2016

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HHS Public Access

Author manuscript

Acta Biomater. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Acta Biomater. 2016 March 1; 32: 231–237. doi:10.1016/j.actbio.2016.01.002.

In situ longitudinal pre-stretch in the human femoropopliteal artery

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Abstract

In situ longitudinal (axial) pre-stretch (LPS) plays a fundamental role in the mechanics of the femoropopliteal artery (FPA). It conserves energy during pulsation and prevents buckling of the artery during limb movement. We investigated how LPS is affected by demographics and risk factors, and how these patient characteristics associate with the structural and physiologic features of the FPA. LPS was measured in $n = 148$ fresh human FPAs (14–80 years old). Mechanical properties were characterized with biaxial extension and histopathological characteristics were quantified with Verhoeff–Van Gieson Staining. Constitutive modeling was used to calculate physiological stresses and stretches which were then analyzed in the context of demographics, risk factors and structural characteristics. Age had the strongest negative effect ($r = -0.812$, $p < 0.01$) on LPS and could alone explain 66% of LPS variability. Male gender, higher body mass index, hypertension, diabetes, coronary artery disease, dyslipidemia and tobacco use had negative effects on LPS, but only the effect of tobacco was not associated with aging. FPAs with less pre-stretch had thicker medial layers, but thinner intramural elastic fibers with less dense and more fragmented external elastic laminae. Elastin degradation was associated with decreased physiological tethering force and longitudinal stress, while circumferential stress remained constant. FPA wall pathology was negatively associated with LPS ($r = -0.553$, $p < 0.01$), but the effect was due primarily to aging. LPS in the FPA may serve as an energy reserve for adaptive remodeling. Reduction of LPS due to degradation and fragmentation of intramural longitudinal elastin during aging can be accelerated in tobacco users.

Keywords

Femoropopliteal artery; Longitudinal (axial) pre-stretch; Human; Peripheral artery disease; Adaptation

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1. Introduction

It has been known for more than a century [1] that arteries are subjected to significant longitudinal (also often termed *axial* in the literature) tethering stretches. In some cases these stretches can be higher than the circumferential stretches due to blood pressure [2]. However, unlike circumferential stretches that can be measured *in vivo*, assessment of longitudinal tethering stretches requires transection of the artery and measurement of its foreshortening in the longitudinal direction. Perhaps due to lack of a direct *in vivo* measurement method, this crucial longitudinal aspect of the arterial function remains poorly explored in humans arteries, and most of the fundamental observations, with a few exceptions [2–5], are based on animal experiments [6–8].

Patel and Fry [9], Learoyd and Taylor [4], Cox [10], Dobrin [5,11], Fung [12] and van Loon [13] were among the first to recognize the unique behavior of the longitudinally pre-stretched (LPS) artery. They found that in healthy young arteries the longitudinal tethering force that keeps the artery pre-stretched at its *in situ* length, does not change with pressurization over the physiologic range. However, when the artery is held at a LPS above or below this value, the longitudinal force changes in response to differences in pressure, thereby doing “longitudinal work” with each cardiac cycle. The energy efficient function stemming from decoupling of the longitudinal tethering force and the internal pressure has long been considered the main physiologic reason for LPS. Recently however, Jackson et al. [14,15] and Humphrey et al. [6] demonstrated that LPS also plays a fundamental role in compensatory adaptation of arteries to changing mechanical and biological environments, thereby allowing the artery to maintain a desired level of homeostatic multiaxial stress state by reducing LPS. Kamenskiy et al. [2] further demonstrated that aging involves similar adaptive mechanisms and employs reduction of LPS for maintenance of homeostatic stresses. Furthermore, the role of LPS adjustments in vascular adaptation to altered mechanical and biological environments appears to be primary for ensuring energy efficient function, because in aged and diseased arteries the actual *in situ* LPS can be significantly lower than the *in vivo* LPS that ensures decoupling of pressure and longitudinal force [16,17].

The interplay of age, disease and LPS is particularly important in muscular arteries, such as the femoropopliteal artery (FPA), because in addition to promoting energy efficient function and serving as a regulator of the multiaxial homeostatic stress state, LPS prevents buckling [18,19] as the artery deforms with limb flexion and extension during locomotion [2,16,20]. It was recently demonstrated [2,16,20] that in order to facilitate this behavior, the FPA, like many other muscular arteries [21,22], has a thickened external elastic lamina (EEL) with longitudinally oriented elastin fibers largely responsible for the LPS. Since elastin is produced and organized primarily during the perinatal period [6] and matures early in life [23], elastic laminae stretch as the artery grows, resulting in considerable tension during maturity. We hypothesize that degradation and fragmentation of elastin due to aging, cyclic mechanical stress, proteolytic destruction, and other disease processes, decreases LPS which may predispose the FPA to more severe kinking during limb flexion [20] thereby contributing to peripheral arterial disease. In our previous work [2] we have reported reduction of LPS in the FPA with age, but the influence of traditional cardiovascular risk

factors that can act as catalysts in this process was not considered. The goal of this current work was to investigate how LPS in the FPA is affected by cardiovascular risk factors, and how these patient characteristics are reflected in histopathological and physiologic features of human FPAs. This was achieved through a combination of mechanical testing, mathematical modeling, histological evaluation, and statistical analysis.

2. Methods

2.1. Materials

Fresh FPAs from $n = 148$ human tissue donors were obtained under an IRB approved protocol from the Nebraska Organ Recovery System (NORS) within 24 h of subject's death. The current sample size includes arteries analyzed in Kamenskiy et al. [2] ($n = 70$). Donors were 14–80 years old (average age 54 ± 16 years), predominantly Caucasian ($n = 141$) males ($n = 122$). Hypertension (HTN) was diagnosed in 49%, diabetes mellitus (DM) in 24%, dyslipidemia in 24%, coronary artery disease (CAD) in 13%, 58% ever used tobacco, and 25% were abusing alcohol. Tobacco use history was further refined into former light, former heavy, current light, and current heavy users. Most arterial segments began in the common femoral artery prior to the take-off of the profunda femoris artery, excised in continuity to the tibioperoneal trunk. For consistency, all mechanical testing and histology analysis data presented below were obtained from superficial femoral segments of the FPA taken approximately 1–2 cm distal to the profunda femoris artery.

2.2. In situ longitudinal pre-stretch

Prior to excision from the body, the *in situ* length of the femoropopliteal artery segment was measured using an umbilical tape. The tape was placed alongside the surgically exposed artery between the locations at which the artery was transected representing the true *in situ* length of the arterial segment. The artery and the tape were then cut together, and while the umbilical tape maintained its length, the artery typically shortened due to *in situ* LPS. LPS was then defined as the ratio of the *in situ* arterial length (umbilical tape length) to the excised artery length.

2.3. Residual stretches and mechanical properties

After excision from the body, each segment of the FPA was further separated into 5 mm rings that were used for measurement of the circumferential opening angle [2], and two 13 mm long segments that were used for longitudinal opening angle measurement [2] and assessment of biaxial mechanical properties using planar biaxial extension [2,16,21].

Experimental data on the passive mechanical properties were used to determine constitutive model parameters for the FPA wall. Based on histological observations [2,16], the FPA was assumed to be incompressible [24], containing an extracellular matrix composed of a randomly organized amorphous ground substance (W_{gr}), longitudinally oriented elastin fibers (W_{el}), two symmetrical families of collagen fibers wrapping around the artery in a helix (W_{col}), and circumferentially oriented smooth muscle cells (W_{smc}) resulting in a strain energy function (W) of the form: $W = W_{gr} + W_{el} + W_{col} + W_{smc}$. Here $W_{gr} = \frac{C_{gr}}{2}(I_1^{gr} - 3)$,

$W_{el}=\frac{C_1^{el}}{4C_2^{el}}\left(e^{C_2^{el}\left(I_4^{el}-1\right)^2}-1\right)$, $W_{col}=\frac{C_1^{col}}{2C_2^{col}}\left(e^{C_2^{col}\left(I_4^{col}-1\right)^2}-1\right)$, $W_{smc}=\frac{C_1^{smc}}{4C_2^{smc}}\left(e^{C_4^{smc}\left(I_4^{smc}-1\right)^2-1}\right)$ and the corresponding invariants of the right Cauchy–Green tensor **C** are defined as $I_1^{gr}=tr\,\mathbf{C}=\lambda_z^2+\lambda_\theta^2+\frac{1}{\lambda_z^2\lambda_\theta^2}$, $I_4^{el}=\lambda_z^2$, $I_4^{col}=\lambda_z^2cos^2\gamma+\lambda_\theta^2sin^2\gamma$, $I_4^{smc}=\lambda_\theta^2$ where γ is the angle between the collagen fibers and the longitudinal direction, λ_z and λ_θ are longitudinal and circumferential stretches, and ($C_{gr}C_1^{el}$, C_2^{el}, C_1^{col}, C_2^{col}, C_1^{smc}, C_2^{smc}, γ) are constitutive model parameters that were determined from the experimental data using Levenberg–Marquardt minimization [2,16]. Experimental data on the mechanical properties, residual stretches and *in situ* LPS were used to calculate the physiological stress-stretch state corresponding to 120 mmHg of blood pressure [2].

2.4. Histological evaluation

Segments of the artery immediately adjacent to the biaxially tested samples were paraffin fixed and analyzed with Verhoeff–Van Gieson (VVG) Stain. Longitudinal sections were particularly enlightening because they allowed characterization of longitudinal elastin in the EEL [2,16,20–22]. VVG stained sections were scanned at 10× resolution and used to measure thickness of the tunica media, defined as the space between the internal and the external elastic lamina. EEL thickness, density and discontinuity were also characterized, with EEL discontinuity measured on a scale 1–5 with 1 representing perfectly continuous fibers. In addition, the thickness of the individual elastic fibers, and the total amount of elastin in the cross-section were quantified with image analysis. All measurements were independently repeated and verified by three operators.

Human FPAs have several histopathological features that are not typical for other arteries. These include severe medial calcification, primarily fibrous plaques [25,26], and structural changes in the EEL. Though additional histological studies are required for a more comprehensive classification, in order to account for these unique histopathological features and the overall gross pathological damage to the FPA wall, arteries were quantified using a modified six-stage scale (Fig. 1). The modification concerned accounting for the most prevalent pathological damage features to both the intima and media, spanning healthy to severely diseased arteries. **Stage I** arteries had no intimal thickening, no lipid pools, and no calcification; **stage II** arteries had minor intimal thickening and some smooth muscle cell proliferation, but no protruding plaques; **stage III** arteries had plaques with minor protrusion into the lumen, and could have had small pools of extracellular lipid, but no calcium; **stage IV** arteries had minor calcification, protruding plaque with <30% stenosis, and moderate pools of extracellular lipid; **stage V** arteries had severe medial calcification, a stenosis >75%, or EEL degradation and enlarged diameter consistent with early aneurysm formation. These arteries could also have large pools of extracellular lipid; **stage VI** arteries had extremely calcified medial layers, total vessel occlusions, or fully developed aneurysms that represent the most severely damaged artery walls. Though the mechanobiological processes driving each of the three disease pathologies presented in Fig. 1 may be different (i.e.,

medial calcification, atherosclerosis, and aneurysm), they all represent damage to the arterial wall that can affect LPS.

2.5. Statistical analysis

In situ LPS was correlated with intimal-medial pathology, histopathological characteristics, calculated physiological mechanical properties, and subject demographics and risk factors using Pearson correlation r with two-tailed significance levels set at $p = 0.05$. Two types of analysis were performed: one with and one without controlling for age. Controlling for age was achieved by first regressing each variable with age, and then analyzing correlations of the resulting residuals. In addition, a multiple linear regression model was constructed to predict *in situ* LPS based on all the listed independent variables. The model was constructed in SPSS v22 (IBM, Armonk, New York) and a stepwise linear regression was used to determine statistically significant predictors. A variable was entered into the model when the significance level of its F value was less than 0.05. Model quality was assessed with adjusted R^2.

3. Results

Age was the strongest predictor of LPS and alone could explain 66% of variation in LPS. Fig. 2 demonstrates a linear decrease in LPS with age ($r = -0.812$, $p < 0.01$) from >1.55 at the age of 18 to 1.0 (same *in situ* and excised FPA lengths) at 80 years old.

Male gender ($r = -0.239$, $p < 0.01$), BMI ($r = -0.206$, $p < 0.05$), HTN ($r = -0.228$, $p < 0.01$), DM ($r = -0.260$, $p < 0.01$), CAD ($r = -0.233$, $p < 0.01$), dyslipidemia ($r = -0.194$, $p < 0.05$) and tobacco use ($r = -0.235$, $p < 0.01$) negatively affected LPS, while alcohol ($r = -0.155$, $p = 0.056$) had no effect. However, when the analysis was repeated controlling for age, only the effect of tobacco use ($r = -0.199$) was statistically significant ($p = 0.014$), and other risk factors had no effect ($p = 0.879$, $p = 0.628$, $p = 0.870$, $p = 0.922$, $p = 0.464$, $p = 0.512$, Fig. 3). Likewise, when risk factors were used in a multivariate linear regression model to predict LPS, only tobacco use made a statistically significant impact improving prediction by 1% (LPS = 1.586 − 0.007 · Age − 0.008 · Tobacco use).

When age was not controlled, statistically significant correlations were established between LPS and arterial diameter ($r = -0.306$, $p < 0.01$), tunica media thickness ($r = -0.223$, $p < 0.05$), longitudinal opening angle ($r = -0.610$, $p < 0.01$), thickness of elastin fibers in the EEL ($r = 0.443$, $p < 0.01$), elastin density ($r = 0.316$, $p < 0.01$), EEL discontinuity ($r = -0.402$, $p < 0.01$), and FPA wall pathology ($r = -0.553$, $p < 0.01$). However, only the association with medial thickness was independent of aging ($p = 0.015$, Fig. 4A), while other morphometric and histopathological characteristics were merely a reflection of it ($p = 0.063$, $p = 0.411$, $p = 0.935$, $p = 0.350$, $p = 0.399$), including even artery wall pathology ($p = 0.408$, Fig. 4B). No correlations were observed with wall thickness ($r = -0.071$, $p = 0.411$), circumferential opening angle ($r = -0.067$, $p = 0.437$), EEL thickness ($r = 0.164$, $p = 0.067$) or total elastin ($r = 0.164$, $p = 0.066$) with or without controlling for age.

Physiological circumferential stretch λ_θ ($r = 0.323$), longitudinal tethering force F_z ($r = 0.561$) and the associated longitudinal stress σ_{zz} ($r = 0.665$) were higher in FPAs that were

more pre-stretched in situ ($p < 0.01$). Radial stress σ_{rr} ($r = -0.232$) was lower ($p < 0.05$) and circumferential stress $\sigma_{\theta\theta}$ ($r = 0.080$, $p = 0.440$) was not different. Only the effects of tethering force F_z and the associated longitudinal stress σ_{zz} were independent of aging ($p < 0.01$).

4. Discussion

The primary focus of vascular mechanics has long been on the circumferential stress and vessel wall thickness; however, recent studies [2,6,16,27] have emphasized the importance of longitudinal stress for adaptation to the dynamic mechanical and biological environments of arteries. Such adaptation may influence many arterial functional aspects, including loss of energy efficient function [16], and accommodation of complex deformations that are particularly important in the FPA due to limb movements [20]. The focus of this work was to elucidate the longitudinal aspects of human FPA function in the context of clinical risk factors and underlying histopathology.

Our data demonstrate that age is the most important contributor to LPS in the FPA and that this variable dwarfs the effects of most traditional cardiovascular risk factors. Young FPAs are significantly pre-stretched *in situ* and LPS gradually decreases throughout life. Interestingly, none of the risk factors, except tobacco use, significantly affect LPS, and the reduction of LPS is not directly associated with intimal-medial pathology. Though more robust risk factor definitions and assessment, including duration and severity of comorbidities, would be desirable to further confirm these results, our findings suggest that decreasing LPS in FPA is likely associated with normal age-mediated remodeling rather than vascular disease. Similar findings were recently reported by Horny et al. in a different arterial segment – the abdominal aorta [28]. To further clarify these results, let us consider them in the context of the structure and function of the FPA wall.

The two principle proteins of the extracellular matrix that give the arterial wall its mechanical properties are collagen and elastin. The stiffness of collagen is significantly higher than that of elastin, and its main purpose is to provide the arterial wall with strength, preventing overdistension and vessel rupture. Elastin on the other hand, is very compliant and serves to store and then return mechanical energy so the artery can elastically recoil after deformation. In the FPA, both the collagen and the elastin are located primarily in the media and adventitia, with elastin being mostly heavily concentrated in the EEL [2,16,20] (Figs. 1 and 2).

The half-lives of collagen and elastin are very different with collagen turning over continuously and elastin being relatively stable. A high concentration of nonpolar hydrophobic amino acids in elastin make it one of the most chemically, thermally, and protease-resistant proteins in the body. In contrast to collagen, the natural turnover of elastin is on the order of a lifespan of the organism [23]. Having formed during the perinatal period and being remarkably stable, continuous elastic fibers stretch significantly as the artery grows in length, resulting in significant longitudinal tension in healthy mature arteries. The elastin thereby represents a significant energy reserve that the artery can utilize to remodel the ECM and maintain homeostatic stress values [2,6]. As demonstrated previously [2], this

homeostasis includes maintaining circumferential wall stress at a constant level, a feat that can be accomplished by reducing the longitudinal stress through release of LPS by degradation and fragmentation of the longitudinal elastin in the EEL.

The biological means for altering the highly stable elastin within the artery wall include proteases that can be secreted and activated by macrophages and smooth muscle cells. Upregulation of matrix metalloproteinases could release some of the longitudinal tension to allow the artery to adapt to its changed environment. Since elastin in the FPA is concentrated in the EEL and is oriented primarily longitudinally, reduction of LPS is an important indicator of arterial remodeling.

Changes to the arterial environment that require involvement of the LPS energy reserve may involve a variety of factors. For example, during hypertension collagen is deposited to increase the strength of the vascular wall and protect it from overstretch, which results in arterial wall stiffening. Stiff and stressed collagen requires greater force to keep the artery in the same longitudinally pre-stretched condition, so the artery adapts by reducing longitudinal force by increasing its length [29] and reducing the LPS, as demonstrated by our current findings.

In the non-damaged FPA, since LPS is mostly attributed to elastin [6] concentrated in the EEL, a reduction of LPS is naturally associated with structural changes in the EEL. In particular, release of the longitudinal tension is associated with thinner elastin fibers, and a less dense and more discontinuous EEL. Interestingly however, the total amount of intramural elastin is not associated with LPS, likely because the elastin fragments remain in the arterial wall during these adaptations [15]. These fragments, however, do not form continuous fibers and thus do not contribute to replenishing the energy reserve provided by the LPS [14,15]. Another interesting finding is the lack of correlation between EEL thickness and LPS, which could be attributed to the EEL being radially compressed in some remodeled arteries. This radial compression can partially be attributed to compacting of the EEL by hypertrophied or proliferated vascular smooth muscle cells [24] in the media, which, as demonstrated by our analysis, is indeed thicker in older arteries with less LPS.

Perhaps the most intriguing finding is the lack of direct correlation between LPS and arterial wall pathology, which was demonstrated after controlling for aging. This finding demonstrates that reduction in LPS may serve as an adaptive mechanism that does not necessarily lead to pathology. For this discussion, we note that arterial pathology does not necessarily imply intimal atherosclerotic disease, as most arteries in fact demonstrated medial calcification rather than intimal disease, which could simply be a result of adaptation. Reduction of LPS may be a part of this adaptive remodeling, which when taken to extremes could become pathologic. The end-stage pathology, whether it is atherosclerosis, medial calcification, or aneurysm, can be a result of maladaptation in response to changes in the artery's local mechanical or biological environment. Traditional cardiovascular risk factors, particularly tobacco use, likely act as catalysts in these processes. Loss of energy efficient function [16] and more kinking [30,31] of the artery during leg flexion and locomotion [20] as a result of LPS reduction could contribute to pathological changes, but further studies elucidating these hypotheses in the human FPA are warranted.

5. Conclusions

In situ longitudinal pre-stretch of the femoropopliteal artery may serve as an energy reserve for adaptive remodeling. Reduction of longitudinal pre-stretch is primarily associated with aging, and this process is accelerated by tobacco use. The mechanism operating to reduce longitudinal pre-stretch in the femoropopliteal artery is degradation and fragmentation of pre-stressed longitudinal elastin in the external elastic lamina. A better understanding of how mechanical, structural and biological factors interact to produce this compensatory adaptation of the artery to changing mechanical and biological environments will assist in better understanding of pathophysiology and will foster the development of better diagnostic and treatment modalities for patients with peripheral arterial disease.

Acknowledgments

Research reported in this publication was supported in part by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Numbers R01 HL125736 and F32 HL124905. The authors also wish to acknowledge the Charles and Mary Heider Fund for Excellence in Vascular Surgery, the MARC U*STAR Program, and the Nebraska Organ Recovery System (NORS) for their help and support.

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Statement of Significance

This work studies *in situ* longitudinal pre-stretch (LPS) in the human femoropopliteal artery. LPS has a fundamental role in arterial mechanics, but is rather poorly studied due to lack of direct *in vivo* measurement method. We have investigated LPS in the $n = 148$ human femoropopliteal arteries in the context of subject demographics and risk factors, and structural and physiologic characteristics of the artery. Our results demonstrate that LPS reduces with age due to degradation and fragmentation of intramural elastin. LPS may serve as an energy reserve for adaptive remodeling, and reduction of LPS can be accelerated in tobacco users.

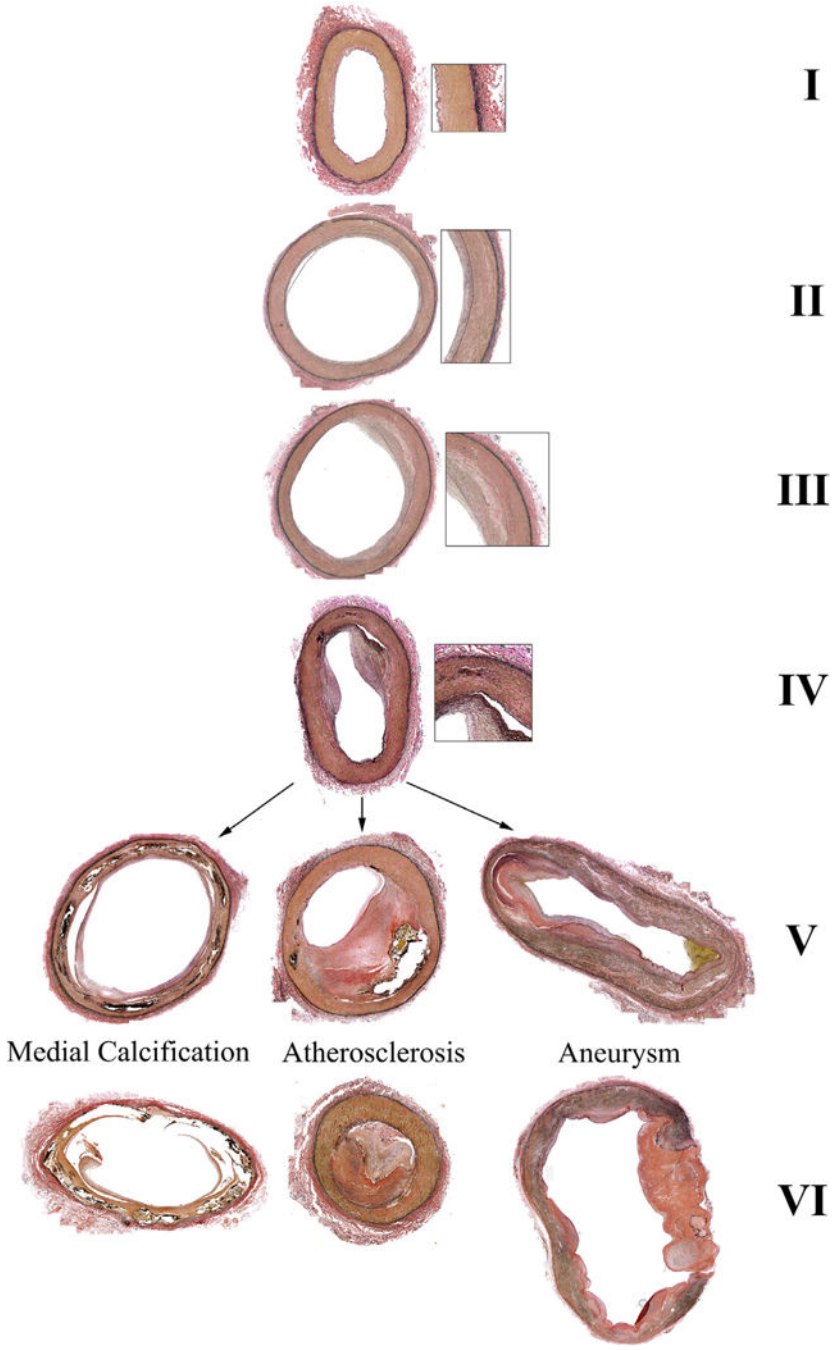

Fig. 1.
Fate of the FPA wall and the modified intimal-medial pathology scale.

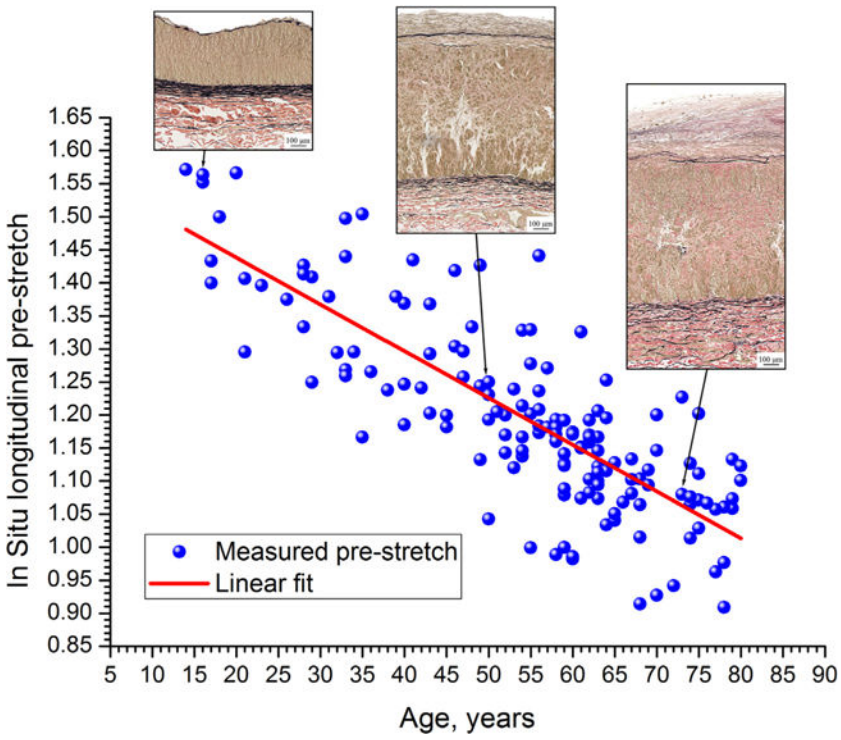

Fig. 2.

Decrease in LPS with age: LPS = −0.00708. Age + 1.57994 and the associated changes in the intramural elastin. Verhoeff–Van Gieson Stain, longitudinal sections.

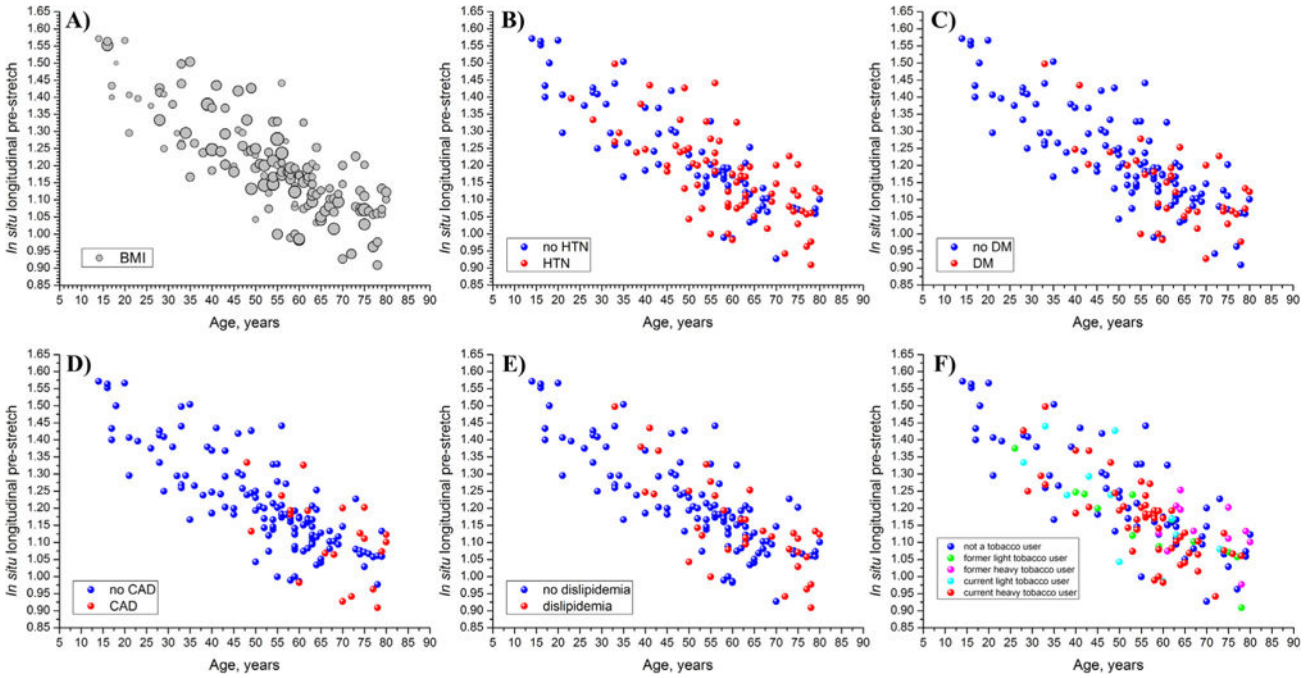

Fig. 3.

Effects of risk factors on LPS: (A) BMI, (B) HTN, (C) DM, (D) CAD, (E) dyslipidemia, (F) tobacco use.

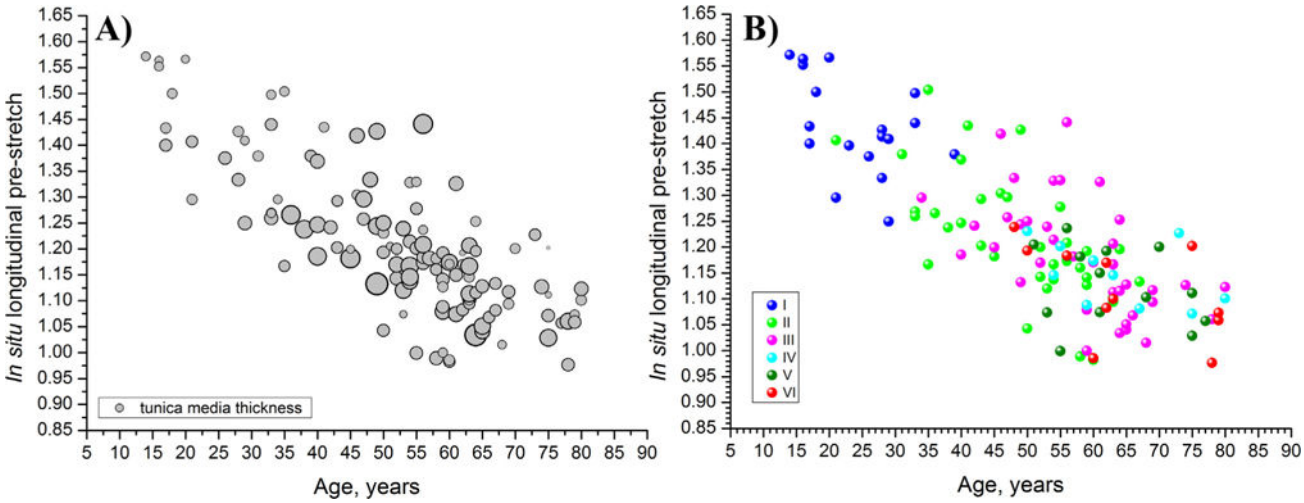

Fig. 4.

Effects of (A) tunica media thickness and (B) intimal-medial pathology on LPS.