Horny, L., Adamek, T., Gultova, E., Zitny, R., Vesely, J., Chlup, H., & Konvickova, S. (2011). Correlations between age, prestrain, diameter and atherosclerosis in the male abdominal aorta. *Journal of the Mechanical Behavior of Biomedical Materials, 4*(8), 2128-2132. doi: 10.1016/j.jmbbm.2011.07.011 **MANUSCRIPT VERSION**

Title: **Correlations between Age, Prestrain, Diameter and Atherosclerosis in the Male Abdominal Aorta**

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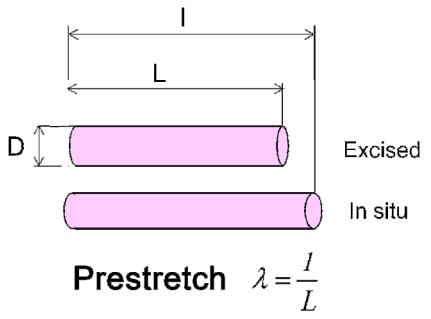

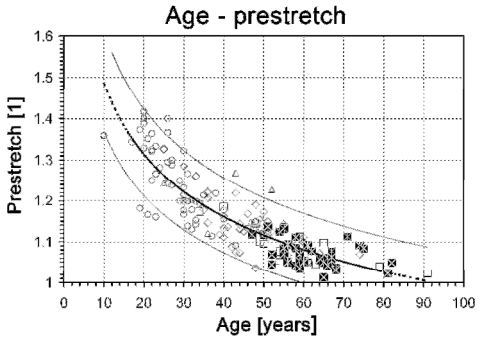

Longitudinal prestretch is well correlated with age. $\lambda = 2.2397 \cdot Age^{-0.1780}$

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Abstract

The longitudinal prestrain of arteries facilitates their physiological function. Remodelling, adaptation and aging result in an age-dependent magnitude of the pretension. Although the phenomenon is known detailed statistics, especially for human arteries, are lacking. This study was designed to propose the regression model capable of estimating the prestrain of the human abdominal aorta. The length of the abdominal aorta before, l, and after excision from the body, L, the diameter, heart weight, thickness of left ventricle and degree of atherosclerosis were collected in autopsy of 156 male cadavers of known age. Longitudinal prestrain was quantified by means of the stretch ratio $\lambda=l/L$. Statistical analysis revealed significant dependence between age, prestrain, diameter and atherosclerosis, which were best fitted to the power law equation. Longitudinal prestretch reduced with age significantly; $\lambda_{mean}=1.30\pm0.07$ for age<30 (n=29), whereas $\lambda_{mean}=1.06\pm0.03$ for age>59 (n=31) with p-value<0.0001. Raw data gave linear correlation coefficients as follows: λ–age R=-0.842; l–age R=0.023; L–age R=0.476; (l-L)–age R=-0.811. It was concluded that longitudinal prestrain decreases nonlinearly with age and both age and diameter are suitable predictors of the prestrain. Data suggests that unloaded length elongates with age in contrast to the elastic retraction.

Keywords: abdominal aorta; aging; atherosclerosis; elasticity; prestrain.

1. Introduction

It has been known for a long time that arteries in vivo undergo significant longitudinal prestrain; they retract upon excision 0–50% (Bergel, 1961; Learoyd and Taylor, 1966; Schulze-Bauer et al., 2003; Sommer et al., 2010; Han and Fung, 1995; Langewouters et al., 1984). Axial prestrain is advantageous from a biomechanical viewpoint. Inflation-extension experiments showed that under a certain value of axial strain arteries can be pressurized with no change of their length (Schulze-Bauer et al., 2003; Sommer et al., 2010). Under such conditions the pressure pulse wave can be transmitted along an artery without significant change in axial force (Van Loon et al., 1977).

The magnitude of the in situ prestrain was proved to be species and location dependent. It increases with increasing distance from the heart (Han and Fung, 1995). Results suggest that this dependency could be explained by means of the intramural collagen-to-elastin ratio (Humphrey et al., 2009). The crucial role of elastin was proved by enzyme digestion and in animal models with an elastin insufficiency (Dobrin et al., 1990; Wagenseil et al., 2009).

Axial prestrain plays important role in the remodelling and adaptation of arteries (Humphrey et al., 2009; Cardamone et al., 2009; Lawrence et al., 2009; Hayashi and Naiki, 2009). Significant lengthening during increased blood flow was observed (Lehman et al., 1990). Elevated axial load also led to lengthening via increased cell proliferation and matrix synthesis (Jackson et al., 2002; Han et al., 2003).

Thus magnitude of the prestrain changes during the lifespan (Learoyd and Taylor, 1966; Langewouters et al., 1984). However, detailed description of the age-dependency, especially in humans, is lacking in the literature (Zulliger and Stergiopulos, 2007).

Direct measurement of the axial prestrain in living individuals is problematic due to the requirement of a sample resection. Another method which could determine the prestrain is therefore desirable. The aim of this study is to find a regression model for longitudinal prestrain estimating.

2. Methods

Data describing the in situ and excised lengths of the male abdominal aorta, as well as the diameter (D), age, degree of atherosclerosis (ATH), thickness of the left ventricle, heart weight (HW), height and post-mortem interval (PMI, time span between the death and autopsy measurement) were collected during regular autopsies of Caucasian cadavers of known age. Post-mortem usage of human tissue was approved by the Ethics Committee of the University Hospital Královské Vinohrady in Prague. No putrefied bodies were involved. The degree of atherosclerosis was examined by the pathologist and quantified in a scale from 0 up to 4 according to morphological features: 0 – intact artery and fatty streaks; 1 – fibro-fatty plaques; 2 – advanced plaques; 3 – calcified plaques; 4 –

ruptured plaques (Kumar et al., 2010). This study includes only male donors because female autopsies are carried out approximately three times less than male. Comparison between male and female data will be the subject of separate study.

2.1 Longitudinal prestrain and diameter.

The abdominal aorta was thoroughly removed and the distance between two markers in situ and after the excision was measured with a ruler. Markers were made just below the renal arteries and above the aortoiliac bifurcation. Longitudinal prestrain was quantified by means of the stretch ratio, λ, defined in (1).

$$\lambda = \frac{l}{L} \tag{1}$$

Here l denotes in situ length and L is the length after removal from the body. Subsequently a ring was cut off from the aortic segment (approx. 2 cm above the bifurcation) and then cut into a strip. The circumference of the aortic segment was determined as the length of this strip and then divided by π to obtain the diameter. The measurement of excised artery was performed approximately 2 minutes after the removal from a body.

2.2 Correlation and regression analysis.

Linear correlation coefficients were computed according to the equation (2), where x and y denote appropriate variables and overbar indicates the mean value. S_x a S_y denote sample standard deviations.

$$R = \frac{\sum_{i=1}^{n}\left(x_i - \bar{x}\right)\left(y_i - \bar{y}\right)}{\left(n-1\right)S_x S_y} \tag{2}$$

Preliminary computations revealed a successful fit with the power law equation (3). It was used to express prestrain–age, diameter–age and diameter–prestrain relationships. Model parameters were estimated with least squares optimisation in Maple 13 (Maplesoft, Waterloo, Canada).

$$y = ax^b \tag{3}$$

The predictive capability of the models was evaluated by means of prediction intervals (confidence interval in which future observations will fall with a probability equal to confidence level α). The probability α=0.95 was considered to be significant. Prediction intervals (PI) were computed after the logarithmic transformation into a linear problem. In such a situation they can be implemented by means of (4)

$$y = a + bx \pm t_{\frac{\alpha}{2}}\left(m\right)S_e\sqrt{1 + \frac{1}{n} + \frac{\left(x-\bar{x}\right)^2}{\sum_{i=1}^{n}\left(x_i - \bar{x}\right)^2}} \tag{4}$$

where a and b are model parameters estimated using (3). S_e denotes residual standard deviation and $t_{\alpha/2}$ is the quantile of the Student's t-distribution with m=n-2 degrees of freedom.

3. Results

A one-year collection of data resulted in 156 donors. Descriptive statistics are listed in Table 1. Table 3 summarizes longitudinal dimensions of arteries since the stretch ratio does not provide this notion.

3.1 Correlation

Computed correlation coefficients (Table 2) proved a strong mutual dependence between the longitudinal prestrain, age, diameter and the degree of atherosclerosis. Higher values were attained

after the logarithmic transformation. This is in accordance with chosen form of the regression model (1).

Besides the tight correlations given in Table 2, the data indicate rather high dependence for HW–D (R=0.579); HW–ATH (R=0.511); HW–age (R=0.464); and HW–prestretch (R=-0.454); computed for raw data. The correlation coefficients between PMI and other quantities did not exceed $|R|$=0.22. It suggests that results were not significantly affected by post-mortem changes.

3.2 Regression analysis

Fig. 1 shows results of the regression analysis. Symbols representing observation points highlight the degree of atherosclerosis. Since the atherosclerosis is quantified in rather a qualitative manner it was not considered for the regression modelling. Nevertheless, graphs show that points with the same ATH are mostly grouped into regions with overlapping boundaries, which confirms the significant correlations presented in Table 2.

Results also show that while longitudinal prestrain decreases with age, the aortic diameter increases. As correlation coefficients suggest, the power law is suitable to fit age–prestretch, age–diameter, and diameter–prestretch nonlinear relationships.

The model predictions are supplemented by prediction intervals which emphasize variances in observations and give the limits for hypothetical future observation. Confidence level of 0.95 covers almost all observations. It implies that PI must be wide enough. The nonlinearity of the problem results in variable lengths of PI. Concerning PI two facts should be mentioned: since the lower limit of the prestretch–age relationship approaches 1 at about age 60, the model suggests that non-prestrained aortas may occur. It implies that the model predicts a high risk of the pretension being lost which can be manifested as an aneurysm or tortuosity. A similar situation occurs in the prestretch–diameter relationship where the aortic diameter exceeds 1.5 cm. Secondly the outliers presented, especially in the prestretch–diameter relationship, may raise questions about the suitability of the power law model. A better fit could likely be obtained with the curve decreasing more steeply; however, calculations proved that power law is superior to exponential, logarithmic and linear alternatives.

4. Discussion

Experimentally validated prestrain should be used in computer simulations (e.g. stress or pulse wave velocity analyses) and experimental techniques (bioreactor, tissue engineering) of artery biomechanics to obtain reliable results. Pretension is, however, experimentally inaccessible in living subjects due to the requirement of the excision of a sample. Hence statistical models can be helpful in estimating prestrain. It is a surprising fact that these models are lacking in the literature (Zulliger and Stergiopulos, 2007).

This study found that longitudinal prestrain of the human abdominal aorta measured post-mortem is well correlated with the age and diameter of the artery, and both can be utilized for estimating prestrain. Predictions based on age are more successful than those based on the diameter. The nonlinear decreasing trend of the prestrain was well described with the power law.

Prestrain presented here, however, can differ from in vivo pretension. In vivo pretension accounts not only for the tension developed by an artery wall itself, it also includes tension of the surrounding tissue which had to be removed during the sample excision. The purpose of the surrounding tissue, however, is especially to support artery position and to reduce the transmural pressure load. In vivo longitudinal tension is also raised with the blood pressure, although the literature suggests that this effect might be negligible (Liu et al., 2007). Presented observations should be considered rather as the lower limit of in vivo prestrain.

Low correlations with PMI support the hypothesis that the measured data were not significantly affected by post-mortem changes. It is in accordance with common opinion that the passive elasticity of arteries does not change substantially up to 7 days after death when kept in cold storage (Medynsky et al., 1998).

The presented models are purely empirical and their usability out of the range of observations is questionable. Specifically, they do not respect the obvious fact that longitudinal prestrain cannot be decreasing throughout the entire life. This fact was indicated in the dotted curves in Fig. 1. The

pretension must be developed. Unfortunately, we have almost no data covering the childhood because such autopsies are not carried out in our hospital (searching the literature also did not reveal suitable sources). Likewise significantly aged (or those with a large aortic diameter) subjects could be modelled unrealistically.

The artery diameter, determined via the length of the arterial strip, can differ from the diameter of the closed ring due to residual strains acting in circumferential direction (Rachev and Greenwald, 2003). The residual strain, however, correlates with aging (Valenta et al., 2002). It suggests that presented diameters can be transformed to in vivo dimensions after applying the appropriate model.

We also tested if the predictive capability of the model can be increased considering multivariate problem. Unfortunately, the inter-correlation between variables resulted in only slight improvement. It was concluded that in terms of a phenomenological approach, the age is the most efficient predictor for both prestretch and diameter.

Interesting question is what the source of the age–prestrain correlation is. Data analysis revealed that l does not correlate with age (R=0.023), and L correlates slightly (R=0.476). The highest age-dependence was found for elastic retraction l-L, R=-0.811. Note also that non-prestrained length L elongates with age (possible remodelling of the unloaded state) in contrast to the elastic retraction (l-L decreases likely due to the stiffening of an artery).

Further studies are needed to obtain more reliable descriptions of age-, remodelling-, and pathology-dependent phenomena of artery pretension. Constituent-based models are especially desirable. They can account for the rate of extracellular matrix synthesis/inhibition, calcium deposition and high-cycle fatigue. Reported data can be utilized in their development.

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Tables

Table 1 Data summary.

	Mean±SD	Min/Max	Median/Mode
Prestretch [-]	1.153±0.097	1.012/1.417	1.133/1.111
Age [year]	45.5±16.2	10/91	47.5/30
Diameter [cm]	1.32±0.22	0.67/2.20	1.31/1.27
Heart weight [g]	430±121	160/840	410/350
Thickness LV [cm]	1.5±0.3	0.6/2.5	1.5/1.5
Atherosclerosis [-]	1.9±1.6	0/4	2/0
PMI [h]	46±31	2/170	37/24

Table 2 Correlation coefficients. Upper triangular table (shaded) shows coefficients obtained after the logarithmic transformation; the lower one represents correlations computed with raw data. ATH were not transformed.

	λ or **ln**(λ)	Age or **ln**(Age)	D or **ln**(D)	ATH
λ or **ln**(λ)	—	-0.873	-0.819	-0.736
Age or **ln**(Age)	-0.842	—	0.890	0.798
D or **ln**(D)	-0.798	0.871	—	0.762
ATH	-0.726	0.811	0.766	—

Table 3 Descriptive statistics of measured longitudinal dimensions.

[cm]	Mean	Standard Deviation	Minimum	Maximum
Excised length *L*	7.9	1.17	3.9	11.5
In situ length *l*	9.1	1.15	5.3	13.0
Elastic retraction *l*-*L*	1.2	0.65	0.1	3.2

Figure captions

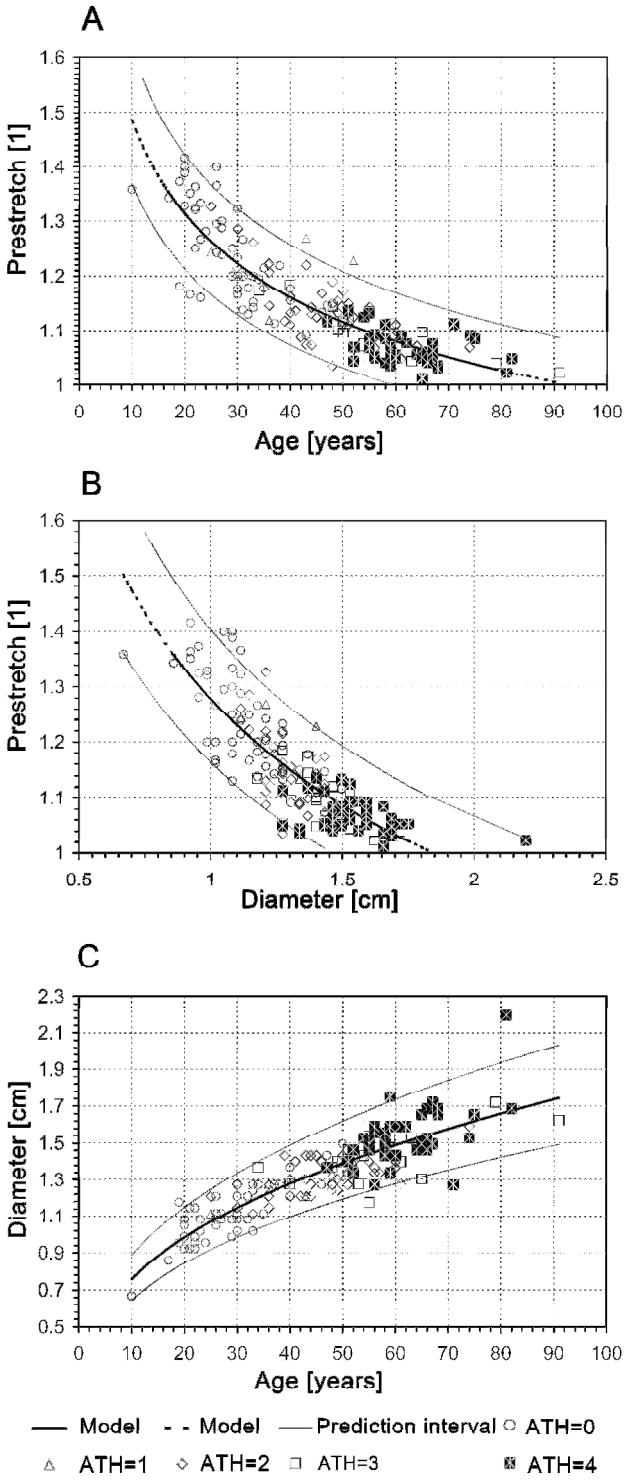

Figure 1 Models and observations. A – age predicts prestretch; B – diameter predicts prestretch; and C – age predicts diameter. The predictions are based on (1) with parameters as follows: age–prestretch a=2.2397, b=-0.1780; diameter–prestretch a=1.2781, b=-0.3999; and age–diameter a=0.3179, b=0.3771. The dotted curves are based on model equations and highlight areas where the models should be used carefully. The symbols used for data-points indicate the degree of atherosclerosis (ATH).

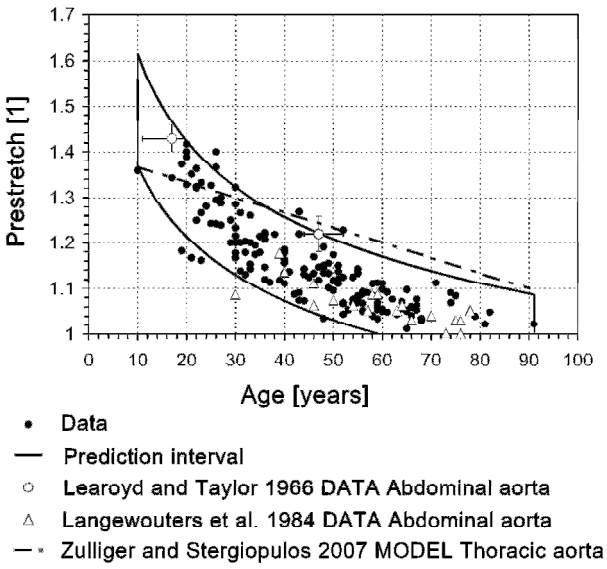

Figure 2 Comparison with literature. There are only few papers reporting longitudinal prestrain in human abdominal aorta. Learoyd and Taylor (1966) involved 12 human donors and published only averaged results (SD is indicated). Langewouters et al. (1984) involved 20 human donors, nevertheless, their sample did not cover the age < 30 years. Their results are in accordance with our data. Zulliger and Stergiopulos (2007) proposed the linear model λ=1.4-Age/300 for human thoracic aorta. The literature however suggests that λ increases with the distance from the heart (Han and Fung, 1995; Learoyd and Taylor, 1966). Thus it seems that λ=1.4-Age/300 somewhat overestimates the prestrain when predicts higher values in thoracic aorta than in abdominal aorta.