

The Adventitia Reduces Left Ventricular Dynamic Afterload Via Smooth Muscle Activation-Dependent Mechanisms

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Introduction and objectives. Ventricular dynamic afterload depends on arterial viscoelastic and geometric properties. Vasoactive factors produced in the adventitia modulate arterial tone. However, it is still not known whether the adventitia is involved in determining the magnitude of the dynamic afterload. The aim of this study was to investigate the role played by the adventitia, via smooth muscle-dependent mechanisms, in determining dynamic afterload.

Methods. The diameter, pressure and flow in brachiocephalic trunks from sheep were measured before and after removal of the adventitia, both in vivo with muscular reactivity preserved (n=8) and in vitro with muscular reactivity abolished (n=8). All studies were performed under similar hemodynamic conditions. Dynamic afterload was determined from elastic and viscous arterial responses, elastic and viscous work, arterial characteristic impedance, and pulse wave velocity. Comparison of in vivo and in vitro findings enabled smooth muscle-dependent changes to be evaluated.

Results. Only in vivo, did removal of the adventitia lead to a reduction in vessel diameter (17.32 [2.02] vs 15.46 [1.28] mm) and to increases in elastic (7.21 [1.39] vs 15.59 [3.00] $\times 10^6$ dyn.cm⁻²) and viscous (5.16 [2.04] vs 9.87 [2.00] $\times 10^5$ dyn.s.cm⁻²) arterial responses, elastic (6.15 [1.08] vs 9.20 [0.76] $\times 10^{-2}$ J/m²) and viscous work (11.61 [2.25] vs 15.20 [2.37] $\times 10^{-3}$ J/m²), impedance (223.97 [136.11] vs 396.33 [182.27] dyn.s.cm⁻³), and pulse wave velocity (397.70 [31.21] vs 598.78 [28.04] cm.s⁻¹) ($P < 0.05$). The reduction in diameter and the increases in elastic and viscous responses are evidence of muscular activation.

Conclusions. The adventitia may contribute to the control of ventricular dynamic afterload by means of mechanisms dependent on muscular tone.

Key words: *Adventitia. Vascular biology. Physiology. Hemodynamics. Arterial impedance. Basic research. Smooth muscle. Dynamic afterload.*

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La adventicia reduce la poscarga dinámica ventricular izquierda mediante mecanismos dependientes de la activación muscular lisa

Introducción y objetivos. Las propiedades viscoelásticas y geométricas arteriales determinan la poscarga dinámica ventricular. Factores vasoactivos producidos en la adventicia modulan el tono arterial. Resta por establecer si la adventicia participa en la determinación del valor de poscarga dinámica. El objetivo de este estudio fue caracterizar el papel de la adventicia en la determinación de la poscarga dinámica mediante mecanismos dependientes del músculo liso.

Métodos. La presión, el diámetro y el flujo se midieron en troncos braquiocéfálicos ovinos antes y después de extraerles la adventicia, en estudios in vivo con reactividad muscular intacta (n = 8) e in vitro con reactividad muscular abolida (n = 8). Las arterias se estudiaron en condiciones hemodinámicas similares. La poscarga dinámica se caracterizó mediante la respuesta elástica y viscosa arterial, el trabajo elástico y viscoso, la impedancia característica arterial y la velocidad de propagación del pulso. Comparar los estudios in vivo e in vitro permitió caracterizar los cambios en la activación dependientes del músculo.

Resultados. Sólo in vivo la extracción de la adventicia determinó una reducción del diámetro (desde 17,32 \pm 2,02 hasta 15,46 \pm 1,28 mm) e incrementos en las respuestas elástica (desde 7,21 \pm 1,39 hasta 15,59 \pm 3,00 10^6 dinas \cdot cm⁻²) y viscosa (desde 5,16 \pm 2,04 hasta 9,87 \pm 2,00 10^5 dinas \cdot cm⁻²), en los trabajos elástico (desde 6,15 \pm 1,08 hasta 9,20 \pm 0,76 $\times 10^{-2}$ J/m²) y viscoso (desde 11,61 \pm 2,25 hasta 15,20 \pm 2,37 $\times 10^{-3}$ J/m²), en la impedancia arterial (desde 223,97 \pm 136,11 hasta 396,33 \pm 182,27 dinas \cdot s \cdot cm⁻³) y velocidad de propagación (desde 397,70 \pm 31,21 hasta 598,78 \pm 28,04 cm \cdot s⁻¹) ($p < 0,05$). El menor diámetro y los aumentos en las respuestas elástica y viscosa evidenciaron la activación muscular.

Conclusiones. La adventicia participaría en el control de la poscarga dinámica ventricular mediante mecanismos dependientes del tono muscular.

Palabras clave: *Adventicia. Biología vascular. Fisiología. Hemodinámica. Impedancia arterial. Investigación básica. Músculo liso. Poscarga dinámica.*

ABBREVIATIONS

VDA: ventricular dynamic afterload
 CBT: common brachiocephalic trunk
 PWV: pulse wave propagation velocity
 W_E : elastic work
 W_V : viscous work

INTRODUCTION

Ventricular afterload is the sum of processes that resist ventricular ejection.¹ The biggest contribution to afterload comes from peripheral vascular resistance—the static or stable component—whereas the dynamic or pulsed component is determined mainly by the geometric and biomechanical properties of the great arteries.¹⁻³ Arteries with smaller diameters give rise to higher impedance to ejection, leading to a higher ventricular dynamic afterload (VDA).¹⁻³ Arterial walls with higher elastic response and viscosity give rise to higher flow impedance—greater output or dissipation of ventricular energy as heat occurs on working against arterial viscosity (viscous work, W_V) and greater ventricular work is required to achieve elastic arterial distension (elastic work, W_E).¹⁻³ In addition, an artery system with smaller diameters and higher elastic response produces a higher wave pulse wave propagation velocity (PWV), and more incident and reflected waves, in turn leading to earlier coincidence of these waves in the central arteries, with the associated increase in VDA.¹ Previous studies have shown that flow impedance, PWV, viscous and elastic response, and as a result W_V and W_E , can be modulated in the great arteries (such as the aorta and the carotid artery) through activation of smooth muscle.²⁻⁴

There are 3 components of the arterial wall, namely, the intima, media, and adventitia.¹ The media, which is mainly comprised of elastin and collagen fibers (passive components) and muscle cells (active component), is the component mainly responsible for the biomechanical behavior of the arteries.^{1,2} The contribution of the intima, mainly comprised of endothelial cells, to the passive viscoelastic properties of the arteries is considered virtually nonexistent.¹ In contrast, the endothelium is recognized to actively regulate the arterial viscoelastic response through release of relaxing or constricting substances that modify muscle tone.^{1,5} Traditionally, the adventitia—which is comprised mainly of adipose tissue, elastin and collagen fibers, and macrophages^{6,7}—was thought to act solely as a physical barrier separating the arteries from other tissues or as a layer providing passive mechanical support, thereby limiting overdistension.^{6,8} At present, it is not known whether the adventitia contributes to biomechanical function of the cardiovascular system through mechanisms dependent on the smooth muscle reactivity (that is, active mechanisms). Previous studies

have shown that the arterial adventitia synthesizes and releases vasoactive factors, and that this layer is affected early in arterial diseases associated with abnormal arterial biomechanical properties.⁶⁻¹⁵ This suggests that the adventitia might actively control the cardiovascular biomechanical properties and, as a result, VDA.

Thus, the aim of the present study was to characterize the role of the adventitia in determining the basal values of left VDA through smooth-muscle-dependent mechanisms.

METHODS

All procedures were carried out according to the guidelines for care and use of laboratory animals issued by the US National Institute of Health (NIH publication number 85-23, reviewed in 1996).

In Vivo Experiments

Eight Corriedale sheep were included in the study (mean [SD] body weight, 30.3 [2.0] kg). The animals were anesthetized by intravenous administration of sodium thiopental (20 mg \times kg⁻¹). Anesthesia was maintained with halothane (1%), administered via the tube deployed for ventilatory assistance (Neumovent 910). The respiratory rate and tidal volume were adjusted to maintain pCO₂ between 35 mm Hg and 45 mm Hg, pH between 7.35 and 7.4, and pO₂ above 80 mm Hg.

The common brachiocephalic trunk (CBT) was approached by thoracotomy and a 6-cm-long segment was marked by suture points at each end. The segments were monitored, in the direction of flow, with flow and pressure meters, and the diameter was measured.^{2,16} Instantaneous flow was measured with a perivascular sensor (Model T206, Transonic Systems Inc, 16A/20A/24A Probes, Ithaca, NY, USA), deployed around the segment.^{2,16} Pressure was measured with a solid-state transducer (Micro Tip, SPC 370 7F, Millar Instruments Inc., Houston, TX, USA) introduced via the right femoral artery (Figure 1).¹⁶ The arterial diameter was recorded by sonomicrometry with a pair of ultrasound crystals (Triton Technology Inc, San Diego, CA, USA) operating at 5 MHz (Figure 1).^{2,16} To ensure that the ultrasound sensors were appropriately deployed, radiofrequency signals were monitored with an oscilloscope (Model 465B; Tektronix TOS 220, Tektronix Inc. Beaverton, OR, USA). The transit time of the ultrasound pulse (1584 ms⁻¹) was converted into distance by the sonomicrometer.^{2,16} Pressure, flow, and arterial diameter were recorded for 30 consecutive beats before and after adventitia removal with the animals in a stable hemodynamic state.¹⁶

In sheep, the adventitia can be removed relatively easily with microdissection equipment because adherence to extravascular tissue and other vascular tissue is weak.¹⁶ When removing the adventitia, the diameter sensors have

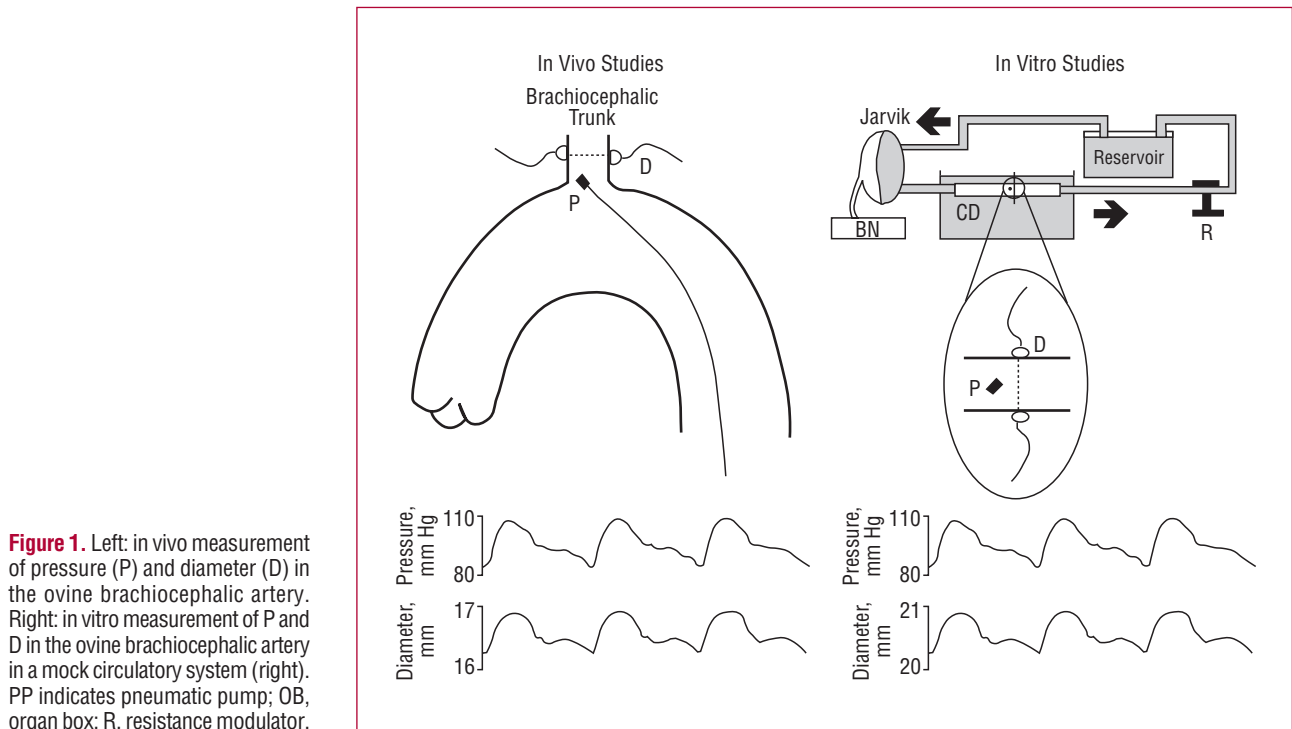


Figure 1. Left: in vivo measurement of pressure (P) and diameter (D) in the ovine brachiocephalic artery. Right: in vitro measurement of P and D in the ovine brachiocephalic artery in a mock circulatory system (right). PP indicates pneumatic pump; OB, organ box; R, resistance modulator.

to be temporarily removed. After removal of the adventitia, the sensors were returned to the exact same site as before. This was achieved by measuring the distance between the origin of the CBT and the sensors before removal and after placement once again.¹⁶

When the animal experiments were completed, the animals were sacrificed by an overdose of sodium pentobarbital followed by administration of potassium chloride. To quantify arterial distension, arterial diameter was recorded at a pressure of approximately 5 mm Hg. Finally, the CBT segment was weighed (with and without adventitia) on a precision balance.^{2,4,5,16}

In Vitro Experiments

Eight sheep, with similar characteristics to those used in the in vivo experiments, were included in the in vitro studies. After the animal had been anesthetized, the CBT was approached by thoracotomy and a 6-cm segment was marked by suture points at either end. The segments were monitored with flow and pressure meters, and the diameter was measured.^{2,16} Pressure was measured with a solid-state transducer (Kongsberg Instruments, Inc., Pasadena, CA, USA) introduced into the artery by means of an incisure (Figure 1).^{2,4} The flow and diameter sensors were deployed as in the in vivo experiments. Once the sensors had been deployed and the animal sacrificed, a segment of the same length as the in vivo study was removed from its site and placed in a mock circulatory system (in vitro studies) (Figure 1).^{4,5,16} The mock circulatory system was able to submit the segments to

hemodynamic conditions that mimicked the magnitude and forms of the wave flow, pressure, and rate recorded in the in vivo experiments.^{4,5,16,17} The segments were perfused with an oxygenated Tyrode solution at a pH of 7.4 and at a temperature adjusted to 37°C.^{4,16} After a stabilization period (5 to 10 min), readings were taken with and without the adventitia.^{4,16} After completing these experiments, the arterial diameter was recorded at a pressure of approximately 5 mm Hg. Finally, the segment was weighed (with and without adventitia).^{2,16}

Data Analysis

Elastic work or maximum elastic deformation (W_E) done by the ventricle to distend the artery, and stored in the form of potential energy in the arterial wall was calculated as³:

$$W_E = - \frac{-2 \times A \times E_{pd}}{\pi} \quad (1)$$

where A is the pulse variation of the cross-sectional area and E_{pd} is the elastic pressure–diameter index. The viscous work or maximum viscous deformation (W_V) done by the ventricle to overcome viscous arterial resistance and dissipated in the arterial wall as heat was calculated as³:

$$W_V = \frac{\omega \times V_{pd} \times A}{\pi} \quad (2)$$

where ω is the angular frequency ($2 \times \pi \times$ heart rate) and V_{pd} is the viscous pressure–diameter index.

E_{pd} and V_{pd} were calculated according to the Kelvin–Voigt viscoelastic model.^{2,4,17} In the model, the total pressure exerted on the wall is broken down into a single element representative of elasticity (spring) and another representative of wall viscosity (damping). It is therefore possible to separate total pressure into an elastic component and a viscous one^{2,4,17}:

$$P_{total} = P_{elastic} + P_{viscous} \quad (3)$$

Rearranging the equation, we obtain:

$$P_{elastic} = P_{total} - P_{viscous} \quad (4)$$

$P_{viscous}$ is proportional to the first time-derivative of the diameter:

$$P_{viscous} = V_{pd} \frac{dD}{dt} \quad (5)$$

where V_{pd} is the viscosity index and dD/dt is the first time-derivative of the diameter.^{2,4,17}

A pressure–diameter index was calculated for each beat analyzed. The hysteresis area of the index decreased as V_{pd} increased iteratively. Once the minimum area had been reached, the iterative loop was detained and the value of V_{pd} obtained was taken as the value of the viscosity index.^{2,4,17} Then, the pressure–diameter ratio once the hysteresis area had been obtained—the pure elastic component—was fitted to the exponential function^{2,4,17}:

$$P = \alpha \times e^{\beta \times D} \quad (6)$$

E_{pd} was calculated as the gradient of the mean diastolic pressure function^{2,4,17}:

$$E_{pd} = \frac{dP}{dD} \Big|_{\text{mean diastolic pressure}} \quad (7)$$

Incremental Elastic Model and Viscous Model

Circumferential stress (δ) and vascular distension (ϵ) were calculated as^{2,4,16,17}:

$$\sigma = 2P \frac{(R_i \times R_e)^2}{(R_e^2 - R_i^2)} \times \frac{1}{R^2} \quad (8)$$

$$\epsilon = \frac{R}{R_0} \quad (9)$$

where P is pressure, R_i and R_e are the internal and external radii, respectively, R is the mean radius [$R = (R_i + R_e)/2$], and R_0 is the arterial radius for pressures of approximately 5 mm Hg. The σ – ϵ ratio was calculated for each beat, and by a similar process to the one described, the hysteresis area was eliminated to yield the viscous

modulus (h).^{2,4,16,17} From the pure σ – ϵ ratio, the incremental elastic modulus (E_{INC}) was calculated as^{2,4,16,17}:

$$E_{INC} = \frac{d\sigma}{d\epsilon} \quad (10)$$

where $d\sigma$ and $d\epsilon$ are the first time-derivatives of stress and distension, respectively.^{2,4,16,17} E_{INC} was calculated for a σ/ϵ corresponding to the mean diastolic stress value.^{2,4,16,17}

Pulse Wave Propagation Velocity and Characteristic Arterial Impedance

The PWV was calculated as^{4,17}:

$$PWV = \sqrt{\frac{E_{INC} \times h_m}{2 \times R_i \times \rho_b}} \quad (11)$$

where h_m is the mean wall thickness and ρ_b the blood density ($\rho_b^m = 1.06 \text{ g} \times \text{mL}^{-1}$).

The characteristic arterial impedance (Z_c) was calculated as¹⁷:

$$Z_c = \frac{PWV \times \rho_b}{CSA} \quad (12)$$

where CSA is the cross-sectional area.

Histological Studies

The CBT segments underwent a histological examination to confirm the integrity of the medial and intimal layers.^{5,16} To do this, histological slices (5 μm thick) were examined under the microscope after hematoxylin-eosin, Gomori, and orcein staining.

Methodological Approach: in Vivo and in Vitro Studies in Brachiocephalic Trunks

The in vivo experiments, done in arteries which retained muscular reactivity, allowed investigation of the role of the adventitia in determining VDA. For these experiments, we analyzed the changes in the factors that determine VDA on eliminating the adventitia.

In vitro studies were performed to distinguish between in vivo effects after removal of the adventitia caused by phenomena related to muscle relaxation or constriction (active changes) and/or by removal of a layer from the arterial wall (passive changes or ones independent of the arterial muscle). These studies allowed analysis of the changes occurring in the factors that determine VDA on removing the adventitia, when the muscle has a reduced capacity to contract or relax. Through comparison of the results of the in vivo and in vitro studies, it was possible to discriminate between participation of smooth muscle and passive phenomena in changes observed in the determinants of the VDA. In addition, bearing in mind that the extent of muscular

TABLE 1. Hemodynamic Parameters*

	In Vivo With Adventitia	In Vivo Without Adventitia	In Vitro With Adventitia	In Vitro Without Adventitia
Systolic blood pressure, mm Hg	110.21 (8.20)	112.16 (8.15)	113.11 (4.82)	111.04 (4.99)
Diastolic blood pressure, mm Hg	81.11 (5.99)	82.11 (6.88)	83.11 (5.01)	83.32 (4.63)
Mean arterial pressure, mm Hg	93.33 (6.71)	94.11 (6.23)	94.37 (5.10)	93.42 (4.45)
Heart rate, beats/min	109.10 (7.78)	108.69 (7.35)	110.45 (5.01)	109.02 (5.08)
Mean flow, mL×min ⁻¹	456.15 (33.31)	454.32 (31.42)	456.13 (15.11)	454.35 (12.98)

*Data are shown as means (SD).

reactivity is the only thing that differentiates between in vivo and in vitro states with the adventitia intact and between in vivo and in vitro states without adventitia, comparison allowed characterization of how smooth muscle determines VDA when the adventitia is intact (physiological conditions) and when the adventitia has been removed (for example, homograft arteries and those in which the adventitia is removed or damaged during dissection), respectively. On the other hand, comparison of the in vivo results with adventitia (normal physiological state) and the in vitro results without adventitia allowed simultaneous analysis of the effect of muscular reactivity and adventitia per se (passive contribution) on the factors that determine basal VDA values.

When selecting the artery to be studied, we sought an artery that, because of its site, would be an important determinant of VDA while not substantially affecting cardiovascular dynamics after removal of the adventitia. The CBT was chosen because it is the only artery in sheep that originates from the aortic arch and heads towards the anterior half of the body, with a diameter and elastic and viscous response values that differ by just 10% to 15% from those of the ascending aorta.⁴ Thus, it was possible to analyze the changes in VDA although these did not lead to cardiovascular changes that would make it impossible to compare situations with and without adventitia.

Statistical Analysis

The data were expressed as means (SD). The 2 types of study (in vivo and in vitro) were compared for situations with and without adventitia by means of the Student *t* test for paired data. Comparisons between groups were done with ANOVA followed by the Bonferroni test. A *P* value less than .05 was considered significant.

RESULTS

Histological studies confirmed that the adventitia had been satisfactorily removed given that the external elastic layer and the medial and intimal layers were intact.

Hemodynamic Parameters

In vivo and in vitro studies were done at similar pressures, flows, and rates, thereby allowing isobaric comparisons and comparisons at the same pressure and rate for the different experimental set-ups (Table 1).

Effects of Removing the Adventitia on Muscle Tone

Figures 2 and 3 show the parameters used to evaluate the contribution of smooth muscle to the biomechanical changes arising from removal of the adventitia. In the in vivo studies, adventitia removal led to a decreased diameter (constriction) ($P<.05$), whereas removal of the adventitia in the in vitro studies did not alter the CBT diameter. The segments studied in vitro had larger diameters than those studied in vivo ($P<.05$).

In the in vivo studies, removal of the adventitia caused an increase in the incremental elastic modulus (Figure 2) ($P<.05$), whereas no differences in elastic response after removing the adventitia were observed in the in vitro studies. The segments with adventitia studied in vitro had a larger elastic response than those with adventitia studied in vivo ($P<.05$).

Only in the in vivo studies did removal of the adventitia lead to an increase in the viscous modulus (Figure 3) ($P<.05$). The arteries studied in vivo had larger viscous moduli than those studied in vitro ($P<.05$), indicating that the viscous modulus depends on muscle reactivity (Figure 3).

In the in vivo studies, the increase in the elastic and viscous moduli along with arterial contraction showed the improved muscle tone (muscle activation) present on removal of the adventitia. In the in vitro studies, the lack of viscoelastic and/or geometric changes arising from removing the adventitia showed that the adventitia did not determine these characteristics per se, that is, passively (Figures 2 and 3).

Effects of Removing the Adventitia on Determinants of Ventricular Dynamic Afterload

Table 2 shows the parameters used to quantify VDA. Only in the in vivo studies did removal of the adventitia

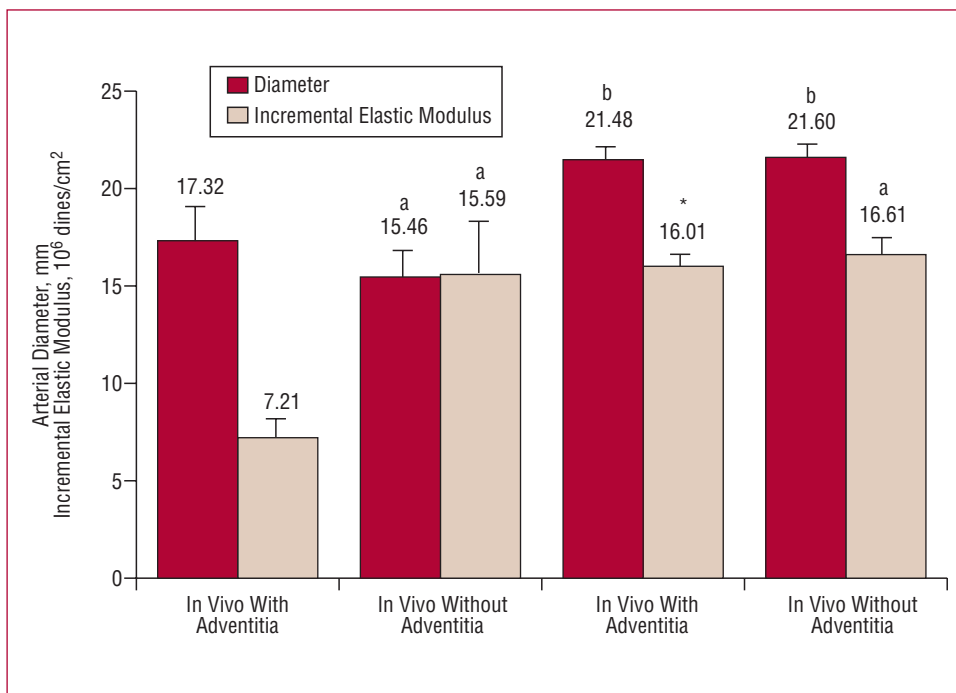


Figure 2. Mean diameter and incremental elastic modulus obtained during the in vivo and in vitro studies, with and without adventitia. The mean values are indicated above each column. ^a and ^b: *P*<.05 compared to in vivo with and without adventitia, respectively. Data are shown as means (SD).

give rise to changes in arterial impedance, PWV, W_E , and W_V (*P*<.05) associated with increased VDA values (*P*<.05).

In vivo study of the segments with adventitia showed greater arterial impedance, PWV, and W_E than the other segments. This indicates how important it is to retain an intact adventitia layer to ensure low values of these determinants of VDA (*P*<.05).

DISCUSSION

The main finding was that removing the adventitia only influenced VDA values in studies in which muscle reactivity was retained. This was shown by the fact that the arterial impedance, PWV, and W_E and W_V only increased after removing the adventitia in the in vivo experiments. On the basis of these findings, we can

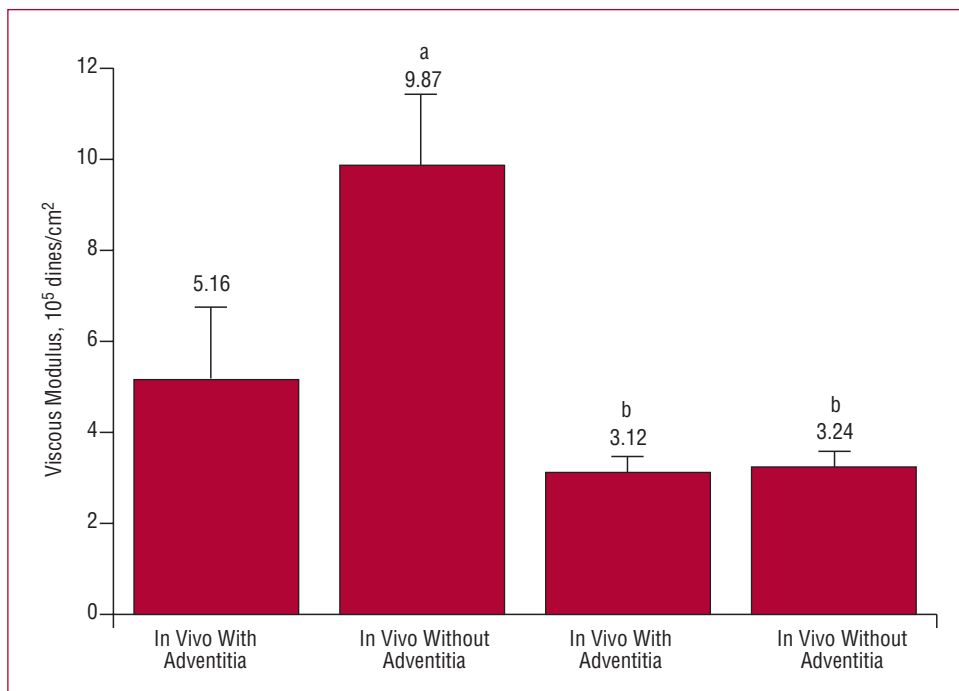


Figure 3. Viscous modulus obtained during the in vivo and in vitro studies, with and without adventitia. The mean values are indicated above each column. ^a and ^b: *P*<.05 compared to in vivo with and without adventitia, respectively. Data are shown as means (SD).

hypothesize that, in vivo and at basal pressure and distension, the adventitia participates in active regulation of VDA. This is achieved by modulating the values of elastic and viscous response and the arterial diameter. In these conditions, the adventitia would keep the VDA low.

In addition, our results show that the action of the adventitia on VDA requires the molecular reactivity to be retained. Therefore, the mechanism by which the adventitia controls the VDA would be muscle-dependent activation. This affirmation is supported by 2 findings. First, the decrease in the diameter in the in vivo experiments with removal of the adventitia (Figure 2) could only be mediated by muscle contraction. If the role of the adventitia in the study conditions was that of limiting overdistension, removal of this layer would have led to dilatation. Second, the increase in the elastic and viscous response (Figures 2 and 3) on removing the adventitia in the in vivo experiments shows that muscle activation took place, as acute modifications to both responses in similar pressure, flow, and heart rate conditions are associated with increased muscle tone.^{2,3} The proven physiologic function of the adventitia, by which muscle tone is supposedly kept low, is in agreement with in vitro studies that have shown that fibroblasts and adipocytes of the adventitia release vasorelaxing substances.⁶⁻¹⁵

Finally, it should be mentioned that the results of the in vitro studies showed that the adventitia did not play a significant passive role in determining VDA at basal hemodynamic states of normal pressure and distension (Figures 2 and 3, Table 3). As a result, the passive role of the adventitia in limiting overdistension of the arteries would not apply in the normal hemodynamic conditions studied. These results agree with those of Schulze-Bauer et al,¹³ who found that at normal pressures, the distensibility of the adventitia is high and not limited mechanically by arterial distension, whereas at high pressures or distension, the distensibility decreases. Distension of the artery is therefore limited in these conditions.

Although in vivo and in vitro analysis of the biomechanical changes produced by reducing the muscle

reactivity by comparing the biomechanical behavior of the arteries with intact adventitia and those without adventitia was not a primary objective of the study, it is worth mentioning that the differences found agree with those reported in previous studies.³

The active role of the adventitia in determining VDA was shown for all the parameters calculated (Table 2). Thus, the elastic and viscous responses increased on removing the adventitia, giving rise to the increases in W_E and W_V necessary for velocity-dependent distension of the arterial system and also for ejection. An arterial system that is unable to dilate quickly enough during ejection provides greater dynamic resistance to ejection.^{1,2} In addition, the greater arterial rigidity and vasoconstriction due to removal of the adventitia led to higher flow impedance. Finally, changes in the arterial wall and diameter resulting from removal of the adventitia caused increases in PWV, leading to an early arrival of the reflected waves in the central arteries (systolic arrival), with the subsequent increase in VDA.¹

Clinical Implications

Whereas the work done by the ventricle to overcome the stable afterload component can be considered absolutely necessary to ensure continuous microcirculation, the work expended to create the characteristic hemodynamic pulses in the large arteries is considered a waste of energy, a result of the inability of the ventricle to generate continuous and stable flows.¹ From this point of view, the high pulses generated in each ejection are an inefficient way for the ventricle to do work and consume oxygen and so, for an appropriate level of peripheral blood flow determined by the tissue metabolic rate, the VDA should be carefully controlled and minimized.¹

Different short-term mechanisms participate in regulating VDA (beat-to-beat)—“global” (for example, autonomic reflexes) and “local” (for example, endothelium-dependent paracrine regulation) which, through regulation of the biomechanical properties and arterial diameter, control VDA values. These mechanisms act mainly by controlling the degree of arterial rigidity.

TABLE 2. Parameters That Determine Ventricular Dynamic Afterload*

	In Vivo With Adventitia	In Vivo Without Adventitia	In Vitro With Adventitia	In Vitro Without Adventitia
PWV, cm×s ⁻¹	397.70 (31.21)	598.78 (28.04)†	710.97 (22.79)†,‡	722.57 (49.39)†,‡
Zc, dynes×s×cm ⁻³	223.97 (136.11)	396.33 (182.27)†	251.52 (19.87)‡	254.66 (29.09)‡
WE, 10 ⁻² J/m ²	6.15 (1.08)	9.20 (0.76)†	17.97 (4.15)†,‡	18.31 (5.67)†,‡
WV, 10 ⁻³ J/m ²	11.61 (2.25)	15.20 (2.37)†	9.61 (2.51)†,‡	9.55 (2.32)†,‡

*PWV indicates pulse wave propagation velocity; WE, elastic work; WV, viscous work; Zc, characteristic impedance.

†P<.05 compared to in vivo with adventitia.

‡P<.05 compared to in vivo without adventitia.

Data are shown as means (SD).

Increases in rigidity lead to increased myocardial oxygen consumption and, as a result, an increase in the work needed to be done to maintain a stable ventricular ejection fraction.^{1,18}

Our results show that the adventitia actively participates in the short-term control of basal VDA and, as a result, suggest that alterations to the adventitia could modify the values of VDA. Thus, interest in the adventitia has recently heightened in view of study findings that showed an association between the active participation of this layer and several cardiovascular diseases (for example, atherosclerosis and restenosis after angioplasty).^{8,10,12-15}

In view of these previous results and our results, we suggest that the function of the adventitia should be reassessed, perhaps as happened 30 years ago with the endothelium. Just as the endothelium was thought to be a passive physical barrier between the arterial wall and the blood but is now recognized as an endocrine/paracrine organ with an important role in short-term control of muscle tone, so the adventitia may also be playing an important role in the control of the cardiovascular system by acting on the arterial muscle. Conceptually, our results agree with recent studies that have suggested that the adventitia of systemic and pulmonary vessels regulate vascular function, both in physiological and pathological situations.¹⁰ In addition, our findings and those obtained recently from *in vitro* experiments provide support for the idea that the adventitia might act as a biological processing center, which receives and integrates information from sources both within and outside the arterial segment and, as a result, releases key regulators of systemic and pulmonary cardiovascular function.¹⁰

Finally, our results show that in vascular studies (for example, those with a ring or strip conformation), removal of the adventitia—the easiest experimental approach—could give rise to changes in the vascular biomechanical properties. This could lead to erroneous conclusions being drawn about the vascular biomechanical characteristics.

CONCLUSIONS

In physiological conditions, the adventitia actively regulates arterial diameter, and the elastic and viscous responses of the arterial walls, through mechanisms dependent on the muscle tone. These actions ensure that the impedance to flow, elastic and viscous work, and the pulse propagation velocity are kept low. The adventitia therefore seem to actively participate in the physiological regulation of VDA values.

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