .188	0.461 ± .069	18.041 ± 2.192	1.471 ± .067	43.223 ± 30.736	2.813 ± .195
Up Th (n=20)	1.039 ± .213	0.478 ± .086	8.157 ± 4.316	1.961 ± .219	96.718 ± 30.617	3.319 ± .067
Low Th (n=20)	1.087 ± .198	0.446 ± .087	15.874 ± 6.544	1.697 ± .267	-64.075 ± 53.268	4.377 ± .451*†
Up Abd (n=20)	0.964 ± .120	0.362 ± .074	2.678 ± 4.279*	2.177 ± .250*	6.821 ± 110.539	4.848 ± .504*†‡
Mid Abd (n=20)	1.047 ± .195	0.392 ± .082	-3.282 ± 11.961*	2.548 ± .477*†	210.018 ± 243.817	5.701 ± .496*†‡
Low Abd (n=20)	1.003 ± .137	0.389 ± .077	-5.503 ± 10.236*	2.549 ± .231*†	58.057 ± 67.684	6.570 ± .251$^{*\dagger\ddagger\S\|\|}$

Intercepts (Int) and Slopes are shown. The numerical values of the linear regression parameters are expressed as mean ± standard error of the mean. n = number of samples in each segment. Definition of segments as in Figure 1. Symbols *, †, ‡, § and ‖ denote significant differences with respect to Ascen, Arch, Up Th, Low Th and Up Abd, respectively.

Part I. No statistically significant differences were found in slopes and intercepts.

Part II. Intercepts: Ascen vs. Up Abd, p=0.02; Ascen vs. Mid Abd, p=0.003; Ascen vs. Low Abd, p=0.001. Slopes: Ascen vs. Up Abd, p=0.018; Ascen vs. Mid Abd, p=0.001; Ascen vs. Low Abd, $p=1.891\times10^{-4}$; Arch vs. Mid Abd, p=0.036; Arch vs. Low Abd, p=0.023. Other differences were not statistically significant.

Part III. Intercepts: Differences were not statistically significant. Slopes: Ascen vs. Low Th, p=0.006; Ascen vs. Up Abd, $p=6.519\times10^{-4}$; Ascen vs. Mid Abd, $p=1.534\times10^{-7}$; Ascen vs. Low Abd, $p=5.439\times10^{-7}$; Arch vs. Low Th; p=0.007; Arch vs. Up Abd, p=0.001; Arch vs. Mid Abd, $p=8.895\times10^{-5}$; Arch vs. Low Abd, $p=6.795\times10^{-5}$; Up Th vs. Up Abd, p=0.039; Up Th vs. Mid Abd, $p=7.306\times10^{-5}$; Up Th vs. Low Abd, $p=8.633\times10^{-5}$; Low Th vs. Low Abd, $p=7.802\times10^{-4}$; Up Abd vs. Low Abd, p=0.009. Other differences were not statistically significant.

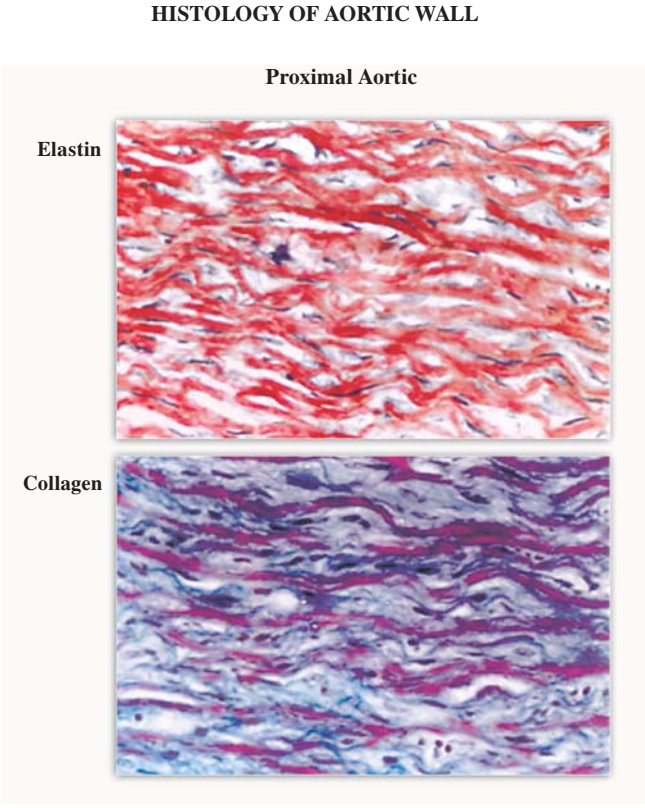


Figure 4. Histology of the aortic wall of a segment obtained from the aortic arch (a) stained with orcein (×400) for quantitative determination of elastin, and (b) Masson's trichrome (×400) for quantitative determination of collagen. Elastin is displayed in orange tones and collagen in green.

ones at physiologic and higher stresses. Elastin content was decreased while collagen was increased from proximal to distal aorta. The thickness of the aortic wall was also decreased from central to peripheral aorta.

Determination of the elastic properties of the aorta in clinical practice over a wide range of stresses is technically difficult. In the present study, stresses corresponding to part II of the elastic modulus-stress curves were considered within the physiologic range, while stresses corresponding to parts I and III of the curves were considered low and high, respectively.[6,11] To date, several *in vitro* studies (see reviews by Kassab[14] and Sokolis[5]) have assessed the elastic properties of the aortic wall in different segments of the aorta in the circumferential direction, mostly in the range of physiologic pressures. Overall, the results from the present study are in agreement with the previous ones, which have suggested that under physiologic stresses the aorta becomes stiffer in the peripheral segments. The present study extends previous observations and defines the elastic properties of the aortic wall in the longitudinal direction at low and high stresses. In addition, it determines the relation between elastic moduli, elastin and collagen content.

Elastic modulus-stress relationship

The elastic modulus-stress relationship was used in

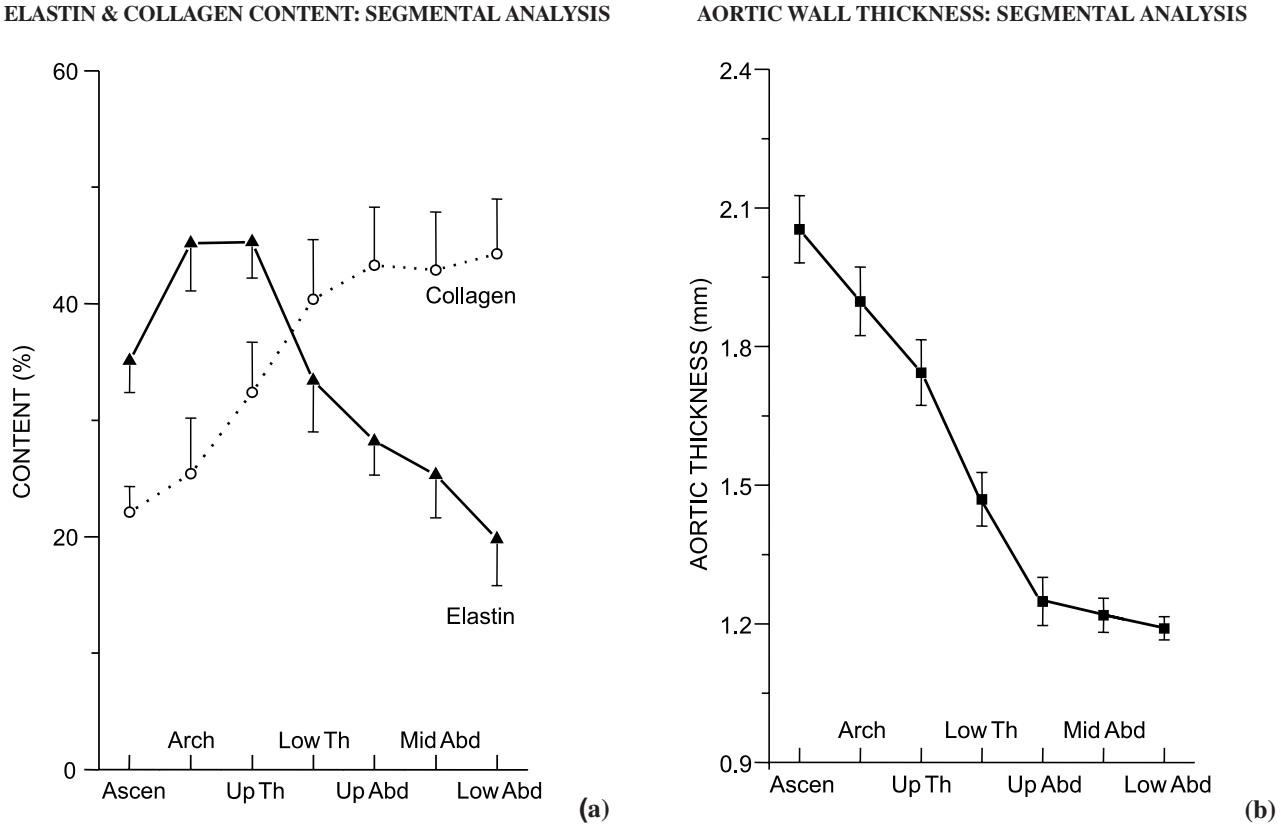


Figure 5. Elastin and collagen content (a), and aortic wall thickness (b) in the seven segments of the aorta. Values are expressed as mean ± standard error of the mean. Definition of aortic segments as in Figure 1. Differences in elastin content: Arch vs. Up Abd, p=0.028; Arch vs. Mid Abd, p=0.012; Arch vs. Low Abd, p=0.001; Up Th vs. Up Abd, p=0.019; Up Th vs. Mid Abd, p=0.008; Up Th vs. Low Abd, p=0.001. Other differences were not statistically significant. Differences in collagen content: Ascen vs. Up Abd, p=0.04; Ascen vs. Mid Abd, p=0.032; Ascen vs. Low Abd, p=0.019. Other differences were not statistically significant. Aortic wall thickness decreased from central aorta to periphery (ANOVA, $p<0.05$).

this study to define the elastic properties of the aortic wall. As previously documented,[6,11] after a short non-linear region, the elastic modulus-stress relationship of the aortic wall was bilinear over a wide range of stresses in all segments of the aorta. Stress-strain relationship, in terms of incremental theory,[7] polynomial,[8] exponential,[9,10,15] or bilinear functions,[16] has been used in previous studies to define the elastic properties of the aortic wall. The elastic modulus-stress relationship provides a mathematical formulation that can be used over a broad range of stresses, from very low to very high. Further, the linearity of the elastic modulus-stress relationship at low, physiologic, and high stresses provides a simple way of making comparisons of the elastic properties of the aortic wall among different segments of the aorta in the same individual, among different species, and between health and disease states.

Relation between aortic wall structure and function

The present study demonstrated a predominance of elastin over collagen in the central as compared to the peripheral segments of the aorta and a predominance of collagen over elastin in the peripheral segments. An explanation for the distinctive shape of the elastic modulus-stress relationship may be gleaned from the pioneering histologic studies of Wolinsky and Glagov,[17,18] and the selective enzyme digestion studies by Roach and Burton,[19] and later by Dobrin and Canfield.[20] It has been suggested[17-22] that, at low stresses (part I), the initial non-linear part of the stress-strain relationship is dependent mostly on the straightening of elastin fibers. At physiologic stresses (part II), the elastin fibers are straightened, and a fraction of the much stiffer collagen is involved in carrying the stresses; at high stresses (part III), mostly collagen is involved in carrying the stresses.

Table 2. Simple and multiple regression analyses. Relations of elastic moduli with elastin and collagen content, and aortic thickness.

Regression equation	r	r^2	p
Part I (n=560)			
M = 0.560 El + 5.485	0.639	0.408	<0.0001
M = -0.214 Col + 31.766	-0.230	0.053	<0.0001
M = 0.545 El - 0.058 Col + 8.022	0.640	0.410	<0.0001
M = 18.831 AT - 5.195	0.609	0.371	<0.0001
Part II (n=560)			
M = -0.453 El + 100.664	-0.147	0.022	<0.005
M = 0.458 Col + 69.138	0.161	0.026	<0.005
M = -0.439 El + 0.447 Col + 84.093	0.215	0.046	<0.005
M = -25.273 AT + 125.384	-0.240	0.058	<0.0001
Part III (n=560)			
M = -6.393 El + 815.701	-0.247	0.061	<0.0001
M = 12.903 Col + 95.812	0.763	0.582	<0.0001
M = -6.503 El + 12.926 Col + 323.084	0.803	0.645	<0.0001
M = -577.659 AT + 1498.147	-0.809	0.655	<0.0001

M – elastic moduli; El – elastin content; Col – collagen content; AT – aortic thickness; n – number of samples.

Such an explanation is supported by the correlations between the elastic moduli and elastin content in part I, as well as between the elastic moduli and collagen content in part III (Table 2). Thus, elastin and collagen content are major independent determinants of the elastic properties of the aortic wall at either low or high stresses.

Segmental variations of aortic function: clinical implications

An accurate description of the elastic properties of the aortic wall in different segments of the aorta is essential for understanding aortic function. Available technology, such as angiography, echocardiography and magnetic resonance imaging,[23-30] allows determination of the elastic properties of the aorta at different segments only under physiologic pressures. Since the elastic properties of the aorta differ from one segment to the other, this information should be taken into consideration in clinical practice, when aortic function is evaluated at different levels of the aorta.

The elastic properties of the aortic wall are a major determinant of aortic pulse wave velocity and aortic expansion during systole. According to the Moens-Korteweg equation, pulse wave velocity is related to the square root of elastic modulus and to aortic pressure.[1,2] Aortic expansion, and thus the storage capacity of the aorta, is also related to the elastic modulus of the aortic wall and to the magnitude of the change of aortic pressure from diastole to systole.[1,2] The elastic modulus-stress relationships at low, physiologic and high stresses (parts I, II and III) (Figure 3, Table 1) allow the following conclusions.

Pulse wave velocity and aortic expansion should vary significantly from segment to segment. At low stresses (part I, Figure 3a), it is expected that aortic pulse wave velocity will be relatively uniform in all segments of the aorta, since significant differences were not found in the elastic moduli among the different segments. At physiologic stresses (part II, Figure 3b), it is expected that aortic pulse wave velocity will increase significantly in the abdominal compared to the ascending aorta and aortic arch, since the elastic moduli increased significantly in the abdominal relative to the thoracic segments. At high stresses (part III, Figure 3c), it is expected that aortic pulse wave velocity will increase significantly from the central to the peripheral aorta, since the elastic moduli increased significantly from the proximal to the distal aorta.

Similarly, changes in aortic expansion, and thus in the storage capacity of the aorta, should vary significantly from segment to segment. At low stresses (part I, Figure 3a), aortic expansion is expected to be similar in all segments of the aorta, since significant differences were not found in the elastic moduli among the different segments. At physiologic stresses (part II, Figure 3b), aortic expansion is expected to be significantly larg-

er in the proximal compared to distal aorta, since the elastic moduli increased significantly in the abdominal relative to the thoracic segments. At high stresses (part III, Figure 3c), aortic expansion in the proximal aorta is expected to be significantly larger compared to the distal aorta, since the elastic moduli increased significantly from the proximal to the distal aorta.

The study was conducted in young healthy animals; thus, these findings may not be applicable to other age groups and/or to disease states. Previous studies[8,9,16,26-35] have shown that the elastic properties of the aorta are changed in several conditions, such as pregnancy, advanced age, physical conditioning, atherosclerosis, arterial hypertension, diabetes mellitus, heritable disorders of connective tissue, congestive heart failure, smoking, and others. Changes in elastin or collagen content in different conditions/diseases will alter aortic function. Conversely, changes of aortic function may provide indirect evidence of underlying histologic changes. Evaluation of the elastic properties of the aorta in disease states at different segments will help to better understand aortic function and dysfunction in health and disease.

In summary, the elastic properties and composition varied in different segments of the aorta. The distal aortic segments were stiffer in comparison to proximal ones, reflecting differences in aortic composition. These differences should be taken into consideration when aortic function is determined in clinical practice.

Acknowledgements

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