Large Artery Remodeling During Aging
Biaxial Passive and Active Stiffness

Mohamed A. Gaballa, Christopher T. Jacob, Thomas E. Raya, Jia Liu, Bruce Simon, Steven Goldman

Abstract—To examine arterial mechanical changes during aging, pressure-radius and axial force-radius curves were measured in vivo in carotid arteries from 6- and 23-month-old Brown Norway X Fischer 344 rats. Incremental passive circumferential stiffness (measured at 50, 100, and 200 mm Hg) was higher (P<0.01) in the 23- compared with the 6-month-old rats (14.02±1.23 versus 6.58±1.51; 2.68±0.56 versus 0.99±0.34; 1.10±0.24 versus 0.69±0.15 dyne/mm²×10⁵, respectively). Incremental passive axial stiffness was increased (P<0.01) in the 23- compared with the 6-month-old rats (7.95±0.70 versus 4.24±0.81; 1.91±0.10 versus 0.61±0.16; 0.58±0.09 versus 0.36±0.06 dyne/mm²×10⁴, respectively). Active incremental circumferential arterial stiffness at 100 and 200 mm Hg was increased (P<0.01) in the older rats. In 6-month-old rats, activation of vascular smooth muscle enhanced (P<0.01) the incremental circumferential and axial stiffness measured at 200 mm Hg. In 23-month-old rats, only active incremental stiffness was increased (P<0.01) at 200 mm Hg. Aging increased (P<0.05) media thickness, collagen content, and the collagen/elastin ratio by 12%, 21%, and 38%, respectively. Elastin density and the number of smooth muscle cell nuclei were decreased by 20% and 31%, respectively, with aging. Thus, structural alterations that occur with aging are associated with changes in both active and passive stiffness. Vascular smooth muscle tone modulates arterial wall anisotropy differently during aging. (Hypertension. 1998;32:437-443.)

Key Words: aging ■ arteries ■ muscle, smooth, vascular ■ norepinephrine

The incidence and prevalence of diseases such as heart failure and hypertension increase with aging. The explanation for this is not clear, but previous work has suggested that structural changes in the vasculature occur during aging that result in increases in vascular or arterial stiffness (see References 1 and 2 for review). While structural changes obviously are important during aging, arterial stiffness is determined by both active arterial tone and passive (structural) stiffness. Arterial tone, in turn, is determined by a balance between vasoconstriction and vasorelaxation. Arterial stiffness is a major determinant of vascular impedance, which affects the pulsatile ejection of blood from the heart. The decrease in aortic distensibility that is associated with aging creates a mismatch between ventricular ejection and aortic flow energies, which results in increased aortic systolic pressure, changes in aortic pressure contour, pulse wave reflection, and characteristic aortic impedance.³

Although the anisotropic biaxial material properties of normal arterial wall are well known, there are no biaxial data for aging. Arterial anisotropy is modulated not only by structural alterations but also by the tone of smooth muscle cells in the arterial wall. It is well established that in both human and animal models of aging, large arteries undergo structural changes in the vessel wall. These changes are associated with histopathologic alterations of the arterial wall that are not due to atherosclerosis.⁴ However, it is not clear how these structural alterations affect biaxial passive stiffness in aging. It is also unclear how alterations in vascular smooth muscle cell contractility modulate active biaxial stiffness in aging arteries. Therefore, the objective of the present study was to examine passive and active biaxial stiffness and structural alterations with aging. The hypothesis was that alterations in both active and passive biaxial stiffness of the arterial wall occur during aging.

Previous studies of vascular smooth muscle contraction and activation in aging have been carried out in arterial ring preparations.⁵-six Limited data are available on the effect of aging on vascular smooth muscle function in intact arterial segments. The advantage of studying an intact arterial segment is that the mechanical properties of arteries can be assessed without altering the normal geometry and with minimal handling.⁷-¹¹ Thus, we used an in situ carotid artery, axial, isometric preparation to measure active and passive circumferential and axial stiffness in 6- and 23-month-old Brown Norway X Fischer 344 (BNXF344) rats.

Methods

Instrumentation and Hemodynamics
Two groups of rats (6-month-old and 23-month-old BNXF344) were used. Rats were anesthetized with thiobutabarbital (100 mg/kg...
IP), and the trachea was cannulated and connected to a rodent ventilator. These methods have been reported previously. In brief, a 2-pressure sensor catheter (model FTC 721, Millar Instruments Inc) was inserted into the ascending aorta via the right carotid artery. One sensor was located in the left ventricle and the second sensor was located in the ascending aorta. To correlate changes in arterial stiffness and left ventricular (LV) function, we measured aortic pressure, LV end-diastolic pressure, and dP/dt.

**Active Arterial Stiffness: Active Pressure- and Axial Force–Volume Relationships in Intact Arterial Segments**

After recording of hemodynamic variables, active pressure–volume data were obtained using techniques developed in our laboratory. In brief, the distal end (from the heart) of the left carotid artery was cannulated with PE-50 tubing and connected to a 3-way stopcock. Through the cannula, modified Krebs-Henseleit (mKH) solution (composition in mM/L: NaCl 118, KCl 5.9, CaCl2 2.5, MgSO4 1.2, NaH2PO4 1.2, NaHCO3 25.0, and glucose 5.6 mixed with BSA 4% and Trypan blue 0.3%) was perfused into the carotid artery. The presence of Trypan blue in the perfusate was used to help visually check for leaks in the artery. Leaking arteries were discarded. The presence of proteins in the perfusate maintains a physiological osmotic pressure gradient across the vessel wall. The proximal end of the left carotid at the junction with the aortic arch was occluded using a vascular occluder. The artery was dissected from the surrounding tissue and cleaned from the connective tissue, and the in vivo length of the isolated segment was recorded. The exposed part of the carotid artery was kept immersed in mKH solution and gassed with 95% O2 and 5% CO2. This procedure allowed us to isolate segments up to 2 cm in length. The transmural pressure was raised to 100 mm Hg, and the segment and the neck cavity were perfused with buffer containing the same mKH solution, maintained at 37°C and aerated with a mixture of 95% O2 and 5% CO2 with a resultant pH of 7.4. The distance between the canulans and occluder was kept constant to ensure that the measurements were performed at in vivo length (stretch ratio = 1). In separate experiments, pressure- and axial force–radius curves were measured at different axial stretch ratios. The vascular occluder end of the segment was fixed to the animal’s neck, and the PE-tubing end was connected via a Y-connector to both an infusion pump to generate transmural pressure and a pressure transducer (Millar Instruments Inc) to monitor the intraluminal pressure. The PE-tubing end was also connected to an isometric force transducer (Grass) to measure the isometric axial force during pressurization.

To measure the active pressure–axial force–radius relationships, we used a protocol similar to that reported previously. In brief, after measurements of hemodynamics and mechanical properties, a 2-cm segment of the right carotid artery was perfusion-fixed at the in vivo mean arterial pressure (MAP; 100 mm Hg) and in vivo length. The segments were then dehydrated and embedded in paraffin. Three successive longitudinal sections of 5-μm thickness were treated by specific staining: picrosirius red was used for collagen staining, orcein for elastin, and hematoxylin after periodic acid oxidation for nuclear staining. Microscopic sections were analyzed using an automatic image analysis system composed of a microscope and a PC microcomputer equipped with a 2-D image digitizing board to capture the image from the microscope. Measurements taken were then quantified (Global Laboratory). All morphological measurements were made at the same optimal contrast and brightness for edge detection by software algorithms. A final magnification of ×1000 was used in all fields studied. First, mean media thickness was measured as the distance between the external and internal elastic lamina (5 sections per slide and 5 measurements in each section). Second, medial elastin content was quantified as the relative area of medial elastin lamina, measured using the standard point and intercept counting method built into the software (10 fields per slide). Third, adventitial collagen content was quantified using the standard point and intercept counting method built into the software (10 fields per slide). Collagen and elastin densities were defined as the ratio of the surface stained by either picrosirius red or orcein to the surface of the field studied. Fourth, the number of vascular smooth muscle cell nuclei was counted within 5 fields in each section; the software then measured the cross-sectional area of each nucleus in the field, and these numbers were averaged for each field. Field size area for nuclear density measurements was defined as the mean thickness of the media multiplied by the length of the artery on screen. Nuclear density was normalized to the average field area of 5800 μm² for all groups. Smooth muscle area was defined as the mean media area minus the area of the elastic lamina within the studied field. Repetitive measurements using the same procedures as above were performed and averaged in the corresponding stained sections of the arterial wall. It should be noted that paraffin embedding can introduce shrinkage in the arterial wall. However, the same treatment was performed for both groups.

**Morphometric Measurements**

Measurements of arterial morphology have been previously described by our laboratory. In brief, after measurements of hemodynamics and mechanical properties, a 2-cm segment of the right carotid artery was perfusion-fixed at the in vivo mean arterial pressure (MAP; 100 mm Hg) and in vivo length. The segments were then dehydrated and embedded in paraffin. Three successive longitudinal sections of 5-μm thickness were treated by specific staining: picrosirius red was used for collagen staining, orcein for elastin, and hematoxylin after periodic acid oxidation for nuclear staining. Microscopic sections were analyzed using an automatic image analysis system composed of a microscope and a PC microcomputer equipped with a 2-D image digitizing board to capture the image from the microscope. Measurements taken were then quantified (Global Laboratory). All morphological measurements were made at the same optimal contrast and brightness for edge detection by software algorithms. A final magnification of ×1000 was used in all fields studied. First, mean media thickness was measured as the distance between the external and internal elastic lamina (5 sections per slide and 5 measurements in each section). Second, medial elastin content was quantified as the relative area of medial elastin lamina, measured using the standard point and intercept counting method built into the software (10 fields per slide). Third, adventitial collagen content was quantified using the standard point and intercept counting method built into the software (10 fields per slide). Collagen and elastin densities were defined as the ratio of the surface stained by either picrosirius red or orcein to the surface of the field studied. Fourth, the number of vascular smooth muscle cell nuclei was counted within 5 fields in each section; the software then measured the cross-sectional area of each nucleus in the field, and these numbers were averaged for each field. Field size area for nuclear density measurements was defined as the mean thickness of the media multiplied by the length of the artery on screen. Nuclear density was normalized to the average field area of 5800 μm² for all groups. Smooth muscle area was defined as the mean media area minus the area of the elastic lamina within the studied field. Repetitive measurements using the same procedures as above were performed and averaged in the corresponding stained sections of the arterial wall. It should be noted that paraffin embedding can introduce shrinkage in the arterial wall. However, the same treatment was performed for both groups.
of rats, and that limitation should not have affected the results of the study.

**Statistical Analysis**

All data are presented as mean ± SD. Statistical comparisons between the 2 groups were performed using the unpaired t test. \( P < 0.05 \) indicates level of significance.

**Results**

**Animal Characteristics and Hemodynamics**

Compared with 6-month-old rats, body weight increased \( (P < 0.05) \) in 23-month-old rats \( (432 ± 626 \text{ versus } 605 ± 615 \text{ g}, \ n = 6) \). Left \( (824 ± 653 \text{ versus } 1114 ± 83 \text{ mg}) \) and right \( (210 ± 23 \text{ versus } 281 ± 49 \text{ mg}) \) ventricular weights increased \( (P < 0.05, \ n = 6, \text{ for both variables}) \), while LV/body weight ratio declined \( (2.08 ± 0.09 \text{ versus } 1.84 ± 0.11, \ P < 0.05) \) during aging. Aging decreased MAP and LV dP/dt \( (125 ± 9 \text{ versus } 104 ± 10 \text{ mm Hg and } 8896 ± 901 \text{ versus } 7169 ± 929 \text{ mm Hg/s}, \ \text{respectively}; \ P < 0.05, \ n = 8) \). LV end-diastolic pressure and pulse pressure increased \( (4 ± 3 \text{ versus } 32 ± 5 \text{ mm Hg and } 15 ± 7 \text{ versus } 8 ± 2 \text{ mm Hg}; \ n = 8, \ P < 0.05) \) with age. There was no change in heart rate.

**Passive Pressure– and Axial Force–Radius Relationships**

The passive luminal pressure–radius curve of the 23-month-old rats is shifted to the left of that of the 6-month-old rats (Figure 1). The outer radii were normalized to their corresponding values at 2 mm Hg (minimum intraluminal distending pressure) to account for the increase in radius of aging rats (Table 2). However, the slope of the pressure-radius curve was increased with age at and above the in vivo MAPs. This finding is more evident when the pressure-radius data are converted into circumferential stress-strain data (Figure 2). This figure shows that aging shifts the stress-strain curve left toward the pressure axis, indicative of stiffer arteries with aging.

Blood pressure in vivo stretches arteries biaxially, ie, in circumferential and longitudinal (axial) directions. Therefore, we measured the change in axial force induced by increasing intraluminal pressure (Figure 1). At in vivo length, axial force decreases because arteries expand and elongate simultaneously with increasing luminal pressure (Figure 3). Aging shifts the axial force–radius and axial force–pressure curves upward, indicative of a higher stiffness component in the axial direction with aging (Figures 1 and 3). In addition, the amount of change of axial tension

![Figure 1. Relationship of passive intraluminal pressure and axial force to normalized outer radius for 6- and 23-month-old BNXF344 rats. ▲ and ○ indicate passive pressure-radius curves for 6- and 23-month-old rats, respectively; ▲ and ◯, passive axial force-radius curves for 6- and 23-month-old rats, respectively. Data are mean±SD.](image1)

![Figure 2. Passive second Piola-Kirchoff (2PKF) axial and circumferential stress–Green strain curves, calculated from the measured pressure-radius relationships for 6- and 23-month-old BNXF344 rats. ▲ and ○ indicate passive 2PKF circumferential stress–Green strain curves for 6- and 23-month-old rats, respectively; ▲ and ◯, passive 2PKF axial stress–Green strain curves for 6- and 23-month-old rats, respectively. Data are mean±SD generated in situ carotid arterial segments.](image2)

![Figure 3. Relationship of active and passive axial force to intraluminal pressure for 6- and 23-month-old BNXF344 rats. ○ and ▲ indicate active force–pressure in 23- and 6-month-old rats, respectively; ▲ and ◯, passive force–pressure in 6- and 23-month-old rats, respectively; NE, norepinephrine, and No Ca++, Ca++-free buffer. Data are mean±SD generated in situ carotid arterial segments.](image3)
as the pressure increases from 0 to 200 mm Hg declines with age, indicative of higher axial stiffness in aging rats. Again, this finding is confirmed when the axial tension–radius data are converted to axial stress–strain data (Figure 2). It is clear from these figures that the axial stress–strain curve is shifted to the left and the slope of the axial stress–strain curve is steeper in aging compared with younger rats (Table 1).

### Active Pressure– and Axial Force–Radius Relationships

The effect of smooth muscle activation using the mixed α1,α2-adrenergic agonist norepinephrine on the arterial pressure–radius and axial force–radius curves is shown in Figure 4. Activation of vascular smooth muscle shifted the pressure-radius curves to the left of the passive curve in the 6-month-old rats only (Figure 4). No effect on the axial force–radius curves after vascular smooth muscle activation in either group was observed (Figure 4). However, aging shifted both the circumferential and axial stress–strain curves to the left in the 23-month-old rats (Figure 5).

### Incremental Circumferential and Axial Stiffness

Incremental passive circumferential and axial stiffness was measured at 50, 100, and 200 mm Hg. Circumferential and axial stiffness was higher ($P < 0.01$ for both variables) in the 23-month-old rats compared with the 6-month-old rats (Table 1). Active incremental circumferential arterial stiffness was measured in the presence of $10^{-7}$ mol/L norepinephrine at 50, 100, and 200 mm Hg. The values at 100 and 200 mm Hg increased ($P < 0.01$) in the 23-month-old rats compared with 6-month-old rats (Table 2). In 6-month-old rats, activation of vascular smooth muscle enhanced ($P < 0.01$) the active incremental stiffness in the circumferential and axial directions when measured at 200 mm Hg (Table 2). However, in the 23-month-old rats, activation of vascular smooth cells enhanced ($P < 0.05$) only the incremental axial stiffness at 200 mm Hg (Table 1).

### Morphology

Aging increased media thickness by 12%, collagen content by 21%, and collagen/elastin by 38%. Elastin density and the number of nuclei were decreased by 20% and 31% with aging, respectively. Smooth muscle area was increased by...
18% with aging. No change in elastin content, collagen density, or nuclear cross-sectional area was observed with aging (Table 3).

### Discussion

It is generally accepted that during aging, arterial stiffness and structure and vascular smooth muscle and endothelial cell functions are altered. The present data show that biaxial passive and active stiffness were increased during aging. In 6-month-old rats, activation of vascular smooth muscle enhanced stiffness bidirectionally; however, in 23-month-old rats, only axial stiffness was increased. Hence, an important finding of this study is that vascular smooth muscle activation modulates anisotropy of the arterial wall differently during aging. Aging was also associated with structural modification of the arterial wall that included increases in medial thickness, collagen content, and collagen/elastin ratio but decreases in elastin density and number of nuclei of vascular smooth muscle cells. Although the specific mechanisms responsible for these changes are unknown, our data suggest that changes in arterial stiffness during aging are due to alterations in both the extracellular matrix and intrinsic function in vascular smooth muscle cells.

Mechanical studies predict that cylinders under intraluminal pressure, such as arteries in vivo, deform differently in the radial, circumferential, and axial directions. The deformation in the radial direction is normally small and usually is neglected in vascular mechanical analysis. However, the axial component is significant. Nevertheless, most studies define arterial mechanical properties on the basis of the change in arterial cross-sectional volume (circumferential dimension) as a function of intraluminal pressure, with the assumption that intraluminal pressure does not change arterial length. Recently, with the advance of ultrasound techniques, it has been shown that arteries expand both circumferentially and axially with an increase in intraluminal pressure. Although it is well established that the arterial wall is anisotropic, ie, direction-dependent, biaxial material properties have been reported only for normal arterial walls and in experimental hypertension. In carotid and femoral arteries from normal dogs, circumferential stiffness was higher than the axial stiffness. However, in aortas from normal dogs, axial stiffness was higher than circumferential stiffness. In contrast, in spontaneously hypertensive rats, both axial and circumferential compliance was similar.

Prior studies demonstrating age-related increase in arterial stiffness have been based on measurements of uniaxial stiffness. To our knowledge, the present study is the first report of arterial biaxial stiffness measurements during aging.

The mechanisms of arterial wall anisotropy are multifactorial. One mechanism is the differences in wall architecture and load-bearing components in the circumferential and axial directions. For example, in carotid arteries from dogs, elastin bears load in both the circumferential and axial directions, whereas collagen and vascular smooth muscle cells bear load primarily in the circumferential direction. Another cause of arterial wall anisotropy may be arterial wall adaptation to the in vivo 2-D state of deformation.

In the present study, biaxial passive and active stiffness were altered during aging. One possible mechanism of increased passive biaxial stiffness during aging is structural change in the arterial wall. This finding is consistent with previous reports in other models of aging. For example, in our study the luminal diameter increased by 21% in 23-month-old compared with 6-month-old BNXF344 rats, whereas other studies reported a 50% increase in the luminal diameter of carotid artery walls of WAG/Rij rats. In agreement with other studies, we also showed that the media thickness, collagen content, and collagen/elastin ratio all increased with aging. In the present work, the increase in collagen content with aging may explain the differences between the passive pressure–radius curves at higher pressures (>100 mm Hg, Figure 1). Although there was no change in elastin content in our study, there was a decrease of 11% in elastin density (a measure of fibrillar organization) with aging. This finding is consistent with previous investigations that reported no change in elastin content and a decrease in the percentage of density of elastin with aging. It has been reported that stress-strain relations at lower stresses are modulated mainly by elastin. The observation that elastin content did not change with aging in this study may explain the lack of difference in the stress-strain data between the 2 groups (Figures 2 and 4). Increased collagen insolubility,

### Table 2. Effect of Axial Stretch Ratio on Outer Radius and Axial Force at 100 mm Hg

<table>
<thead>
<tr>
<th>Axial Stretch Ratio</th>
<th>6-mo</th>
<th>23-mo</th>
<th>6-mo</th>
<th>23-mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outer Radius, mm</td>
<td>526 ± 67</td>
<td>459 ± 115</td>
<td>1396 ± 270*</td>
<td>1804 ± 183*</td>
</tr>
<tr>
<td>Axial Force, m</td>
<td>0.970 ± 0.05</td>
<td>0.861 ± 0.05</td>
<td>0.928 ± 0.04</td>
<td>3727 ± 299*</td>
</tr>
</tbody>
</table>

Data are mean ± SD. 6-mo and 23-mo indicate 6-month-old rats (n = 6) and 23-month-old BNXF344 rats (n = 4), respectively.

### Table 3. Morphometric Measurements for Rat Carotid Arteries in 6- and 23-Month-Old BNXF344 Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>6-mo</th>
<th>23-mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial thickness, μm</td>
<td>50.85 ± 1.36</td>
<td>57.15 ± 3.32*</td>
</tr>
<tr>
<td>Elastin density, %</td>
<td>14.35 ± 1.06</td>
<td>11.52 ± 1.40*</td>
</tr>
<tr>
<td>Elastin content, μm²/mm</td>
<td>15.274 ± 1066</td>
<td>13.685 ± 1653</td>
</tr>
<tr>
<td>Collagen density, %</td>
<td>47.37 ± 3.28</td>
<td>50.79 ± 2.84</td>
</tr>
<tr>
<td>Collagen content, μm²/mm</td>
<td>49.888 ± 4.358</td>
<td>60.433 ± 3.075</td>
</tr>
<tr>
<td>Collagen/elastin</td>
<td>3.26 ± 0.06</td>
<td>4.51 ± 0.76*</td>
</tr>
<tr>
<td>Nucleus CSA, μm²</td>
<td>22.17 ± 1.98</td>
<td>24.72 ± 3.15</td>
</tr>
<tr>
<td>Nucleus number (normalized)</td>
<td>24.7 ± 2.9</td>
<td>17.1 ± 2.6*</td>
</tr>
<tr>
<td>Smooth muscle area, μm²</td>
<td>3.913 ± 45.7</td>
<td>4.780 ± 373*</td>
</tr>
</tbody>
</table>

Data are mean ± SD. 6-mo and 23-mo indicate 6- and 23-month-old BNXF344 rats, respectively. CSA, cross-sectional area. n = 6 for both groups.

*P < 0.005; 23- compared with 6-month-old rats.
decreased elastin cross-linking, and increased elastin degradation with age have been reported.23,24 These alterations in the extracellular matrix result in a stiffer arterial wall. Such changes have been thought to be responsible for the changes in physiological and mechanical measurements that show increased arterial wall stiffness during aging in both humans and animals.25,26 Another possible mechanism of increased passive stiffness is the increase in apoptosis. This hypothesis is supported by the finding that the nuclear count of smooth muscle cell decreased by 31% in the 23-month-old rats. Interestingly, nuclear cross-sectional areas were not significantly altered with aging. Collagen fibers were not observed in the media. This suggests 2 possibilities for the decrease in nuclear density. One of the possibilities is vascular smooth muscle cell hypertrophy. This hypothesis is supported by the increase in smooth muscle area with aging. Another possibility is the induction of apoptosis causing the decrease in nuclear count, but this does not explain the increase in medial area.

The increased active biaxial stiffness during aging is probably due to alterations in both structure and vasoactive function. Vascular smooth muscle contraction stimulated by catecholamines plays a role in determining in vivo arterial stiffness.7,15 In normal rat carotid arteries, activation of vascular smooth muscle contributes to circumferential stiffness more than longitudinal stiffness, further modifying arterial anisotropy.13 The findings in the present study and previous work suggest that alterations in pulse pressure, MAP, vascular smooth muscle function, and extracellular matrix remodeling may explain the increase in active biaxial stiffness. The increase in pulse pressure with aging reported in this study is consistent with other reports showing that increased pulse pressure is associated with structural changes in the arterial wall.27 In addition, despite the decrease in MAP with aging, it appears that the vessel wall is modified in the same direction as that observed primarily with hypertension.8 However, there is an underlying age-associated pattern of change that may be independent of the changes in blood pressure and intrinsic to aging arterial cells. First, we and others show morphological and biochemical alterations in arteries from aging animals without hypertension. However, the magnitudes of these alterations are less than those observed in rat strains in which there are age-associated increases in blood pressure.18,19 Second, lowering blood pressure using chronic administration of angiotensin-converting enzyme inhibitor delays but does not prevent the aging-associated changes in the arterial wall.17 Finally, studies show that aging is associated with decreased production of vasoactive substances independent of hemodynamic factors.28–32

In summary, the major new findings of the present study are that (1) under passive conditions, aging alters arterial wall anisotropy, (2) activation of vascular smooth muscle tone alters arterial wall anisotropy differently during aging, and (3) uniaxial stiffness data such as circumferential stiffness measurements should be interpreted cautiously when studying the effect of aging.

Acknowledgments

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19. Li Z, Miyashita Y, Cheng L, Lakatta E, Froehlich J. Remodeling of the arterial wall anisotropy differently during aging, and (3) alterations in the extracellular matrix result in a stiffer arterial wall. Such changes have been thought to be responsible for the changes in physiological and mechanical measurements that show increased arterial wall stiffness during aging in both humans and animals.25,26 Another possible mechanism of increased passive stiffness is the increase in apoptosis. This hypothesis is supported by the finding that the nuclear count of smooth muscle cell decreased by 31% in the 23-month-old rats. Interestingly, nuclear cross-sectional areas were not significantly altered with aging. Collagen fibers were not observed in the media. This suggests 2 possibilities for the decrease in nuclear density. One of the possibilities is vascular smooth muscle cell hypertrophy. This hypothesis is supported by the increase in smooth muscle area with aging. Another possibility is the induction of apoptosis causing the decrease in nuclear count, but this does not explain the increase in medial area. The increased active biaxial stiffness during aging is probably due to alterations in both structure and vasoactive function. Vascular smooth muscle contraction stimulated by catecholamines plays a role in determining in vivo arterial stiffness.7,15 In normal rat carotid arteries, activation of vascular smooth muscle contributes to circumferential stiffness more than longitudinal stiffness, further modifying arterial anisotropy.13 The findings in the present study and previous work suggest that alterations in pulse pressure, MAP, vascular smooth muscle function, and extracellular matrix remodeling may explain the increase in active biaxial stiffness. The increase in pulse pressure with aging reported in this study is consistent with other reports showing that increased pulse pressure is associated with structural changes in the arterial wall.27 In addition, despite the decrease in MAP with aging, it appears that the vessel wall is modified in the same direction as that observed primarily with hypertension.8 However, there is an underlying age-associated pattern of change that may be independent of the changes in blood pressure and intrinsic to aging arterial cells. First, we and others show morphological and biochemical alterations in arteries from aging animals without hypertension. However, the magnitudes of these alterations are less than those observed in rat strains in which there are age-associated increases in blood pressure.18,19 Second, lowering blood pressure using chronic administration of angiotensin-converting enzyme inhibitor delays but does not prevent the aging-associated changes in the arterial wall.17 Finally, studies show that aging is associated with decreased production of vasoactive substances independent of hemodynamic factors.28–32

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