Wall Tissue Remodeling Regulates Longitudinal Tension in Arteries

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Abstract—Changes in blood pressure or flow induce arterial remodeling that normalizes mechanical loads that are imposed on arterial tissue. Arteries are also under substantial longitudinal stretch (axial strain) that may be altered by growth or atrophy of tissues to which they are attached. We therefore tested whether axial strain is also regulated in a negative feedback manner through arterial remodeling. Axial strain in rabbit carotid arteries was increased from 62±2% to 97±2% without altering other mechanical loads on wall tissues. Strain was reduced within 3 days and completely normalized by 7 days. Remodeling involved tissue elaboration, endothelial cell replication rates were increased by 15-fold, and smooth muscle cell replication rates were increased by >15-fold, and substantially elevated DNA, elastin, and collagen contents were recorded. Also, increased rates of apoptosis were indicated by degradation of DNA into oligonucleosomes, and matrix remodeling was reflected in enlarged fenestrae in the internal elastic lamina and increased expression and activation of gelatinases, especially matrix metalloproteinase-2. Intriguingly, reduced axial strain was not normalized, presumably because remodeling processes, apart from cell contraction, are ineffective in decreasing strain, and arterial smooth muscle orientation precludes large effects of contraction on axial strain. (Circ Res. 2002;90:918-925.)

Key Words: remodeling ■ axial strain ■ extracellular matrix ■ proliferation ■ apoptosis

Arteries undergo compensatory remodeling when the mechanical forces that are imposed on them are altered. Accordingly, changes in arterial wall thickness tend to normalize circumferential tensile wall stresses after blood pressure is altered, whereas adjustments in vessel diameter normalize shear stress when blood flow rate changes.1 This remodeling in response to hemodynamic loads influences vascular development, long-term adaptation in the mature circulation, and the progression of important vascular pathologies including hypertension and atherosclerosis.2

Almost all arteries are also under in situ longitudinal stretch of 40% to 65%.2 These longitudinal tensions are maintained by arterial tethering to contiguous tissues; therefore, lateral tissue growth or atrophy during development, or with weight gain/loss, pregnancy, parturition, exercise regimens, or a host of pathophysiological changes will alter these forces. We hypothesized that longitudinal forces, like changes in shear stress and circumferential tension, provide important mechanical cues that drive arterial remodeling. A corollary to this hypothesis is that changes in longitudinal forces also regulate development and adaptation of the arterial system.

We have developed an in vivo model to test whether this longitudinal stretch of arteries is regulated in a negative feedback fashion, as are pressure-derived circumferential wall tension and flow-induced shear stress. We found that increases in axial tension in rabbit carotid arteries were normalized within days through very rapid arterial tissue growth and remodeling. Smooth muscle cells mediated this regulation of axial tension because it took place in the presence or absence of endothelium. Smooth muscle cells also drive remodeling in response to altered circumferential stretch; therefore, these results demonstrate, for the first time, that a single cell population can discriminate tensile forces that are imposed in two different directions and elicit independent adaptive remodeling in response to these loads.

Intriguingly, when an alternate model was used to partially offload axial tension, decreased longitudinal tension was not normalized; instead, arteries became tortuous, a frequent feature of pathological arterial remodeling.3-5 This incapacity to reestablish axial strain may be due to the circumferential orientation of smooth muscle, which prevents contractile function from initiating increases in lengthwise tension. In any event, the findings underscore the adaptive significance of arterial development that ensures substantial axial tension in healthy mature arteries.

Finally, the observations of the present study and previous work raise intriguing questions concerning how arterial tissues are selectively remodeled in response to distinct mechanical forces. How is newly synthesized tissue, whether

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daughter cells or extracellular matrix, delivered such that increases in shear stress result in increased vessel diameter, increases in circumferential tensile stress cause wall thickening and increases in longitudinal tensile stress induce lengthwise arterial growth? We present arguments that a substantial level of prevailing longitudinal tension is important to this selective tissue remodeling.

Materials and Methods

Surgical Elevation of Axial Strain

Adult, male, New Zealand White rabbits (Riemen’s Fur Ranch, St Agatha, Canada) were anesthetized and both common carotid arteries were exposed. Suture markers were sewn into the adventitia of the left carotid arteries and their separation was measured. For determinations of normal axial strain, arteries were then excised and retraction of the tissue between the suture markers was used to determine mean axial strain [(in situ length—in vitro length)/in vitro length×100%], which was 62±2%. In 5 control animals, these data were acquired while continuously monitoring arterial blood pressure. The left carotid artery was freed from surrounding tissue, double ligated near its downstream end, and transected between the ligation, so that retraction could be measured in the pressurized artery as well as after excision.

Experimental rabbits were given heparin, then a segment of the left carotid artery downstream from the suture markers was double ligated, and the intervening segment was excised. The ligatures were used to appose the cut ends of the artery, thus increasing axial strain imposed on the upstream carotid artery (Figure 1A) to 97±2% (Figure 1B). To restore blood flow to the left carotid artery, the right carotid was sectioned and its distal cut end was anastomosed to the left vessel just upstream from the ligation sites (Figure 1A) and incisions were closed.

In 5 anesthetized preparations, arterial diameter was recorded before and after increasing axial strain, while arterial blood pressure was continuously monitored. These data were combined with arterial wall thickness determinations (see the expanded Materials and Methods section found in the online data supplement available at http://www.circresaha.org) to assess circumferential tensile wall stress before and after altering axial strain.

In an additional group of experimental animals, the left carotid artery was completely denuded of endothelium before performing the vascular surgery. Axial strain was measured 1 week later.

In sham-operated animals, the surgeries were performed exactly as for experimental animals, including the end-to-side anastomosis, except that no change in axial strain was imposed on the vessels. This control was assessed at 1 day after strain was increased, when risk of artifacts were greatest, and at 1 week, when remodeling first yielded maximal responses. No differences from unmanipulated arteries were detected. As an additional control at other time points, the right carotid artery was ligated as far upstream and downstream as possible. Marker sutures were placed on the left carotid artery, and then the left carotid artery was clamped at its upstream and downstream ends for the same time that arteries were occluded in experimental animals (1 hour). Otherwise, these rabbits were treated exactly as experimental animals.

Blood Flow Measurements

Blood flow rates in left carotid arteries were measured under anesthesia with ultrasonic transit time flowmeters at 1 day, 1 week, 5 weeks, and 12 weeks after surgery.

Manipulation of Blood Flow Rate

The surgical procedure used to increase axial strain (Figure 1) did not cause detectable changes in shear stress (see Results and online data supplement). To confirm that shear-induced remodeling did not indirectly affect axial strain, we assessed axial strain in left carotid arteries 1 week after ligation of the right carotid artery. We7 and others8 have shown that this procedure causes a doubling of shear stress in the left carotid artery.

Axial Strain and Arterial Tissue Constituents

Rabbits were killed 1, 3, 7, 35, or 84 days after surgery with 0.1-mL intravenous injection of T-61 (Hoechst),9 and axial strain was measured as described above. Additional tissues, harvested at 1 week, 5 weeks, and 12 weeks after surgery and 5 weeks after sham procedure, were stripped of adventitia and bisected longitudinally. One half of each artery was used to determine DNA contents and the other half was used to determine elastin and collagen contents, as previously described.10

Tissue Fixation and Vessel Morphometry

In rabbits killed at 3 days, 7 days, and 12 weeks after surgery, carotid arteries were perfusion-fixed at 100 mm Hg. Excised segments were prepared for histological cross-sections and for en face confocal microscopy (see the following section). Histological cross-sections were stained with hematoxylin and eosin, and standard morphometric techniques were used to assess medial thickness (h), internal circumference (C), medial cross-sectional area (h×C), and arterial diameter (C/π).

Confocal Microscopy and Morphometry of the Internal Elastic Lamina

Tissue segments prepared for confocal microscopy were opened longitudinally and examined en face with a Bio-Rad model 1024
laser scanning confocal microscope. Natural autofluorescence of elastin allowed visualization of the internal elastic laminae (IEL) and the fenestrae that perforate them.11 Image analysis software was used to determine the mean areas and densities (fenestrae/mm²) of the fenestrae.

Cell Proliferation
To assess daily cell replication rates, the thymidine analogue, BrdU (Sigma), was injected intramuscularly at 17, 9, and 1 hour before death in animals used for histology.9 BrdU was detected by immuno-staining with a biotinylated mouse anti-BrdU (Oncogene, BrdU staining kit, HCS24), and sections were counterstained with hematoxylin. Positive and total numbers of cells were counted in 5 nonserial cross-sections of arteries per animal and percent cells staining with a biotinylated mouse anti-BrdU (Oncogene, BrdU staining kit, HCS24), and sections were counterstained with hematoxylin. Positive and total numbers of cells were counted in 5 nonserial cross-sections of arteries per animal and percent cells replicating/day were determined.

Gelatin Zymography and Immunoblotting
Segments of vessel were harvested at 1, 3, and 7 days after surgery and 1 day after sham procedure. Protein was extracted and then equal amounts of protein from each extract were electrophoresed on a 10% SDS-polyacrylamide (SDS-PAGE) containing 0.1% type I gelatin (Sigma). Gelatin degradation was observed as white lytic bands in the gels.

Proteins extracted as described above were electrophoresed (10% SDS-PAGE), then transferred onto polyvinylidene difluoride membranes (Bio-Rad). The membranes were probed with monoclonal anti-human matrix metalloproteinase-2 (MMP-2) purified IgG antibody (ICN) and appropriate secondary antibody, then treated with enhanced chemiluminescence detection reagent (Amersham Life Science) and exposed to x-ray film.

Detection of Apoptotic Degradation of DNA Into Oligonucleosomes
Experimental vessels were harvested at 1, 3, and 7 days after surgery, DNA was extracted, and 5 µg of arterial DNA plus 30-bp oligonucleotide (to control for variability in loading of wells) were incubated with [32P]dCTP and 10 U of Klenow polymerase (Pharmacia Biochem). Radiolabeled DNA was electrophoresed on a 1.8% agarose gel and blotted onto Hybond nylon membrane (ICN). End-labeled DNA fragments were visualized by exposing the membranes to x-ray film.

Apoptotic cells were detected in histological sections by terminal deoxynucleotidyl transferase dUTP nick end-labeling (TUNEL) as previously described.12

Experimental Decreases in Axial Strain
To test whether arteries remodel in response to decreased axial strain, we offloaded axial tension by inserting interposition grafts, between marker sutures before and after vessel excision were determined at the time of surgery and at 12 weeks after surgery. Additional animals were killed 5 weeks after surgery and casts of the left carotid artery were prepared by infusing, via the aorta, Batson’s methylmethacrylate at physiological perfusion pressure.

Statistical Analysis
Significant differences between experimental groups and controls were assessed with ANOVA followed by Dunnett’s tests. Tissue contents/cm vessel length for control animals were corrected for arterial strains imposed by surgery (see Table 2 in the online data supplement). A value of P<0.05 was considered significant. Data are presented as mean±SEM.

An expanded Materials and Methods section can be found in the online data supplement available at http://www.circresaha.org.

Results
Arterial Tissue Remodeling Rapidly Normalizes Increases in Axial Strain
Axial strain in control carotid arteries of 62±2% (Figure 1B) was increased to 97±2% in experimental animals; however, remodeling of arteries normalized axial strains within 1 week. Strain returned to 72±1% at 3 days after surgery and strains at 7 days (67±3%) and 5 weeks after surgery (55±3%) were not significantly different from that of control arteries. No change in axial strain was observed in sham-operated animals.

Arterial pressure was not a major determinant of axial strain. When arteries were freed from contiguous tissue, double ligated, and transected between the ligations, to allow the upstream segment of artery to retract lengthwise while pressurized, only 20.2±1.8% of axial strain persisted. Furthermore, the arterial pressure acting on the ligated end of the artery (end-plate pressure) artifically contributed to, and indeed could fully account for, this residual strain (see online data supplement). These findings indicate that in vivo axial strain in these arteries is attributable to loads imposed by the contiguous tissues to which the vessel is attached.

Increases in axial strain were restored to control values (59±4%) within 7 days after complete denudation of endothelium, which was confirmed by Evans blue dye staining (not shown). We infer that regulation of axial strain is endothelium-independent.

Arterial Tissue Growth in Response to Increased Axial Strain
BrdU labeling detected very few replicating cells in control arteries (Figure 2A), as previously reported for mature blood vessels13,14; however, there was >50-fold increase in endothelial cell replication rate and a 15-fold increase in medial cell replication rate by 3 days after axial strain was increased (Figures 2B and 2C). At 7 days, cell replication rates remained significantly elevated. Cell replication gave rise to significant increases in vessel DNA contents, a measure of cell number because most cells are diploid in healthy arteries. DNA/cm of excised vessel length was increased significantly at 1, 5, and 12 weeks after surgery (Figure 3).

The growth response to elevated axial strain was also manifest as matrix accumulation. Total elastin/cm and collagen/cm of in situ vessel length were elevated significantly at 1 week, 5 weeks, and 12 weeks after surgery (Figure 3). No changes in tissue contents were observed in sham-operated animals at 5 weeks.

This vessel growth was manifest as increased vessel wall thickness and circumference. Arterial diameter increased by 11% at 7 days after surgery (online Table 2 in the online data supplement available at http://www.circresaha.org) and remained elevated at 12 weeks. Medial cross-sectional area was increased by 22% at this time. These changes in vessel dimensions were not due to experimental changes in shear stress, which was unaffected by sham or experimental surgeries (online Table 2).

Matrix Remodeling Also Contributes to Normalization of Axial Strain
We previously showed that en face confocal microscopy can be used to examine remodeling of the internal elastic lamina (IEL) of arteries.11 We now report large increases in the size of fenestrae that pass through the IEL after axial strain was increased (Figures 4A and 4B). The total area of fenestrae per
field was almost doubled by 3 days and remained elevated at 7 days after surgery (Figure 4C). This enlargement was not due to passive stretch of these structures because strain had returned to control levels at the latter time (Figure 1B). At 12 weeks, total area of fenestrae/field had returned to control levels.

The intrafield coefficient of variation of the size of fenestrae was significantly increased at 3 days after surgery and it remained elevated at 7 days, but not 12 weeks (Figure 4D). Increased variability in fenestrae size is most likely attributable to formation of new, and enlargement of preexisting, fenestrae. The density of fenestrae (4320±540 fenestrae/mm² in controls) was not significantly affected by the surgical procedure.

Gelatin zymography of extracts from control arteries revealed a lytic band with a molecular weight of 70 kDa and a very faint band at 62 kDa (Figure 5A). Immunoblotting with an anti–human MMP-2 antibody confirmed that these bands were the latent and active forms of MMP-2 (Figure 5B). Tissue extracted from arteries harvested 1 day after surgery produced much increased activation of MMP-2 and additional lytic bands at 66 and 88 kDa (Figure 5A). The faint 66-kDa band was also detected by the MMP-2 antibody in immunoblots, and we infer that it represents an MMP-2 cleavage product. The 88-kDa and 66-kDa bands were not detected at 3 and 7 days after surgery, but MMP-2 activation (62-kDa band) remained higher than in control arteries at these times. Sham-operated animals (with anastomoses) yield zymograms that were identical to control animals at 1 day after surgery (Figure 5A).

**Apoptosis Participates in Arterial Remodeling After Axial Strain Is Increased**

When DNA extracted from experimental vessels harvested at 1, 3, and 7 days after elevation of axial strain was end-labeled with [32P]dCTP and electrophoresed on an agarose gel, DNA fragments in multiples of 200 base pairs were detected (Figure 6). This DNA ladder, a hallmark of apoptosis, was not detected in unmanipulated carotid arteries. TUNEL labeling revealed that both endothelial and smooth muscle cells underwent apoptosis; furthermore, apoptosis was not localized to specific locations of the vessel wall, eg, the inner versus outer media (data not shown).

**Remodeling in Response to Altered Axial Strain Was Not Due to Changes in Hemodynamic Forces**

Arteries were stretched lengthwise by approximately 22% when axial strain was increased from 62% to 97%. Conservation of mass demands a corresponding, short-term reduction in vessel diameter and/or wall thickness. Changes in these variables will affect circumferential wall stress, according to the Law of Laplace, and/or blood flow–derived shear stress. We found that a 17% decrease in wall thickness was accompanied by a (nonsignificant) 4.5% decrease in vessel diameter (online Table 1). When these data were combined with arterial pressure to estimate circumferential wall stress, no significant change from control values was detected (online Table 1). Effects of circumferential wall stress were not considered further.
Modest effects of increasing axial strain on arterial diameter, when combined with blood flow rate data, produced no short- or long-term effect on shear stress (online Tables 1 and 2). To further assess possible effects of shear on axial strain, we performed ligations of the contralateral carotid artery, which causes a doubling of shear stress.7,8 Seven days later, axial strain (60.0±7%) was not significantly different from that of control arteries (P=0.05). These findings indicate that changes in neither circumferential tensile stress nor shear stress can account for the rapid remodeling that normalized increases in axial strain.

Decreased Axial Strain Is Not Normalized
When axial strain was reduced to 33±2% by surgical implantation of an interposition graft, axial strain remained unchanged at 12 weeks (33±4%). Furthermore, vascular casting revealed that all of these vessels became highly tortuous (Figure 7). Apparently, a substantial axial strain is required to maintain morphological stability of large arteries.

Discussion
Arterial Remodeling in Response to Altered Longitudinal Strain
Tissue remodeling under the influence of mechanical forces generated by blood pressure and blood flow is a primary determinant of arterial structure; however, arteries are also under substantial lengthwise tension that is imposed by attachments to contiguous tissues. The hypothesis underlying
ultimately gave rise to increased DNA contents, and there was substantial accumulation of elastin and collagen. Increased cell number was inferred from increased DNA content because vascular cells are predominantly diploid; however, a small subpopulation of polyploid smooth muscle cells may have expanded under this stimulus. We emphasize that experimental stretch of arteries initially dilated tissue contents/cm; therefore, the growth response we have reported exceeded that required to simply normalize wall structure. Indeed, arterial tissue, especially extracellular matrix, accumulated at a nearly unprecedented rate after axial strain was increased. Net tissue accumulation after arterial injury dramatically increased blood flow rate, or the onset of experimental hypertension proceeds much more slowly than we observed with increased longitudinal tension. Furthermore, developmental accumulation of wall tissue constituents approaches the rates described herein only for a brief episode in the immediate perinatal period. Unsurprisingly, not all of this growth was axial; instead, vessel diameter was chronically elevated. That this occurred while blood flow rates were normal suggests that complete normalization of axial strain took precedence over negative feedback regulation of shear stress.

The participation of apoptosis as well as cell proliferation in this tissue remodeling, despite net growth, is consistent with reports that cell death accompanies normal arterial development and the growth-related remodeling elicited by hypertension. It is likely that some cell death is necessary for local tissue reorganization during most or all modes of arterial remodeling.

We also found that matrix reorganization, ie, growth of fenestrae that perforate the elastic laminae, contributed to remodeling in the axial direction, just as it contributes to circumferential growth when blood flow rate is elevated. Enlarged fenestrae were not due to passive stretch because strain had returned to control levels by 7 days, when fenestrae remained much enlarged. Furthermore, enlargement was delayed after imposition of stretch, a finding that suggests an active process. An increase in variability in size of the fenestrae was also consistent with formation of new, and enlargement of preexisting, fenestrae. At 12 weeks, the size of fenestrae returned to control levels, probably because elastin accumulation partially refilled these structures. Previous work has shown that accumulation of newly synthesized elastin is somewhat concentrated around the fenestrae.

Presumably, enlargement of fenestrae and other aspects of matrix remodeling are due at least partly to the activities of matrix degrading enzymes. Two matrix metalloproteinases, MMP-2 and MMP-9, are elastolytic and are frequently implicated in arterial tissue remodeling. Latent MMP-2 is expressed constitutively in large arteries, whereas expression and activation of MMP-9 are often initiated during arterial remodeling. Gelatin zymography and immunoblots revealed the presence of latent MMP-2 in control arteries, as previously described. Both the expression and activation of this enzyme were upregulated one day after axial strain was increased and MMP-2 activation remained elevated at 3 and 7 days. In addition, a gelatinolytic band at 88 kDa was detected at this time. This band probably discrimination these forces.

Autoradiogram of DNA gel illustrating degradation of DNA into oligonucleosomes, a hallmark of apoptosis. DNA was extracted from unmanipulated control carotid artery and arteries at 1, 3, and 7 days after axial strain was increased (n=3 for each group). The bottom band in each lane represents a 30-bp oligonucleotide that was added to all samples to control for variability in loading of the gels. Lane S contains DNA size markers at multiples of 100 bp.

Regulation of axial tension survived endothelial denudation; therefore, medial smooth muscle cells are probably both the sensor and effector for this remodeling. This finding is intriguing because smooth muscle cells are also sensors of circumferential tension. We infer that arterial smooth muscle can distinguish and respond with appropriate remodeling to tensions that are exerted on them in two orthogonal directions. We know of no other cell type for which this has been demonstrated. Presumably discrete mechanotransducer mechanisms within these cells discriminate these forces.

Axial strain was normalized partly through very rapid tissue synthesis; essentially, the stretched artery grew into its new length. Dramatically accelerated cell proliferation rates in this study was that axial tension is subject to negative feedback control, as are circumferential tension and shear stress. The current study confirmed that tissue remodeling rapidly normalizes increases in axial strain. Assessment of changes in shear stress and circumferential tensile stress ruled out these forces as significant contributors to tissue remodeling in our experimental model because neither was significantly altered by our experimental procedures. Furthermore, experimental increases in shear stress failed to elicit the rapid remodeling we detected after axial strain was increased.

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represents the active form of MMP-9. We have not demonstrated that these enzymes are critical to offloading of axial strain and other matrix-degrading enzymes may be produced or activated; however, we have demonstrated the upregulation of matrix-degrading activity in concert with other aspects of stretch-induced medial remodeling.

Strikingly, arteries failed to normalize axial strain after it was decreased, rather than increased, by placement of interposition grafts. Indeed, all vessels that contained long-term interposition grafts developed pronounced tortuosity even though the surgical procedure left substantial residual strain (approximately 30%). These findings suggest that anatomic stability of arteries depends on the presence of a substantial axial load. A future publication will fully characterize responses to decreased longitudinal strain.

That regulation of arterial strain occurred when it was increased but not when it was decreased contrasts with other modes of mechanically-induced arterial remodeling. Increased or decreased circumferential tension induces thickening or thinning of the artery wall, whereas chronic increases or decreases in blood flow rate elicit structural increases or decreases in vessel diameter. An obvious explanation for our finding is that most cellular mechanisms that achieve arterial remodeling do not increase axial strain. Cell proliferation and matrix synthesis offload axial strain, and apoptosis and matrix degradation create voids in the tissue space that cannot increase axial strain. Contractile function can be a potent initiator of tissue remodeling, but circumferentially oriented smooth muscle cells in most arteries are poorly positioned to exploit contraction to adjust axial dimensions.

Our finding that experimental increases in axial arterial tension stimulate arterial growth strongly suggests that the physiologic and pathophysiologic increases in axial tension, transmitted from contiguous tissue, will have a similar effect. We therefore hypothesize that developmental growth of many tissues stimulates lengthwise growth of intrinsic blood vessels. In the mature circulation, the same concept may apply to the vasculature of female reproductive tissues during the menstrual cycle, that of maternal tissues during pregnancy, and to the coronary circulation during cardiac hypertrophy. Failure of arteries to normalize decreases in axial strain has important implications for vascularization of atrophying tissue, eg, the uterus after parturition or the regressing corpus luteum, that merit further investigation.

Implications for Remodeling Induced by Altered Blood Pressure and Blood Flow

Both increased blood pressure and increased blood flow stimulate arterial growth, but a different panel of cellular responses must ultimately produce wall thickening with hypertension and increased diameter when flow is elevated. These include differential effects on contractile tone in the earliest phases of remodeling and differential remodeling of elastin at later times. Newly synthesized elastin accretes onto the inner and outer surface of elastic lamellae to contribute to wall thickening, whereas altered blood flow results in modulation of the size of fenestrae, which contributes to adjustments of vessel diameter. Undoubtedly, other remodeling processes further contribute to differential growth of wall thickness and vessel diameter.

An equally significant but virtually ignored issue relates to how growth responses, whether induced by mechanical or other stimuli, lead to increased vessel diameter and/or wall thickness without increasing vessel length. This is important because the ends of most arteries are anatomically fixed at their origins at parent vessels and their terminations into daughter branches; consequently, increases in vessel length imply the development of tortuosity. Tortuosity is a manifestation of profound arterial growth, eg, the development of convoluted collateral vessels after arterial occlusion; however, substantial growth occurs without evidence of this gross anatomic abnormality.

Conceivably, smooth muscle cells could deliver new tissues, whether matrix or daughter cells, only in the radial and/or circumferential directions, but this is unlikely. Instead, we have argued that the development of tortuosity is obviated by the substantial longitudinal strain that characterizes most arteries. Accordingly, tissue synthesized at any site along the artery may be delivered in all directions including axially; however, axial growth at this site allows the remainder of the artery to retract lengthwise under tension. Because vascular tissue is incompressible, this retraction is accompanied by increased thickness and/or circumference, ie, axial growth at one site is translated into circumferential or radial growth of the rest of the vessel.

We further argued that if continued growth fully offloads axial tension, then further tissue elaboration will cause tortuosity, as occurs with the tremendous enlargement of collateral vessels in arterial occlusive disease. It is also noteworthy that aging is accompanied by continuous, slow growth of arteries that is often exacerbated by hypertension and by gradual offloading of axial tension. These factors may produce the tortuosity that is common in aged arteries. Our findings generally support this interpretation, except that tortuosity occurred after axial tension was only partially offloaded. Apparently, arterial morphology becomes unstable at finite levels of axial strain.

In summary, we have shown that increased axial stretch of arteries is rapidly normalized through the combined effects of tissue growth and remodeling. These findings support the hypothesis that axial strain is physiologically significant and may be important for maintaining normal arterial morphology during arterial growth responses. Incapacity to normalize decreased axial strain underscores the importance of finite axial strain under normal conditions.

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