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Elastin in large artery stiffness and hypertension

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Abstract

Large artery stiffness, as measured by pulse wave velocity (PWV), is correlated with high blood pressure and may be a causative factor in essential hypertension. The extracellular matrix components, specifically the mix of elastin and collagen in the vessel wall, determine the passive mechanical properties of the large arteries. Elastin is organized into elastic fibers in the wall during arterial development in a complex process that requires spatial and temporal coordination of numerous proteins. The elastic fibers last the lifetime of the organism, but are subject to proteolytic degradation and chemical alterations that change their mechanical properties. This review discusses how alterations in the amount, assembly, organization or chemical properties of the elastic fibers affect arterial stiffness and blood pressure. Strategies for encouraging or reversing alterations to the elastic fibers are addressed. Methods for determining the efficacy of these strategies, by measuring elastin amounts and arterial stiffness, are summarized. Therapies that have a direct effect on arterial stiffness through alterations to the elastic fibers in the wall may be an effective treatment for essential hypertension.

Keywords

extracellular matrix; mechanics; pulse wave velocity; compliance

1. Introduction

It is well established that total peripheral resistance is increased in hypertension and that this is related to structural changes in the resistance vessels. The resistance vessels exhibit inward eutrophic remodeling, which may be caused by chronic vasoconstriction [1]. Numerous investigations have focused on the mechanisms underlying this remodeling, but none have been able to prevent hypertension. Hypertension is an increasingly global disease and it is estimated that 1.56 billion people will have hypertension by 2025 [2]. Recently, there has been an increased focus on changes in the large elastic arteries that accompany hypertension. It has been shown that blood pressure is independently associated with pulse-wave velocity (PWV), which is a direct measure of large artery stiffness [3]. PWV is increased even at the very early stages of hypertension when arterial pressure is at a borderline level [4], suggesting that arterial stiffening may be a causal factor in essential hypertension.

Passive stiffness of the large elastic arteries is determined mainly by the extracellular matrix (ECM) components in the arterial wall. While smooth muscle cells (SMCs) contribute significantly to the mechanical behavior of small, muscular arteries, they contribute

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minimally to the mechanical behavior of large elastic arteries [5]. The major ECM components in large elastic arteries are the proteins elastin and collagen. Elastin provides reversible extensibility during cyclic loading of the cardiac cycle [6], while collagen provides strength and prevents failure at high pressure [7]. Elastic fibers are degraded and fragmented with age and disease, leading to increased stiffness of the arterial wall [8]. Increased arterial stiffness is an important, independent predictor of cardiovascular mortality in patients with hypertension as well as end-stage renal failure, diabetes, and most recently in middle-aged and older adults [9]. Besides functioning as a risk marker, increased stiffness begins a negative feedback cycle that increases the mechanical load on the heart and accelerates heart failure.

2. Elastic fibers in the arterial wall

Elastic fibers are organized in the medial layer of large elastic arteries as an interconnecting, fenestrated network. Each layer of elastic fibers has an associated layer of circumferentially oriented SMCs and collagen fibers and the composite structure is known as a lamellar unit. The number of units is established during development and is directly related to the tension in the wall, so that the tension/lamellar unit is constant across mammalian species and throughout the arterial tree [10]. In an unloaded artery, the elastic lamellae appear undulated and wavy. As the pressure increases, they straighten as they begin to bear load and are mostly straight at physiologic pressures [11]. The collagen fibers also appear undulated and wavy in an unpressurized artery, but in contrast to the elastic lamellae, less than 10% of the collagen fibers are straight and load-bearing at physiologic pressures [12]. As the pressure increases above physiologic values, more collagen fibers become load bearing and their stiffness limits arterial distension, providing the classic nonlinear behavior observed in arterial mechanics [13] (Figure 11).

The mechanical properties of the arterial wall depend on the complex mix of ECM components produced by the SMCs. Elastic fibers are assembled during tissue development and function for most of the lifespan of a vertebrate animal [14]. It is important to differentiate between mechanically-functional elastic fibers, the insoluble protein elastin and the soluble protein tropoelastin, although the terms are sometimes used interchangeably. Tropoelastin is the soluble, monomeric form of elastin secreted by cells. Its initial assembly involves the formation of elastin aggregates on the cell surface, with the assistance of the crosslinking enzyme, lysyl oxidase, and helper proteins such as fibulin-4 and/or fibulin-5. The crosslinked aggregate is transferred from the cell surface to microfibrils composed primarily of the fibrillins, MAGPs, and one or more of the fibulins (Figure 2). The aggregates are then further assembled and crosslinked to form the complete elastic fibers [15]. Elastin and the associated proteins (lysyl oxidase, fibrillins, fibulins, etc.) are expressed at the highest levels during the late embryonic and neonatal period and are expressed minimally in adult animals [16]. One of the challenges of producing functional elastic fibers in adult animals is recreating the complex temporal, spatial and structural interactions necessary for elastic fiber assembly.

3. Genetic mutations in the elastin gene

Mutations in the elastin gene (*ELN*) generally fall into two disease classes. Loss of function mutations, such as premature stop mutations, large intragenic deletions, and complete gene deletion, lead to supravalvular aortic stenosis (SVAS, OMIM 185500), an autosomal dominant disease that predominantly affects the large elastic arteries [17-21]. The cardiovascular phenotype includes hypertension, aortic stenosis, increased arterial stiffness and eventual cardiac failure and death. Pathologic studies of the affected vessels show hypertrophy and hyperplasia of SMCs, fragmentation of elastic lamellae and changes in

ECM composition [22]. Most of the premature termination mutations associated with SVAS result in either an unstable mRNA transcript that is degraded through nonsense mediated decay (NMD) [21], or the generation of a truncated protein that lacks the sequences in exon 30 and 36 required for self-association and interaction with microfibrils [23]. The mutant elastin protein is essentially nonfunctional and, importantly, does not interfere with the assembly or function of elastin from the normal allele. Hence, SVAS mutations result in elastin haploinsufficiency at either the mRNA or functional protein level and it is the decreased amount of normal elastin that is responsible for disease pathogenesis. There is a direct correlation between elastin levels and abnormal tissue function, with the greatest changes occurring in the large elastic arteries and, to a lesser extent, the lung. Skin, another elastin-containing tissue, is relatively unaffected.

A second group of elastin mutations defines an autosomal dominant form of cutis laxa (ADCL, OMIM 123700) and arises from nucleotide deletion, insertion, or exon-splicing errors that produce missense sequence, usually near the 3' end of the transcript [24-27]. While skin is the major organ affected in ADCL, mutations of this type can result in abnormalities in other organ systems [28-31]. In contrast to the loss of function mechanism associated with SVAS, evidence suggests that the molecular basis of the ADCL phenotype is a dominant-negative effect, with the mutant elastin transcript adversely affecting elastic fiber assembly, turnover, or function. In affected tissues of individuals with ADCL, there is loss, fragmentation, or severe disorganization of elastic fibers [30], with the onset of symptoms beginning at any age. The clinical phenotype is variable, ranging from loose and sagging skin—the defining phenotype in this disease—to severe pulmonary complication and mild internal organ involvement [28]. Although ADCL mutations are not directly associated with hypertension, a polymorphism in the 3' untranslated region of *ELN* is significantly correlated with PWV and hypertension [32].

Cutis laxa can also arise from mutations in genes other than elastin and can be inherited as X-linked or recessive (ARCL) forms [33]. A common element in these other types of the disease is that the causative mutations are in genes for proteins that are involved directly or indirectly with elastic fiber synthesis, secretion or function. For example, lysyl oxidase requires copper as a cofactor that is transported into the cell by ATP7A, the gene mutated in the X-linked form of cutis laxa. Fibulin-4 and -5 play critical roles in elastic fiber assembly and mutations in the genes for these proteins have been linked to ARCL Type I [34-39]. Therefore, mutations in elastin and/or the associated proteins necessary for assembly and maintenance of the elastic fibers may affect the mechanical properties of the large arteries.

4. Animal models of reduced elastin amounts and hypertension

The contribution of elastin to arterial stiffness and hypertension can be studied systematically with genetically modified mice. Elastin knockout (*Eln-/-*) mice die within a few days of birth. The arteries of wildtype (WT) and *Eln-/-* mice look similar until embryonic day (E) 17.5, after which there is a marked increase in cell number in *Eln-/-* arteries and a subendothelial accumulation of cells that eventually blocks the lumen, preventing blood flow [40]. At E18, morphological and ultrastructural differences between WT and *Eln-/-* arteries are minor [41] and left ventricular systolic blood pressures are similar (Figure 3A). However, even at this early stage, there are significant differences in incremental arterial stiffness (Figure 3B). By P1, the left ventricular pressure in *Eln-/-* mice is double that of WT, the aortic stiffness is significantly increased (Figure 3C), the SMCs in the wall are disorganized and overproliferating, and the vessels are tortuous and have local stenoses and dilations [42]. Hence, increases in arterial stiffness precede changes in blood pressure and arterial morphology. The last three days of mouse development correspond to dramatic increases in blood flow and blood pressure in the mouse. The *Eln-/-* mouse dies

because without elastin, the arteries cannot withstand the increased stresses that accompany the hemodynamic changes in late embryonic development. Elastin plays a mechanical role in the arterial wall, but also functions as a signaling molecule. In isolated SMCs, soluble tropoelastin inhibits proliferation, induces the formation of organized actin stress fibers and serves as a chemoattractant [43]. The combination of mechanical and cell signaling changes in *Eln-/-* mice may contribute to the observed cardiovascular alterations.

Elastin heterozygous mice (*Eln+/-*) serve as a model of SVAS and allow investigation into the cardiovascular effects of reduced elastin amounts. Adult *Eln+/-* mice have high blood pressure, increased arterial stiffness and smaller, longer vessels. Despite these changes, they have only mild cardiac hypertrophy and a normal lifespan [44-46]. The lack of expected cardiovascular changes in hypertension is not due to reduced remodeling capability in *Eln+/-* arteries. If blood pressure is artificially raised in adult *Eln+/-* mice by restricting blood flow to one kidney, the arteries thicken and the heart weight increases as expected [47]. Blood pressure and in vitro arterial mechanics were measured at multiple ages in *Eln+/-* mice to determine if increased arterial stiffness precedes the development of hypertension. It was found that stiffness is significantly increased in the *Eln+/-* aorta by P7, while systolic blood pressure is not significantly increased until P14, indicating that increased large artery stiffness may be a required precursor for increased blood pressure in this animal model [48].

Eln+/- mice show unique changes in arterial wall structure in the form of increased lamellar units in all elastic arteries. Subsequent analysis of SVAS patients shows a similar adaptation in the arterial wall structure of humans with reduced elastin levels [45]. The increase in lamellar units and lack of remodeling response to the baseline level of increased blood pressure in *Eln+/-* mice suggest that the arteries are able to remodel in response to increased hemodynamic stresses during the developmental period [44]. Ultrastructural studies show that the additional layers arise just before birth in the inner layer of the adventitia [42]. This region supports a population of SMC progenitor cells [49] that may contribute to the formation of additional lamellar units. Studying the development of increased lamellar units in *Eln+/-* mice will be important for reproducing functional elastic lamellae in injured or aged arteries.

Mice have been generated that express human elastin in a bacterial artificial chromosome (BAC-ELN) [50]. Crossbreeding the BAC-ELN mice with the *Eln+/+, Eln+/-* and *Eln-/-* lines produces mice with a spectrum of elastin amounts from 30 – 120% of normal levels. Data from these mice show that elastin amounts are inversely proportional to arterial stiffness and blood pressure (Figure 4), which is consistent with data obtained in humans with SVAS. Expression of the human elastin gene in *Eln+/-* mice increases elastin amounts from about 60% of normal levels to 80% and reverses the changes in both arterial stiffness and hypertension. These data show that high blood pressure can be prevented by addressing the symptoms causing increased vessel stiffness, namely reduced elastin amounts.

5. Elastin and arterial stiffness in aging

In normal aging, the elastic lamellae become fragmented and discontinuous and the mechanical load is transferred to collagen fibers, which are 100 – 1000 times stiffer than elastic fibers. Studies on purified elastic material from pig aorta show an inverse relationship between the amount of stretch and the amount of cycles before failure, which is consistent with fatigue failure in elastomeric materials [8]. While elastin is one of the most stable proteins in the ECM, it can be degraded by proteolytic enzymes with “elastase-like” activity. These include proteases of almost every class, including serine (eg., neutrophil and pancreatic elastase) and cysteine (cathepsins) proteases, as well as several members of the matrix metallo-protease (MMP) family. Increased expression of MMP-2, for example, is

evident in aged rats and is localized to sites of fragmentation in the elastic lamellae [51]. Increased expression of MMP-1 and MMP-9 have been reported in aneurysmal aortas, which are characterized by fragmentation of both elastin and collagen fibers [52]. High serum MMP levels are associated with increased arterial stiffness, as measured by PWV [53]. In addition to increased MMP expression, decreased expression of tissue inhibitors of MMPs (TIMPs) may also cause elastic fiber fragmentation.

Elastic fibers that are damaged during aging or as a result of tissue injury are generally not replaced, because elastin expression is turned off in adult animals. Instead, more collagen is produced, which decreases the amount of elastin compared to collagen and shifts the arterial mechanical properties into the stiffer range of collagen fibers. In some animal models of induced hypertension, elastin expression is increased, but less than collagen expression, so the elastin to collagen ratio is still skewed toward increased collagen amounts [54]. In other hypertension models, the ratio of elastin to collagen remains constant, but the newly synthesized elastin does not assemble properly [55], so the amount of elastin does not directly correlate with mechanical behavior of the wall. Lastly, because of the stability and low turnover of both elastin and collagen, it is difficult to reverse the changes in ECM composition and return to normal mechanical function, even after the injury stimulus is removed [56].

The arterial wall may also stiffen due to calcification of the elastic lamellae. The presence of calcium deposits in the media of large arteries increases significantly with age and there is a strong correlation between aortic calcium content and arterial stiffness in humans. In a rat calcification model, the accumulation of calcium in the arterial lamellae is accompanied by a concomitant increase in PWV [57]. There is evidence that calcium binds directly to the elastin protein and that the increased calcium levels lead to SMCs expressing bone mineralization proteins normally expressed by osteocytes [8].

The stiffness of elastin and collagen fibers can be increased through additional crosslinking by advanced glycation end-products (AGEs). AGEs accumulate slowly with normal aging and at an advanced rate in diabetes. AGEs form protein-protein crosslinks on the collagen molecule. In contrast to normal collagen crosslinking, which only form at discrete sites at the ends of the molecule, AGEs form crosslinks throughout the length of the molecule. AGE-mediated crosslinks may also prevent enzymatic digestion and slow degradation, increasing the overall collagen content in the arterial wall [58]. AGE-mediated crosslinks occur similarly in the elastin protein and increase with age in the human aorta [59].

6. Arterial stiffness and hypertension

The main function of the large elastic arteries is to serve as capacitance vessels that distend during systole and retract during diastole, pushing blood to the distal vessels. The stiffer the artery, the more pressure is required to distend the walls. Stiffness here is the “functional” or “effective” stiffness, not the material stiffness because it depends on the thickness of the vessel wall. A vessel made out of the same material that is thicker than another vessel will require more pressure to distend the same amount [8]. Several factors have been discussed that increase vessel wall stiffness, i.e. fragmentation of elastic fibers, additional collagen amounts and crosslinking of elastin and collagen. However, wall thickening alone, even without changes in the mix of ECM proteins in the wall, will increase the effective stiffness.

As blood is ejected from the heart, a pressure wave is created, traveling at some PWV, which depends on the effective stiffness of the artery, the timing and magnitude of wave reflections and minimally on the inertial and viscous loses. The pressure wave will be partially reflected at arterial junctions and will be diffusely reflected as the effective stiffness changes throughout the arterial tree. The reflections travel back toward the aorta, increasing

the pressure at different points in the cardiac cycle [8]. In young individuals, PWV is relatively slow and the reflections arrive late in the cardiac cycle increasing diastolic pressure. In older individuals, PWV is increased and the reflections arrive early in the cardiac cycle increasing systolic pressure. Because of the nonlinear mechanical properties of the arterial wall, the increased pressure increases arterial stiffness and PWV even more, exacerbating the effects of the wave reflections. Wave reflection analysis shows that increased PWV will increase blood pressure. Clinically, it has been shown that PWV is increased even before significant hypertension can be measured [4], targeting reductions in arterial stiffness as a possible therapeutic intervention.

7. Treating hypertension by increasing arterial elasticity

Ideal targets for therapeutic intervention are proteins that modify the synthesis, degradation or crosslinking of elastin and consequently reverse arterial stiffening. Because of the complex nature of elastic fiber assembly, pharmaceutical application of elastin or tropoelastin in hypertensive patients will most likely not reduce arterial stiffness. However, factors that increase synthesis of elastin by cells may encourage synthesis of other ECM proteins required for assembly, increasing the likelihood of producing functional elastic fibers. A number of soluble factors have been shown to modulate elastin synthesis. Upregulators include: transforming growth factor-β (TGF-β), insulin-like growth factor-1 (IGF-1), interleukin-1β (IL-1β), glucocorticoids and retinoic acid. Downregulators include: tumor necrosis factor-α (TNF-α), interferon-γ, phorbol esters and vitamin D3 [60]. Traditional hypertensive therapies, like angiotensin-converting enzyme (ACE) inhibitors may alter elastin synthesis by targeting one of these factors. Understanding the signaling pathways in elastin synthesis will help develop treatments that have beneficial effects on elastin synthesis and arterial stiffness, in addition to directly lowering blood pressure.

Preventing elastin degradation by targeting proteolytic enzymes is another strategy to decrease arterial stiffness. Local application of TIMP-1 in a rat aneurysm model preserves elastin in the arterial media and prevents aneurysm rupture [61]. Calpain-1 inhibition blocks the angiotensin II (Ang II) mediated increase in MMP-2 activity in cultured SMCs [62] and may prevent age-related arterial stiffening. Doxycycline is a broad spectrum MMP inhibitor that favorably alters the ratio of MMP-2 to TIMP-2 in a rat model of hypertension. Doxycycline treatment attenuates the development of hypertension and prevents thickening of the arterial wall [63].

Blocking or reversing medial calcification may also decrease arterial stiffness. ACE inhibitors reduce aortic calcification and arterial stiffness in a rat calcification model [64] and in rats with chronic kidney disease [65]. Of course, ACE inhibitors also reduce blood pressure, so it is difficult to determine the direct effects of reduced stiffness on the blood pressure. Matrix-gla protein (MGP) is a potent inhibitor of arterial calcification and its activity depends on Vitamin K. High doses of Vitamin K reduce arterial calcium content and restore arterial stiffness to normal values in a rat calcification model [66]. Pioglitazone has also been shown to reduce arterial stiffness and blood pressure in a rat calcification model [67]. It has been hypothesized that elastic fiber fragmentation accelerates calcification. When MMP-induced fragmentation is blocked with doxycycline, medial calcification is prevented [68].

Elastin and collagen crosslinks can be altered by modifying the activity of lysyl oxidase, which crosslinks both proteins during fiber assembly. Treatment of young animals with beta-aminopropionitrile (BAPN), an irreversible inhibitor of lysyl oxidase [69], prevents the crosslink-formation necessary for normal function of elastin and collagen fibers, leading to disrupted fibers and a subsequent decrease in arterial rupture strength [70]. BAPN treatment

in a hypertension model of adult rats reduces aortic collagen content and ameliorates the development of hypertension [71], but long-term treatment will likely interfere with normal crosslinking in collagen fibers that are continuously turned over and eventually compromise arterial strength. Aging-related crosslinks could be targeted by inhibiting or breaking AGE-induced crosslinks in elastin and collagen. Aminoguanidine inhibits AGE production and prevents age-related increases in cardiac weight and arterial stiffness in rats [72]. Alagebrium (ALT-711) breaks AGE-induced crosslinks and reduces arterial stiffness and pulse pressure in diabetic rats, old monkeys, old spontaneously hypertensive rats and aged humans with systolic hypertension [8]. Ultimately, the best treatment for arterial stiffness and hypertension may be a combination of therapies that encourages assembly, slows degradation, and prevents changes in the stiffness of elastic fibers (Figure 5).

8. Measuring elastin amounts and arterial stiffness

Any treatment attempting to decrease arterial stiffness through alteration of the elastic fibers must quantify changes in elastin amounts. However, purification of mature, crosslinked elastin is problematic because its insolubility precludes its isolation using standard wet-chemistry techniques. Instead, relatively harsh experimental approaches designed to remove non-elastin “contaminates” are employed to generate an insoluble product that has the amino acid composition expected of elastin. Tropoelastin mRNA can be measured using RT-PCR and tropoelastin protein can be quantified using immunoassays, but these approaches only provide an indication of elastin production at a single time point. In adult cells, elastin production is very low, so even small increases may not be measurable using either technique. Tropoelastin and elastin polypeptides (α-elastin and κ-elastin) can be measured with the commercial Fastin Elastin Assay (Biocolor), but the assay requires digestion of the crosslinked elastin protein in any cell or biological sample. Insoluble elastin can be quantified by hot alkali treatment of tissues to isolate the insoluble elastin from all other proteins [73]. The insoluble portion is then hydrolyzed, lyophilized, resuspended and quantified using a ninhydrin assay [74,75]. Crosslinked elastin can be measured indirectly by determining levels of desmosine, an amino acid specific to elastin crosslinks. Because desmosine levels are low, immunoassays (RIA and ELISA) have traditionally been used to provide the necessary sensitivity [76-78]. Qualitative observations of elastin amounts can be made using light and electron microscopy. While numerous investigators have quantified the percentage of elastin staining in these two-dimensional images, the numbers will depend on consistent staining and sectioning and do not provide volumetric measures of the total elastin amount. Mecham [79] provides a detailed discussion of elastin purification and quantitation methods.

Changes in arterial stiffness must also be measured and are often done in vitro for animal models. In vitro tests allow investigation of the mechanical behavior for many different loading protocols and allow calculation or estimation of numerous parameters. In vitro measures of arterial stiffness can be obtained from uniaxial or biaxial loading of arterial specimens. Uniaxial strip or ring tests are the simplest to set up and analyze, but they provide limited information about the complex state of loading the artery experiences in vivo [80]. Planar biaxial tests are suitable for specimens with large diameters and short lengths [81]. Although planar biaxial tests provide multi-directional mechanical data, they also do not mimic the physiologic loading state of the artery. The closest representation of the in vivo state is a pressure-diameter, force-length test for cylindrical artery specimens [82] (Figure 6). Most systems can be scaled up to accommodate arteries from mice to sheep and commercial systems are available (i.e. Danish Myotechnology). Many investigators concentrate only on the pressure-diameter behavior in the circumferential direction and neglect the force-length behavior in the longitudinal direction. It is important to consider the longitudinal direction because arteries are stretched longitudinally in vivo and the amount of

stretch changes with age and disease [83]. The pressure-diameter behavior shifts with applied longitudinal stretch and the in vivo stretch may vary between experimental groups [84,46].

A common in vivo measure of arterial stiffness, used for both animal studies and human patients, is the ratio of the change in pressure to the change in diameter between systole and diastole. There are many different forms of this calculation, including the change in area or volume instead of diameter, and incorporating the wall thickness to determine a material stiffness instead of just an effective stiffness. The inverse of stiffness, or change in diameter over change in pressure, is the compliance. The most common imaging platform to determine changes in dimension is ultrasound, although MRI is occasionally used. The stiffness calculation requires that pressure be measured in the same artery as the dimensions, which is often difficult in humans. Noninvasive pressure measurements at the brachial artery may not match the pressure at the artery being imaged, for example the carotid artery, due to wave reflections. Pressure can also be measured invasively using a luminal pressure transducer [85].

PWV has emerged as an important in vivo measure of arterial stiffness due to its correlation with increased cardiovascular risk. The most common measure of aortic PWV is to record the arterial pulse wave at the common carotid artery, as well as at the femoral artery. The pulse wave can be detected using pressure transducers, Doppler ultrasound, or applanation tonometery. The distance between the two points is measured superficially and the time delay between each pulse wave is obtained. The distance/unit time gives the velocity of the traveling wave. MRI can also be used to measure PWV and offers the advantage of more localized measurements along the arterial tree, but availability and cost preclude the regular use of MRI in the clinic [85]. Similar techniques can be used to measure PWV in animal models, although the reference points are often adjusted. For example, in the mouse it is common to measure the pressure wave at the aortic arch and at a known distance downstream in the abdominal aorta [86].

9. Conclusion

Traditional hypertensive therapies have aimed at reducing blood pressure through various mechanisms, including the renin-angiotensin system (RAS) and beta-blockers that reduce cardiac output. These therapies reduce the physiologic arterial stiffness indirectly, by lowering the mean pressure, but most do not have a direct effect on the mechanical properties of large arteries. If arterial stiffness is a precursor to hypertension, decreasing blood pressure alone is not enough. Indeed, elderly patients with isolated systolic hypertension, which is the form most directly related to increases in large artery stiffness, are resistant to traditional therapies [9]. Therapies or strategies that directly alter the stiffness of the vessel wall may be more effective because they would halt the negative feedback cycle of stiff vessels increasing the load on the heart. Because elastic fibers are a major determinant of the mechanical properties of large arteries, treatments that target the assembly, degradation or stiffness of elastic fibers will be critical in treating essential hypertension.

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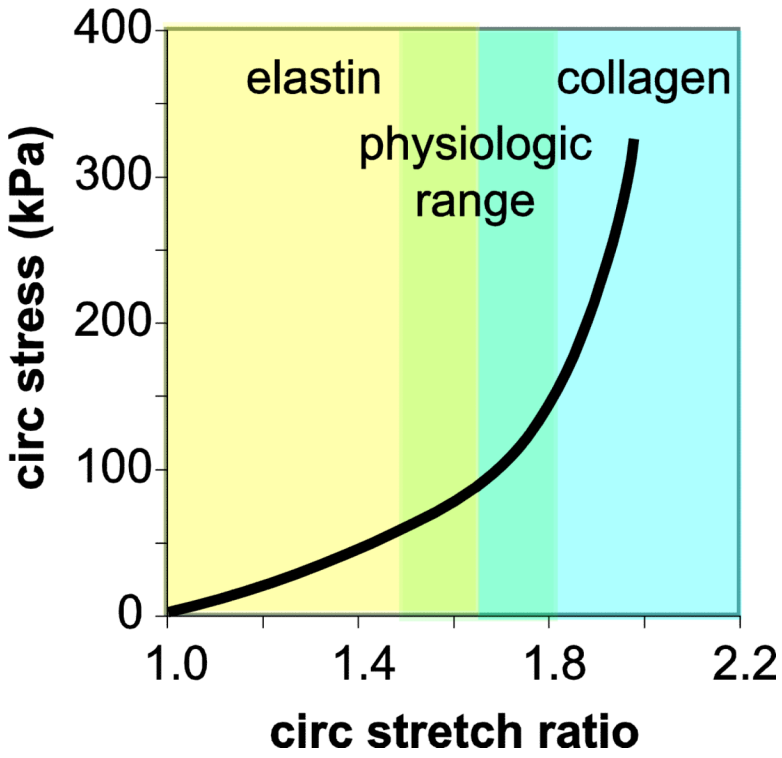

Figure 1.
Representative circumferential stress-stretch relationship for the mouse ascending aorta (data from Carta et al. [87]). Other large elastic arteries from different vertebrate animals show similar behavior. The low pressure, low stretch region dominated by elastin and the high pressure, high stretch region dominated by collagen are shown. At normal blood pressures, the regions overlap in the physiologic range.

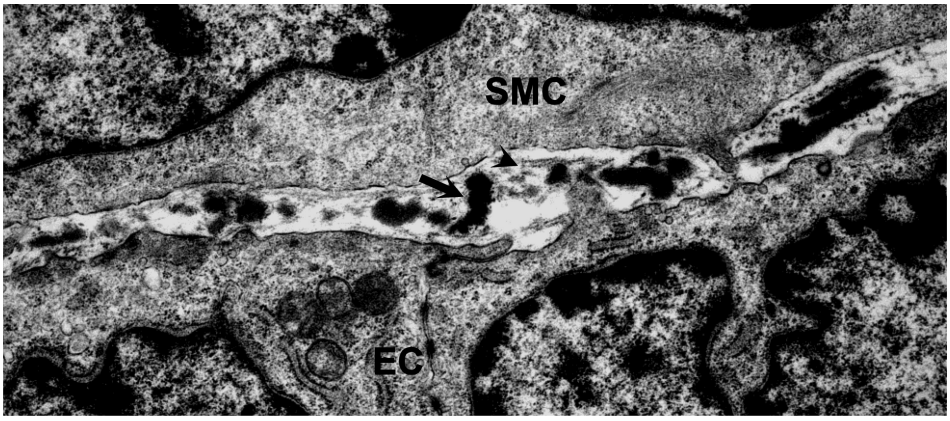

Figure 2.
Elastic fiber assembly in E14 mouse aorta. Electron micrograph of the inner elastic lamina between the endothelial cells (EC) at the luminal surface of the vessel and the first layer of SMCs in the vessel wall. Elastin aggregates (arrow) associate with microfibrils (arrowhead) near the cell surface.

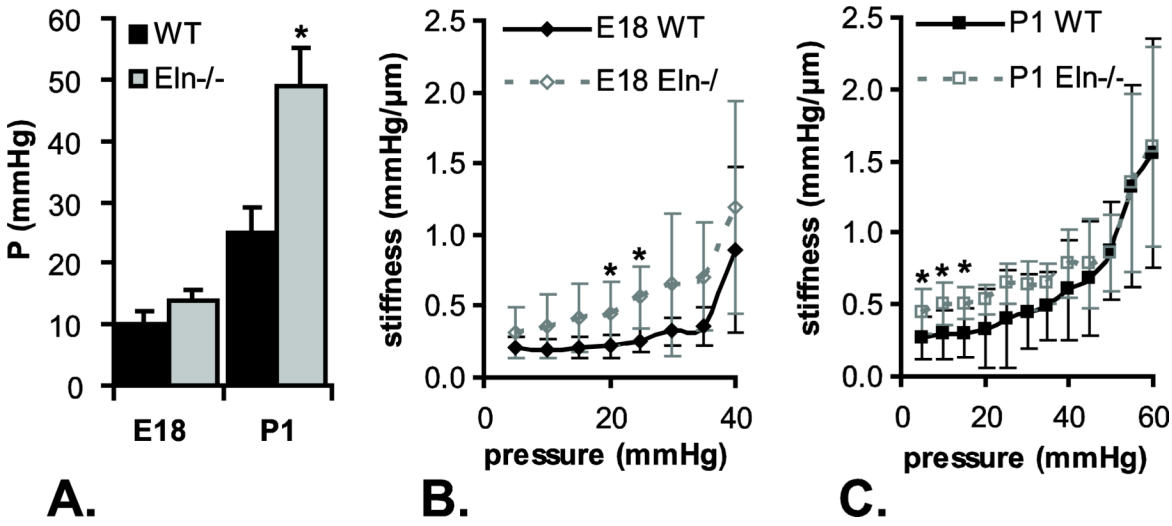

Figure 3.

Left ventricular blood pressure and aortic stiffness in WT and *Eln-/-* mice (data complied from Wagenseil et al. [42,41]). There are no differences in systolic pressure at E18, but by P1 the pressure in *Eln-/-* mice is almost double that of WT (A). The incremental stiffness of the ascending aorta is significantly increased in *Eln-/-* mice for at least two pressure steps at E18 (B) and P1 (C). In both cases, the stiffness differences are in the low to mid pressure range in the region dominated by elastin. The aortic stiffness increases with pressure as more collagen fibers are recruited. * = $p < .05$ between WT and *Eln-/-* by unpaired t-test with unequal distributions.

Genotype	% Elastin	SP (mmHg)
Bac+Eln+/+	120	105 ± 10
Eln+/+	100	122 ± 28
Bac+Eln+/-	80	125 ± 17
Eln+/-	60	175 ± 19
Bac+Eln-/-	30	183 ± 14

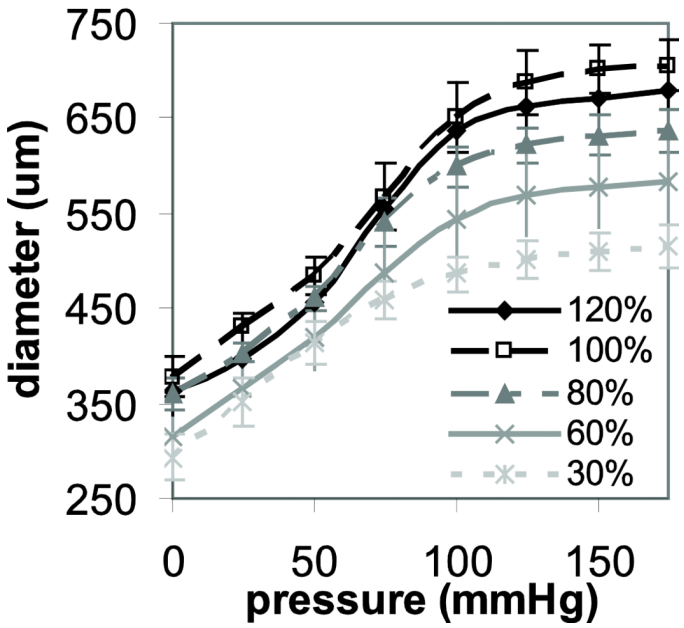

Figure 4.

Blood pressure and arterial stiffness are inversely related to elastin amounts (data compiled from Faury et al. [88], Hirano et al. [50] and Wagenseil et al. [46]). Approximate elastin percentage and systolic pressure (SP) are shown for each mouse genotype (top). The pressure increases as the elastin amounts decrease. Diameter-pressure curves for the left common carotid artery (bottom). The curves become more horizontal, increasing in stiffness, as elastin amounts decrease. The 30 and 60% systolic pressure and diameter-pressure curves are significantly different ($p < .05$) from 100%.

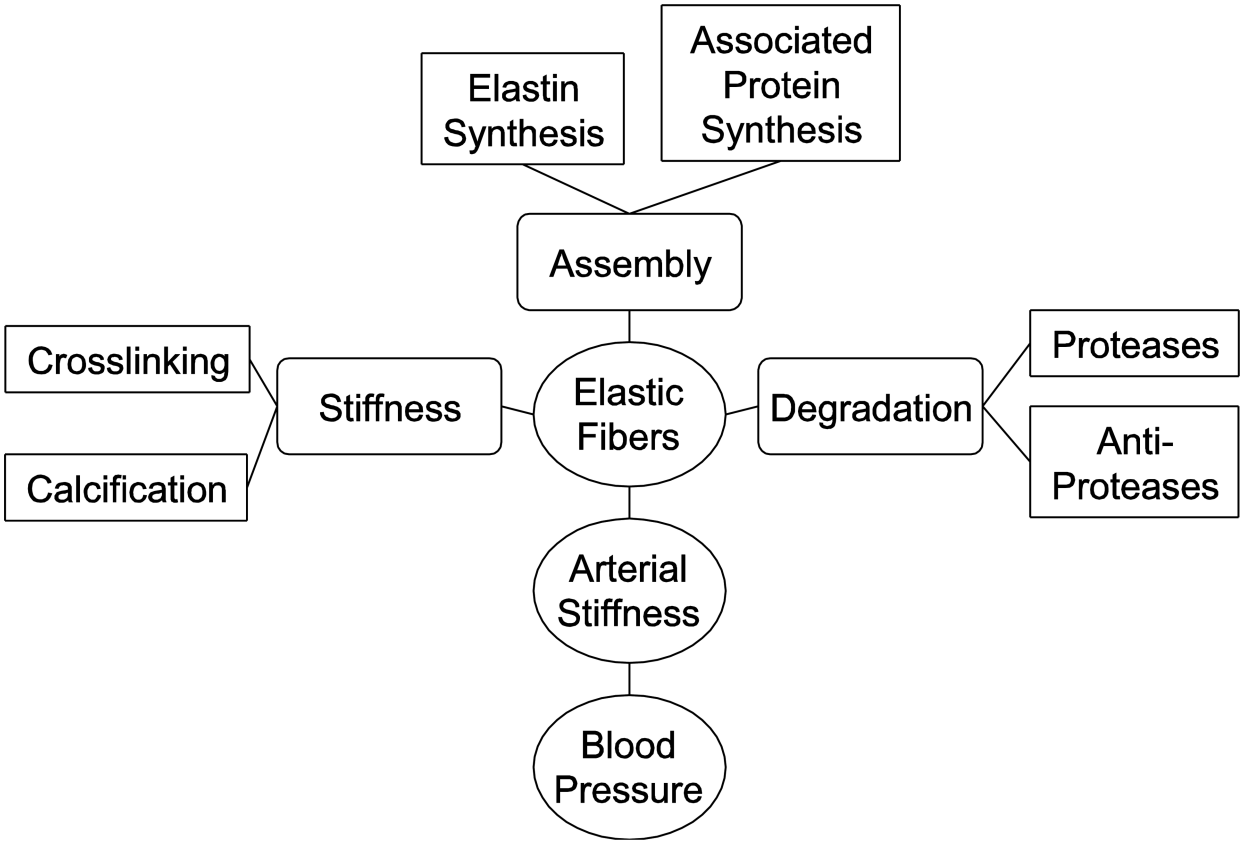

Figure 5.
Possible targets for therapeutic strategies to alter elastic fibers and affect arterial stiffness and blood pressure. Stiffness of the elastic fibers is modified through crosslinking and calcification. Assembly of the elastic fibers depends on synthesis of elastin and associated proteins. Degradation of the elastic fibers is controlled through protease and anti-protease activity.

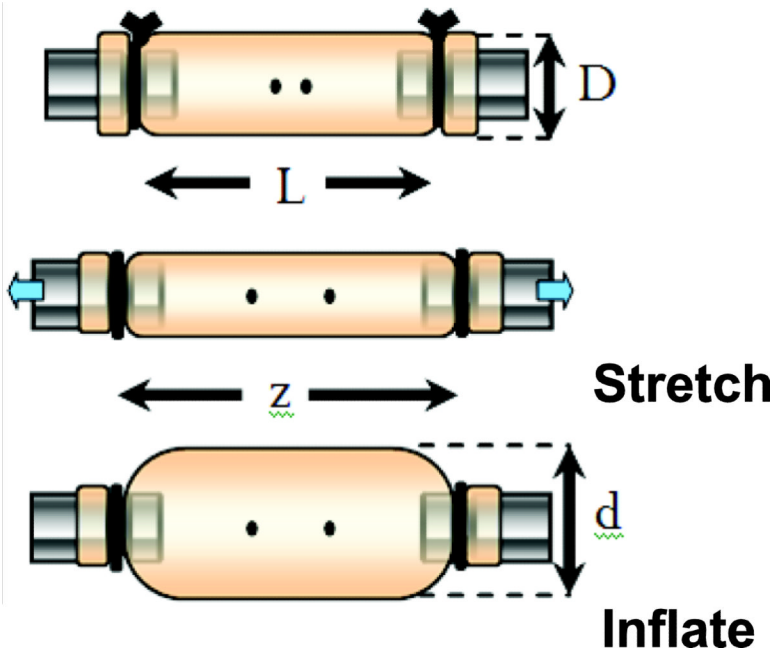

Figure 6.
Pressure-diameter, force-length diagram for a cylindrical artery specimen. The artery is mounted on hollow cannulae at the unloaded length (L) and diameter (D). The artery is stretched to some length (z) and inflated with fluid pressure through the cannulae to some diameter (d). Reproduced with permission from Christopher Pozzo.