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Abnormalities of Vascular System

Chapter 1

Age-associated Arterial Remodelling and Cardiovascular Diseases

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Abstract

Arterial remodelling is a major risk factor for a variety of age-related diseases and represents a potential target for therapeutic development. During ageing, the structural, mechanical and functional changes of arteries predispose individuals to the development of diseases related to vascular abnormalities in vital organs such as the brain, heart, eye and kidney. For example, aortic stiffness increases nonlinearly with advancing age – a few percent prior to 50 years of age but over 70% after 70 years of age. The elevated stiffness in large elastic arteries leads to increased transmission of high pressure to downstream smaller blood vessels, in turn affecting the microcirculation and end-organ functions. Meanwhile, the augmented remodelling of small arteries accelerates central arterial stiffening. This chapter is to provide an overview of age-associated changes in the arterial wall and their contributions to both central and peripheral vascular abnormalities associated with ageing. Therapeutics that specially target the different aspects of arterial remodelling are expected to be more effective than the traditional medications, particularly for the treatment and management of vascular ageing-related diseases.

1. Introduction

Based on their structure, location and function, arteries are distinguished by three classes - large elastic or conduit arteries, medium sized muscular or distributing arteries, and arterioles or small arteries [1]. The elastic arterial system includes aortic root, coronary arteries, common carotid arteries, brachiocephalic arteries, subclavian arteries, axillary arteries, brachial arteries, thoracic aorta, abdominal aorta, common iliac arteries, femoral arterials, popliteal arteries

and tibial arteries. Elastic arteries are characterized by a large lumen and relatively thin wall of the blood vessels, which expand as blood pumping from the heart and recoil when the heart relaxes to force blood onward between beats. The muscular arteries are the numerous branches originated from the elastic trunks. The walls of these arteries are thick, making up over one-fourth of the cross-sectional diameter. The arterioles are small arteries with a diameter around 100 to 400 μm, primarily controlling the peripheral resistance and the blood flow to the capillary bed [2].

The vascular wall of all arteries consists of three tissue layers, referred to as tunics (from the Latin term *tunica*) (Figure 1). The tunica intima is lined with a single layer of flattened, polygonal endothelial cells that are resting on basal lamina and loose connective tissues, referred to as the sub-endothelial layer. The tunica media is the thickest layer consisting of elastic laminae, each ~2-3 μm thick and spaced 5-20 μm apart. Thin layers of connective tissue and smooth muscle cells are arranged circumferentially within the space. The internal elastic lamina is a fenestrated sheet of elastin forming a boundary between the tunica media and the tunica intima. A second fenestrated membrane formed at the junction of the tunica media and the tunica adventitia is called the external elastic lamina. The number and distribution of elastic fibers correlate with the calibre of the artery [3]. The medial layer of muscular arteries occupies a larger portion of the cross sectional area than that of elastic arteries. Conversely, the elastic medial layer tends to exhibit a lower circumferential modulus than muscular medial layer. The tunica externa or adventitia contains bundles of collagen and a few elastic fibers longitudinally arranged around the vessel wall. Fibroblasts, mast cells and some smooth muscle cells are also present in the tunica adventitia. Arterioles differ from large arteries in the thickness of the vascular wall, which consists of endothelium, a fenestrated internal elastic lamina, and one or two layers of smooth muscle cells, lacking the sub-endothelial layer. The internal elastic membrane disappears in terminal arterioles [4,5].

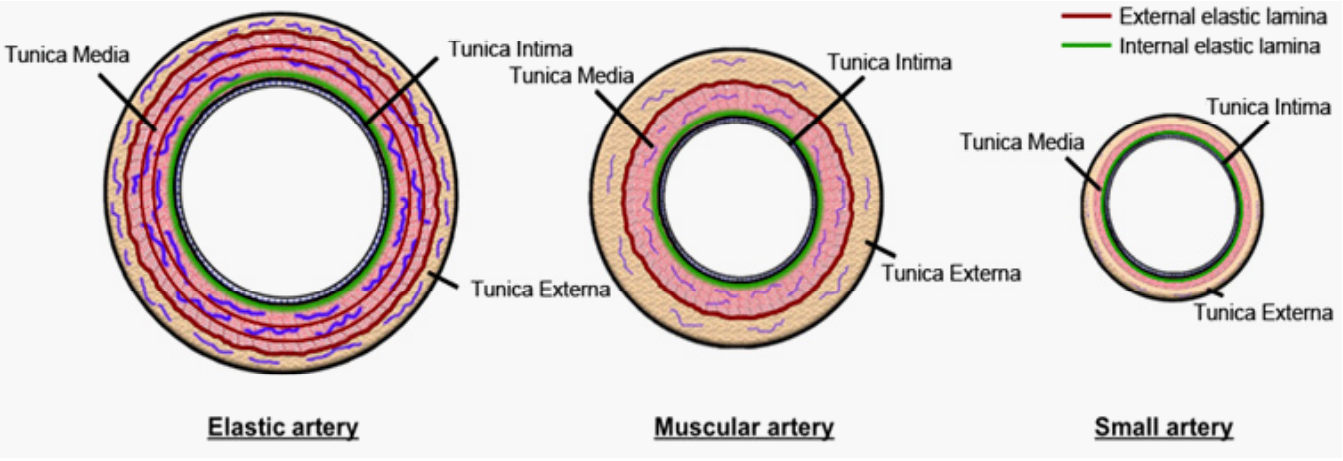

Figure 1: From the most interior to the outer layer, the arterial wall is composed of tunica intima, tunica media and tunica externa layers.The vessel wall of elastic artery is characterised by layers of elastic fibers in the tunica media and tunica externa, where as that of muscular artery contains mainly smooth muscle cells with less elastic fibers. The tunica media of small artery consists only one layer of elastic lamina and smooth muscle cells.

Arterioles contain oxygenated blood and control the flow into the capillary beds *via* vasodilation and constriction, which are regulated by neuronal and hormonal signals as well as the surrounding tissue environment [6]. The smooth muscle cell contraction significantly reduces the vessel lumen of arterioles. Changes in the internal diameter of arterioles regulate vascular resistance, arterial blood pressure and heart rate [7]. Due to the peripheral resistance, up to 50% of the left ventricular stroke volume is stored during systole in aorta and proximal large arteries and discharges during diastole [8]. The elastic properties of the large arteries help to reduce the fluctuation in pulse pressure over the cardiac cycle and assist in the maintenance of organ perfusion when cardiac ejection ceases, known as the "Windkessel effect" [8]. The elastic arteries become less compliant with age, resulting in a diminished Windkessel effect, an increased pulse pressure and elevated systolic blood pressure, which predicts the development of cardiovascular diseases, including myocardial infarction, stroke and heart failure. The present chapter discusses the macroscopic and microscopic changes in the structure and function of arterial wall [i.e. remodelling] during vascular ageing. In addition, potential therapeutic strategies targeting arterial wall remodelling will be highlighted for important clinical applications.

2. Vascular remodelling

Here, vascular remodelling refers to any structural and functional changes in the blood vessel wall. In response to local mechanical, hemodynamic and neurohumoral stimulations, the arterial wall is continually remodelled, as reflected at the tissue level by modifications in luminal diameter, wall thickness, medial and/or adventitial cross-sectional areas [9]. The pattern of vascular remodelling reflects the summation of many short term vasomotor events. For example, in conduit arteries, chronic changes in blood flow cause alterations in the architecture of the blood vessel wall in order to normalize the shear stress [10]. Increases in blood flow are associated with an increase in lumen diameter (outward remodelling), where as decreases in flow are associated with a decrease in lumen diameter (inward remodelling) [11]. Apart from the shear stress created by blood flow, the hoop stress induced by transmural pressure promotes the thickening of the arterial wall in the circumferential direction [12-15]. By considering changes in wall cross-sectional area, the type of remodelling can be defined as hypertrophic, eutrophic or hypotrophic, when the cross-sectional area is increased, unchanged, or decreased, respectively [16]. In resistance arteries, a chronic increase in blood flow induces hypertrophic outward remodelling, characterized by increases in luminal diameter and cross-sectional area, in association with improved capacity of the endothelium to induce vasodilatation [17]. Reduced blood flow results in inward hypotrophic remodelling, accompanied by hyporeactivity of the arterial smooth muscle cells [16-18].

Endothelial cells plays an important role in arterial remodelling by sensing the shear or frictional force between the blood flow and the vascular endothelium, in turn releasing

vasoactive autacoids such as nitric oxide (NO), endothelium-derived hyperpolarizing signals, prostaglandins and growth factors, to regulate the ability of arteries to alter their architectures [19,20]. Mechanical forces elicited by the flow of blood (shear stress) and pressure (cyclic strain) change gene expression in endothelial cells and activate endothelial nitric oxide synthase (eNOS), which produces NO to regulate arterial remodelling. Removal of the endothelium limits the ability of blood vessel to remodel [21]. The tunica media of the arterial vasculature is characterized by the prominent presence of smooth muscle cells, which execute the vasodilatory and vasoconstrictive functions [22,23]. Upon stimulation by mitogens [e.g. platelet-derived growth factor, transforming growth factor beta (TGFβ) and vascular endothelial growth factor], the normally quiescent smooth muscle cells are activated to become hyperplasia, which contributes to the development of arterial stiffness [24-28]. Endothelium-derived NO inhibits growth factor-stimulated proliferation and migration of vascular smooth muscle cells [29]. Endothelial dysfunction is a hallmark of vascular ageing [30]. In old arteries, the ability of endothelium to promote vasodilatation is significantly reduced [30,31]. This reduction could be due to the reduced eNOS expression, NO bioavailability in the vessel and also the reduce amount of soluble guanylyl cyclase presence in aging vascular smooth muscle cells [32,33]. Apart from ageing, classic cardiovascular factors such as arterial hypertension, hypercholesterolemia, diabetes and smoking are all associated with endothelial dysfunction [34].

The structural components of the arterial wall consist primarily of elastin, collagen (type I and III) proteoglycans and glycoproteins of the extracellular matrix, which determine the mechanical properties such as the elasticity, tensile stiffness and compressibility [3,35-37]. Elastin confers compliance to the wall, allowing the artery to recoil and dampen pulsatile pressure waves, whereas collagen serves to resist the distension of arterial wall at increased blood pressures [38]. The wall stress is born by elastin at low pressure and collagen fibers at high pressure, whereas the latter provides tensile strength and prevents over-distension [39,40]. Collagens are 100-1000 times stiffer than elastin [41]. Accordingly, arteries become stiffer as they distend, by a factor of 100 between mean pressures of 60 and 180 mmHg [42]. Elastin matures in early life and is the dominant extracellular matrix protein deposited in the arterial wall, contributing up to 50% of its dry weight [43]. It confers resilience and extensibility of the arteries. Elastic fibers stretch as vessel grow and create both longitudinal and circumferential tensions to smoothen stress distribution across the arterial wall [44,45]. Arteries proximal to the heart contain higher proportions of elastin and lower number of smooth muscle cells per unit volume than those of the peripheral conduit and distal muscular arteries [46]. Thus, the carotid, iliac and femoral arteries are stiffer than aorta [47-49]. Both circumferentially and longitudinally oriented elastin fibers are distributed throughout the medial layer in proximal elastic arteries (such as the thoracic aorta), whereas muscular arteries contain mainly longitudinal elastin located within the external elastic lamina [50,51].

Collagen and elastin deposition are regulated by matrix metalloproteinases (MMPs) [52]. NO regulates the latency of MMPs to control the matrix composition of the blood vessel wall, in particular collagen and elastin [53-55]. With age or under pathological conditions, the balance between proteases and their inhibitors is lost, as a result of increased MMP gene expression, the activation of zymogens or the secretion of enzymes by infiltrated inflammatory cells [56,57]. In aorta, collagen type I represents ~80-85% of the total collagen content and is organized in thick bundles to confer the rigidity and tensile strength of the vessel wall, whereas ~5-10% collagen type III forms small fibers to promote vascular elasticity. Thus, the ratio of collagen type I and III determines the tensile resistance of the artery [35,58,59].

Smooth muscle cells synthesize and maintain a balanced distribution of elastic and collagen fibers in the arterial wall [35,58]. Increase in pressure stretches the arterial wall, leading to changes in the contractile state and/or the synthetic activity of smooth muscle cells [10]. In conduit arteries, the relatively small portions of smooth muscle cells cause only a modest reduction in lumen diameter, even when maximally contracted [60]. They anchor to the surrounding extracellular proteins via extensions of the cytoskeleton and transmit the contracting muscle tension to the arterial wall [61]. Smooth muscle contraction redistributes tensile force between elastin and collagen,in turn modulating the arterial stiffness [61]. However, the nature of connections between smooth muscle cells and the matrix molecules is not fully understood. Elastin synthesis and smooth muscle cell proliferation are tightly correlated during the development of intimal thickening [62,63]. In summary, arterial remodelling is complex and dynamic process involving not only the changes of wall material and structure, but also the interactions between endothelium and vascular smooth muscle in response to flow-mediated shear stress and blood pressure-induced hoop stress.

3. Age-associated arterial remodelling

Ageing is associated with significant alterations in structure and function of the arterial wall, such as the decreased production of vasodilators and increased synthesis of vasoconstrictors [20], augmented collagen deposition and fragmentation of elastin fibrils [3], hypertrophy and hyperplasia of vascular smooth muscle cells [64,65], which collectively contribute to thealterations in blood pressure. With age, systolic blood pressure rises continuously, whereas the diastolic blood pressure increases until the age of 50 and declines after the age of 55 [66, 67]. Accordingly, the difference between systolic and diastolic pressure (pulse pressure) progressively enlarges and accelerates in later years due mainly to stiffening of the large arteries [67-69]. The elevation of mean arterial blood pressure reflects an increased vascular resistance combined with a well-preserved cardiac output [70]. Hemodynamically, increased pulse pressure results from a loss of compliance in large conduit arteries and augmented wave reflections from the periphery. The following sections describe the age-induced structural, mechanical and functional changes in the three types of arteries that influence the global hemodynamic

regulation in a coordinative manner.

3.1 Elastic arteries

Age-induced structural, mechanical and geometrical changes, such as thickening, stiffening, dilation and elongation, limit the buffering capacities of large elastic arteries [71-74]. Between the age of 20 and 90 years in healthy individuals, the intima-medial layer of carotid arteries thickens nearly three-fold [75,76]. In the absence of observable vascular diseases, proliferation and migration of smooth muscle cells cause the intima of the conduit arteries to thicken [77]. The remodelling process restores the homeostatic responses to changes in the blood flow and circumferential stretch, thus maintaining a normal shear stress and wall tension [78]. Theoretically, wall thickening compensates for the rise in blood pressure. However, during aging or hypertension, the mechanism become 'maladaptive' and the wall stress significantly increases to stimulate adverse vascular remodelling in the large elastic arteries [79]. Impaired endothelial function leads to increased resting vascular smooth muscle tone, i.e.the wall tension, and further deteriorates the process of arterial remodelling [60].

The most commonly used approach for determining central arterial stiffness in humans is aortic or carotid-femoral pulse wave velocity (PWV), which measures the time delay and the distance travelled by a pulse [80]. Increased aortic stiffness, indexed as an increased PWV, is an independent risk factor for cardiovascular events [66,69]. During aging, the elastin content in large arteries remains stable, but the relative ratio of elastin to collagen decreases [81,82]. Fatigue fracture of the elastin fibers occurs in the proximal aorta where these fibers are most prominent. In the abdominal aorta, which is made up of a much larger proportion of collagen and smooth muscle fibers, stiffening is caused by localized calcium deposition [83-88].In addition, the accumulation of less distensible collagen fibers contributes to the progressive arterial stiffness with age [60,89,90]. Increased cross-linking of collagen and localised collagen fibrosis contribute to the higher wall stiffness and elastic modulus in old arteries [3,91-93]. The expressions of both collagen type I and III are downregulated in large arteries with age, whereas that of collagen type VIII increases to promote smooth muscle cell migration and proliferation [41]. Changes in smooth muscle cell stiffness also contribute to the global increase in aortic stiffening with ageing [94]. However, Angiotensin II, the principal effector of renin-angiotensin-aldosterone system (RAAS) increases smooth muscle cell stiffness [95]. The material stiffness of the aged artery (also known as arteriosclerosis) causes significant mechanical alterations, such as reduced compliance and increased impedance [96]. With age, the greatest decrease in distensibility and increase in PWV occur in proximal regions, when compared to those of the remote segments of aorta [68,97]. An increase in age of 10 years decreases distensibility by 30% in carotid arteries [98]. Due to variations in structure and quantity of the extracellular matrix components, femoral arteries exhibit differences in compliance when compared to carotid arteries [99]. With age, a pressure-dependent response contributes to the

stiffening of carotid artery, whereas a pressure-independent, intrinsic compositional change stiffens the wall of femoral artery [100]. The elevated stiffness in large elastic arteries leads to increased transmission of high pressures to downstream smaller blood vessels, in turn affecting the microcirculation and end-organ functions [101-104].

Large elastic arteries not only change the mechanical properties, but also increase the diameter, length and tortuosity with age [105]. The balance between the mechanical and geometrical properties of the arteries progressively breaks down during ageing [73]. Advanced age is associated with a significant dilation or enlargement of central elastic arteries [74]. The aortic root dilates by over six percent between the fourth and eighth decades [74,87,104,106]. The diameter of the thoracic aorta increases by decade until age 50, flattens at 50-80 years of age and increases again after age 80 [107]. Proximal arteries, typically those containing more elastin, increase the diameter faster than distal arteries with less elastin [44]. The dilation may help to offset the wall stiffening by maintaining the capacity to store volume during systole. The length of the ascending aorta increases significantly with age (12% per decade) and correlates with the augmentation of central arterial stiffness, even in adults without apparent cardiovascular diseases [74]. The enlargement and elongation of large elastic arteries is more likely due to the degradation and fragmentation of elastin fibers and elastic laminae, which releases the arterial wall stress [108]. The failure of elastic fibers to sustain physiological hemodynamic stress is an indication of material fatigue and mechanical ageing in the arterial wall. As a result, the arterial tortuosity of both proximal and distal segments of the aorta increases continuously over one's lifespan, leading to asymmetric blood flow [44]. Elastic arteries that contain more smooth muscle cells and less elastin show minimal age-induced mechanical and geometrical changes [44]. Nevertheless, compared to the central conduit vessels near the heart, the peripheral elastic arteries have little impact on the elastic reservoir function, pulse pressure and cardiac preload.

3.2 Muscular arteries

Muscular arteries, such as the common femoral artery and the internal carotid artery, contain primarily longitudinal elastic lamina located near the media/adventitia boundary, whereas smooth muscle cells dominate in the media [46,109]. They are more compliant longitudinally than circumferentially. Different from the central elastic arteries, normal aging does not cause enlargement in distal muscular arteries [87,110]. Age-induced remodelling is predominantly longitudinal and the arteries become more tortuous rather than increasing in diameter [111, 112]. The stiffness and wall thickness of muscular arteries remain unchanged during aging [87,98,113]. With age, the axial force and stress decreases whereas the circumferential stress remains constant [111]. Degradation and fragmentation of elastin and proliferation of smooth muscle cells result in decreased axial pre-stretch of ageing human femoropopliteal arteries [111]. In contrast to the modest change in mechanical properties, endothelial function of mus-

cular arteries, assessed as flow-mediated dilation (FMD) in the brachial artery, deteriorates substantially with age [114-116].

In human pulmonary arteries, the extensibility and compliance decrease with increasing age. However, the medial collagen contents of the vessels exhibit a steady fall at about one percent per decade [117]. Ageing is accompanied by an increase in thickness and a decrease in the cellularity of the tunica media [27]. The content of elastin (relative to the dry weight of the vessel) appears to increase with age, due probably to the decrease in cellularity [118, 119]. Nevertheless, the reduction of the arterial wall compliance is more likely due to the age-related molecular changes in the medial elastic fibers. Fracture of elastins is associated with smooth muscle cell trans-differentiation leading to osteogenesis and deposition of calcium in the arterial wall [120-123]. Calcification is frequently encountered in aged muscular arteries and significantly affect the wall properties [124]. Calcium deposition is found in both intima and media of the vessel wall [124-127]. Calcification of the tunica media in coronary arteries independently predicts cardiovascular morbidity and mortality [128].

In muscular arteries, smooth muscle cells dominate the tunica media [85]. With age, the intima is thickened and contains layers of smooth muscle cells [129,130]. The increased intima-to-media ratio is a strong predictor of future cardiovascular events [96,131-133]. Intimal hyperplasia is primarily due to the proliferation and migration of smooth muscle cells from the media/adventitia to the sub-endothelial layer with additional deposition of significant quantities of extracellular matrix proteins [134]. During this process, vascular smooth muscle cells undergo phenotypic changes from “contractile” to “synthetic” in turn altering the vessel wall structure and mechanics [132,135]. Cyclic strain acts as a signal to stimulate the growth and activation of smooth muscle cells [136,137,138]. With age, endothelial dysfunction occurs when the balances between pro- and anti-oxidants, vasodilators and vasoconstrictors, pro- and anti-inflammatory molecules, and pro- and anti-thrombotic signals are perturbed [139,140]. Thus, although the structure of the peripheral muscular arteries is only minimally affected by aging, impaired vasomotor function associated with endothelial dysfunction contribute to peripheral resistance [138,141].

3.3 Small arteries

Small arteries account for more than 40% of total peripheral resistance [142,143]. They have relatively high amount of smooth muscle cells that produce myogenic tone [144]. Myogenic contraction occurs spontaneously in response to enhanced stretch without the stimulation by specific vasoactive mediators. It is mediated in part by tensile strain of integrins attached to the extracellular matrix, which are highly sensitive to ambient calcium levels [145-147]. The proximal resistance arteries are the main site for vasoconstriction, which partially protects the distal resistance arteries from pressure overload [143]. However, prolonged elevation

of the myogenic tone stimulates vessel wall remodelling, which restores the wall stress and tone while increasing vascular resistance [148,149]. Proximal small arteries that exhibit less myogenic tone undergo outward hypertrophic remodelling [150-153]. The smaller arterioles, which mount a more rigorous myogenic response, exhibit inward eutrophic remodelling (a narrower lumen with no change in smooth muscle mass) [154]. Both hypertrophic and eutrophic remodelling increases the ratio of the media cross-sectional area to lumen area [155]. Because of incompressibility of the wall mass, a given change in tone and circumferential shortening elicits an enhanced effect on lumen diameter of the small arteries [156]. According to Poiseuille's law (flow is related to the fourth power of the vessel radius), slight alteration in lumen of arteries results in significant changes in arterial resistance [87,157]. The increased wall-to-lumen ratio of small resistance arteries, especially the inward eutrophic remodelling, has the greatest value for predicting life-threatening cardiovascular events [158-161]. Assessment of wall-to-lumen ratio of retinal arterioles represents an attractive tool to identify patients with increased cerebrovascular risk [161].

With age, the stiffness of the wall components is progressively increasing [162], whereas the distensibility of small resistance arteries increases or remains the same [151]. The distensibility is preserved in ageing arteries by geometric adaptation of the arterial wall [162]. The altered structure and function of small arteries exacerbate central arterial stiffness [163-166]. Mechanical strain and pulsatile stretching promote vascular smooth muscle cell migration, hypertrophy or hyperplasia, and matrix synthesis, resulting in a remodeled vascular wall [167-170]. Integrins, the cell-surface adhesion receptors, mediate the crosstalk between vascular smooth muscle cells and the extracellular matrix environment [171]. Specific integrin receptor subtypes form complexes with fibronectin, and to a lesser extent collagen, to regulate cytoskeletal dynamics and maintain vascular myogenic force at a given pressure [172,173]. Changes in integrin expression profile are associated with the remodelling of both the arterial wall and extracellular matrix [18,174,175]. In particular, the transformation of cytoskeletal protein actin, from globular to filamentous, results in smooth muscle cell stiffening [176,177].

Myogenic constriction plays a key role in the steady-state control of regional blood flow [159,178]. With advancing age, the marked increase of PWV in central large arteries together with a lack of stiffening in peripheral muscular arteries promote the transmission of potentially deleterious pulsatile energy into the peripheral microcirculation [156]. Long-term elevation of pulse pressure promotes the remodelling of small resistance arteries. Inward remodelling limits hyperemic flow reserve of the microcirculation and causes focal tissue ischemia [70, 166,179-181]. Age-associated cardiovascular diseases in brain and kidney are characterized by impaired regulation of local blood flow and microscopic tissue damages [156]. In kidney, the glomerular capillaries are particularly vulnerable to pulsatile damages [182]. Myogenic response of the afferent arteriole protects the glomerulus against elevated systolic pressures

[183]. Impaired renal autoregulation results in an elevated glomerular capillary pressure and accelerated decline in kidney function [184]. Brain atrophy is correlated with cardiovascular risk factors and microvascular abnormalities [185]. Cerebral micro-bleeds are highly related to the alterations in pulse pressure [186]. High local flow facilitates penetration of excessive pulsatile energy into the microvascular bed, contributing to repeated episodes of microvascular ischemia and tissue damage [187]. In brain, small vessels within the regions with white matter lesions exhibit thickened media and reduced internal diameter, thus a markedly increased media-to-lumen ratio [159]. Silent cortical and subcortical infarcts contribute to the development of age-related cognitive decline and dementia [188-193]. Importantly, chronic kidney disease, microvascular brain damage and cognitive impairment are frequently clustered together, supporting a shared mechanism of pathogenesis [194-196].

4. Therapeutics targeting arterial remodelling

Cardiovascular diseases account for ~50% and ~25% of deaths in the developed and developing countries, respectively, making it the number one cause of total mortality worldwide [197]. In 2010, the leading risk factors and diseases accounting for global deaths and disability-adjusted life years are hypertension (~18 and 7%), ischemic heart disease (~14 and 5%), tobacco smoking (~12 and 6%) and cerebrovascular disease (~11 and 4%), all of which are related to vascular abnormalities [34]. Therapies targeting common risk factors for cardiovascular diseases, such as hypertension and dyslipidemia, are effective in reducing the total mortality. For example, aggressively lowering blood pressure to below 120 mmHg significantly decreases all-cause mortality in patients with increased cardiovascular risks [198]. However, relatively few therapeutics are available for specifically modulating the arterial wall, changes in which play a key role in the progression of many cardiovascular metabolic and renal complications.

4.1 Arterial stiffness

Arterial stiffening has been regarded as an “inevitable” consequence of ageing [131, 199]. In humans, femoral PWV increases by ~5.4% for each decade of life, whereas aortic PWV changes two-fold faster with age [200, 201]. A ~3% increase in PWV is expected to alter pulse pressure by ~5 mmHg and substantially alters cardiovascular risk [202,203]. Arterial stiffness falls into two categories: passive and active [80]. For the former, disruption and fatigue fracture of the elastic fibers result in the transfer of pressure stress to collagens, leading to age-related arterial stiffening. The elastic modulus is commonly used to describe the properties of the wall materials such as collagen and elastin. On the other hand, arterial stiffness is determined not only by the elastic modulus but also by the dimensions of the blood vessel, such as wall thickness [204]. Apart from the structural components, vascular endothelium plays an important role in the functional regulation of arterial stiffness [205]. Changes in endothelial

function and smooth muscle tone influence the stiffness of the elastic and muscular arteries [36]. Vasoconstrictors such as noradrenaline, endothelin-1 or angiotensin II increase large artery stiffness [201, 206], whereas vasodilators such as glyceryl trinitrate elicits opposite effects [201, 207-209].

Central arterial stiffness is a powerful and an independent predictor of total mortality among older individuals [210-212], in patients with end-stage renal failure [213,214], among hypertensive individuals and in subjects with type 2 diabetes [215-218]. Aortic stiffness causes hypertension, whereas the latter aggravates this degenerative process [219-222]. Traditional antihypertensive agents, such as thiazide diuretics, β-blockers and calcium channel blockers indirectly reduce arterial stiffness by lowering mean arterial pressure, rather than having a direct effect on the large arteries [223]. However, a concomitant reduction in diastolic pressure have adverse clinical consequences because of the reduced perfusion in coronary arteries [224]. Nitrates primarily relax smooth muscle cells in large conduit muscular arteries thus attenuating arterialstiffness and remodelling [225]. Infusion of BQ-123, an endothelin antagonist,via a catheter results in a significant decrease in PWV and increase in arterial distensibility. Prostacyclin, apart from acting as a vasodilator, elicits anti-remodelling actions and attenuates smooth muscle cell proliferation. In ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), the largest angiotensin receptor blocker cardiovascular outcome study, both telmisartan (an angiotensin II receptor blocker) and ramipril (an angiotensin-converting enzyme inhibitor) prevent cardiovascular events largely by restoring the endothelial functions and decreasing arterial stiffness in normotensive patients [226-230]. The β-blocker nebivolol improves endothelial function by acting as a NO donor [231]. Arterial stiffness may be modified by therapies that reduce inflammation, such as hydroxy-3-methylglutarylcoenzyme A reductase inhibitors (statins) [232,233]. Combined treatment with vitamins C and E improves endothelium-dependent vasodilation and arterial stiffness in untreated, essential hypertensive patients [234]. The advanced glycation end-products (AGE) accumulate in the arterial wall slowly with age and at an advanced rate in diabetic patients [235,236]. AGE increase the stiffness of collagen fibers by forming protein-protein crosslinks and preventing enzymatic digestion [237]. Non-enzymatic breaking of AGE crosslinks improves arterial compliance and reduce pulse pressure in the elderly [236,238]. Despite these progresses, currently there lacks effective therapies that specifically target the structural and/or mechanical components in large arteries.

4.2 Smooth muscle cell proliferation

With age, vascular smooth muscle cells undergo functional changes to alter the normal structure of the arterial wall, predisposing it to the formation of neointima, atheroma and aneurysm [239-241]. From the second decade of life, intimal thickening develops as an adaptive response to luminal pressure and shear stress on the arterial wall [4,81-83]. Neointima comprises

layers of smooth muscle cells separated by thin elastic and collagen fibers. It exhibits concentric development in the aorta and eccentric appearance in the coronary arteries [242, 243]. Intimal thickening represents a pre-atherosclerotic lesion [85]. Small plasma-like deposits of glycosaminoglycans are present within the thickened intima [84]. Sub-endothelial deposition of cholesterol and phospholipids promotes the development of advanced atherosclerotic lesions [4]. While intimal hyperplasia during restenosis leads to luminal narrowing, the outward remodelling during atherosclerosis compensates for the plaque growth and postpones the progression to flow-limiting stenosis [244,245]. In the affected area of aneurysm, smooth muscle cells are switched from the contractile to a metabolic state, thus affecting the catabolism of elastic fibers and collagens [246]. Changes of the internal elastic lamina, including irregular thickness, focal absence, splitting, reduplication and calcifications, facilitate smooth muscle cell proliferation and migration [247]. In addition, endothelial dysfunction and lesions, as well as inflammatory cell recruitment and infiltration play an important role in smooth muscle call activation [248-250].

Angiotensin II is not only a potent vasoconstrictor but also a pro-inflammatory molecule stimulating cell growth and matrix deposition during arterial remodelling [251]. It initiates arterial remodelling via inducing smooth muscle hypertrophy, hyperplasia and migration [252]. The developing neointima expresses high levels of angiotensin-converting enzyme [253]. Blockers of angiotensin II receptor inhibit neointimal formation and reduces restenosis [254-256]. However, large clinical trials do not support similar effects of angiotensin-converting enzyme inhibitors on neointimal formation and restenosis [257-259]. Smooth muscle cell activation is associated with the loss of elastic fibers in the arterial wall. Passive elastin degradation occurs with age, as a result of disorganization and fracture associated with the total number of cardiac cycles throughout life [260]. The enzymatic degradation of elastins involves MMPs-activation [261]. Elastase decreases elastin content whereas collagenases modulate collagen composition. High serum MMP levels are associated with increased arterial stiffness [261]. Reversing the alterations to elastic fibers by targeting the proteolytic enzymes has been investigated as a therapeutic treatment for arterial ageing [260-264]. Theoretically, a combination of therapies is needed to inhibit the degradation and promote the proper assembly of elastic fibers. However, the quantification and calculation of arterial stiffness are often difficult in human, thus hindering this approach for therapeutic development.

4.3 Arterial calcification

The incidence of aortic calcification increases steadily with age, affecting ~4% in the third decade of life and almost all subjects by the age of 50. Echocardiography is able to detect arterial calcification in approximately 30% of subjects over the age of 60 [131]. The fragmented elastin serves as a nidus for calcium deposition. Arterial calcification is not only a degenerative process during ageing, but also actively involved in the pathogenesis pathways

of atherosclerosis, diabetes and renal failure [126]. Calcification of the ascending aorta and its arch reduces their elasticity and affects the hemodynamic parameters, leading to systolic hypertension, left ventricular myocardial hypertrophy, diastolic dysfunction and valve incompetence [126]. Abdominal aortic calcium deposits are closely associated with the presence of calcified plaques in the coronary arteries and independently predict cardiovascular morbidity and mortality [265]. Therefore, therapeutic strategies targeting the abdominal region of the aorta may be useful in slowing the process of aortic stiffening and have an impact in reducing overall cardiovascular risk.

Risk factors for vascular calcification are similar to those of atherosclerosis [266]. The calcifying vascular cells (a subpopulation of smooth muscle cells with osteoblastic characteristics) are present in atherosclerotic plaques and produce mineral that clusters locally as small lumps, histologically resembling atherosclerotic plaque [267]. Statin-based hypolipidemic therapy reduces the intensity of calcification of vessel walls and cardiac valves [268-273]. Apart from the calcification associated with atherosclerosis in the arterial intima, a more diffuse deposition of calcium salts termed medial elastocalcinosis is seen in the arterial media of patients with diabetes or renal failure [123,274,275]. Hyperglycemia causes activation of vascular smooth muscle cells to differentiate into osteoblast-like cells [276]. In patient with chronic kidney disease, diabetes enhances arterial calcification irrespective of the stage of renal insufficiency [277]. Pharmacological control of elastocalcinosis may be a new approach to the treatment of essential systolic hypertension [278]. Suppression of endothelin by sinitrodil, a NO donor, induces mineral loss in the aorta. Treatment with eplerenone, an aldosterone receptor inhibitor,inhibits calcific aortic stenosis in animal models [279,280]. The increase in arterial calcium deposition is related to the decreased bone mineral density in humans [121, 122,281]. Optimal control of calcium and phosphate concentrations attenuates the progression of vascular lesions in patients with end-stage renal disease, for whom vessel calcification remains a major problem [282,283]. Drugs used for osteoporosis treatment (calcitriol, estradiol, bisphosphonates) may interfere with the calcification processes occurring in the vessel wall [284,285]. For example, increase in arterial stiffness and calcification is associated with the administration of vitamin D and nicotine [286]. On the other hand, drugs used to treat cardiovascular problems (statins, angiotensin convertase inhibitors, warfarin, heparins) may have an effect on bone tissue metabolism.

4.4 Arteriolar myogenic tone

In small resistance arteries, the activation of myogenic tone represents a major determinant in the regulation of local hemodynamics [287]. The myogenic response is initiated when the mechanical signal induces membrane depolarization of the vascular smooth muscle cells, in turn causing Ca^{2+} mobilization and activation of contractile proteins [288,289]. Thus, in response to changes in intravascular pressure, vascular smooth muscle cells, which

are arranged circumferentially or near perpendicular to the long axis of the vessel, become shortened to constrict the blood vessel [290]. Smooth muscle cell depolarization is mediated by the activation of cation channels, the closure of K^+ or the opening of Cl^- channel, which subsequently activate voltage-gated Ca^{2+} channels (VGCC) [291-295]. The molecular identity of the cation channel(s) leading to stretch-induced depolarization remains to be characterized [296]. Endothelial cells induce hyperpolarization of smooth muscle cells in small resistance arteries via the activation of small-conductance Ca^{2+}-activated K^+ channel (SK_{Ca}, blocked by apamin or UCL 1684) and intermediate-conductance Ca^{2+}-activated K^+ channel (IK_{Ca}, blocked by charybdotoxin or TRAM-34) [297-300]. Progressive reduction of endothelium-dependent hyperpolariation is observed during ageing in normotensive animals and humans [301-304].

Vasodilating drugs, such as hydralazine, dipyridamole and calcium channel blockers, act to decrease resistance of the smaller arterioles [296], whereas adrenergic stimulation enhances myogenic vasoconstriction [305]. Blockage of VGCC by nifedipine or nisoldipine (L-type Ca^{2+} channel blockers) eliminates active myogenic constriction but does not affect mechanosensation and membrane depolarization of smooth muscle cells [306-309]. Myogenic responses of small arterioles less than 25 μm in diameter (such as those in skeletal muscle) are relatively insensitive to Ca^{2+} channel blockers [310]. Drugs targeting the regulation of myogenic constriction possess therapeutic potentials for pathologies including hypertension, cerebral or coronary vasospasm, and vascular complications associated with insulin resistance and overt diabetes [296]. Different vascular beds use distinctive intracellular mechanisms for myogenic tone regulation. The heterogeneity across tissues provides potential benefit for designing specific therapeutic interventions of the myogenic tone [308,311-313]. For example, Rho-kinase inhibitors are more effective than nitroglycerin to induce vasodilatation in vasospastic coronaries for patients with refractrory angina [314]. In kidney, myogenic constriction of afferent arterioles attenuates the transmission of high pressure to the glomerular capillaries, thus preventing hyperfiltration and glomerulosclerosis [315,316]. Pharmacological agents modulating the specific myogenic mechanisms would confer an advantage over those with general activities on vascular activations [172].

5. Concluding remarks

Vascular ageing is characterized by the structural, mechanical and functional alterations of the arterial wall and represents a fundamental process underlying the development of many ageing-related diseases. For example, an increased media-to-lumen ratio of small arteries is associated with an increased prevalence of cardiovascular events, whereas the augmented intima-media thickness in large arteries predicts the occurrence of both stroke and myocardial infarction. Arterial remodelling involves both cellular (e.g. endothelial and smooth muscle cells) and non-cellular components (e.g. elastins and collagens). With age, endothelial dysfunction, smooth muscle cell proliferation and migration, extracellular matrix synthesis or degradation

collectively contribute to the stiffness of central elastic arteries, which increases the systolic and pulse pressure, leading to microcirculatory complications in end organs such as brain, kidney and heart.

Aging-associated arterial remodelling is fundamentally intertwined with the arterial alterations associated with other well-known risk factors (e.g. excess food intake, altered metabolism, smoking, hypertension and lack of exercise). Understanding how aging, stiffness, and blood pressure interact over time is a complex conundrum. Some lifestyle and pharmacological interventions have proved to be effective in preventing or ameliorating hypertension. However, the majority of therapeutics target the consequences rather than the pathophysiology of vascular ageing. For example, traditional antihypertensive therapies, including the RAAS, calcium channel and beta-blockers, indirectly reduce the stiffness of arteries by lowering total peripheral resistance but not the arterial remodelling directly associated with aging. There lacks effective agents that specifically modulate the mechanical properties of the arterial wall.

Arteries exhibit differences in their microstructural organization, constituent mass ratios and mechanical responses depending on the anatomic locations and physiologic functions, which predispose them to varying mechanical responses and pathologies. Considering the versatile and dynamic nature of the vascular beds, the prevention of arterial ageing would require early intervention, life long treatment and site-specific approaches. The endothelium is a favourite early target of vascular ageing. Nevertheless, *in vivo* assessment of arterial structure and function will provide more accurate insights to define disease-free age-related changes in arteries and then consider the most effective therapeutic target for modulating the process of arterial remodelling.

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7. References

1. Rhodin, J.A., Architecture of the vessel wall. Comprehensive Physiology, 2011.

2. Pittman, R.N., The circulatory system and oxygen transport. 2011.

3. Tsamis, A., J.T. Krawiec, and D.A. Vorp, Elastin and collagen fibre microstructure of the human aorta in ageing and disease: a review. Journal of the Royal Society Interface, 2013. 10(83): p. 20121004.

4. Glagov, S., et al., Micro-architecture and composition of artery walls: relationship to location, diameter and the distribution of mechanical stress. Journal of Hypertension, 1992. 10: p. S101-S104.

5. Sutliff, R.L., New insights into mechanisms regulating pulmonary adventitial fibroblast proliferation. Acta Physi-

ologica, 2017. 219(1): p. 17-19.

6. Pittman, R.N. Regulation of tissue oxygenation. in Colloquium Series on Integrated Systems Physiology: From Molecule to Function. 2011. Morgan & Claypool Life Sciences.

7. Joannides, R., et al., Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. Circulation, 1995. 91(5): p. 1314-1319.

8. Belz, G.G., Elastic properties and Windkessel function of the human aorta. Cardiovascular Drugs and Therapy, 1995. 9(1): p. 73-83.

9. Mulvany, M.J., et al., Vascular remodeling. Hypertension, 1996. 28(3): p. 505-6.

10. Kamiya, A. and T. Togawa, Adaptive regulation of wall shear stress to flow change in the canine carotid artery. American Journal of Physiology-Heart and Circulatory Physiology, 1980. 239(1): p. H14-H21.

11. Mulvany, M.J., Small artery remodelling in hypertension. Basic & clinical pharmacology & toxicology, 2012. 110(1): p. 49-55.

12. Hayashi, K. and T. Naiki, Adaptation and remodeling of vascular wall; biomechanical response to hypertension. Journal of the mechanical behavior of biomedical materials, 2009. 2(1): p. 3-19.

13. Wolinsky, H., Effects of hypertension and its reversal on the thoracic aorta of male and female rats. Circulation Research, 1971. 28(6): p. 622-637.

14. Matsumoto, T. and K. Hayashi, Mechanical and dimensional adaptation of rat aorta to hypertension. TRANSACTIONS-AMERICAN SOCIETY OF MECHANICAL ENGINEERS JOURNAL OF BIOMECHANICAL ENGINEERING, 1994. 116: p. 278-278.

15. Humphrey, J., Vascular adaptation and mechanical homeostasis at tissue, cellular, and sub-cellular levels. Cell biochemistry and biophysics, 2008. 50(2): p. 53-78.

16. Mulvany, M.J., Vascular remodelling of resistance vessels: can we define this? Cardiovascular research, 1999. 41(1): p. 9-13.

17. Pourageaud, F. and J.G. De Mey, Structural properties of rat mesenteric small arteries after 4-wk exposure to elevated or reduced blood flow. Am J Physiol, 1997. 273(4 Pt 2): p. H1699-706.

18. Martinez-Lemus, L.A., M.A. Hill, and G.A. Meininger, The plastic nature of the vascular wall: a continuum of remodeling events contributing to control of arteriolar diameter and structure. Physiology, 2009. 24(1): p. 45-57.

19. Gibbons, G.H. and V.J. Dzau, The emerging concept of vascular remodeling. New England Journal of Medicine, 1994. 330(20): p. 1431-1438.

20. Sandoo, A., et al., The endothelium and its role in regulating vascular tone. The open cardiovascular medicine journal, 2010. 4(1).

21. Langille, B.L. and F. O'Donnell, Reductions in arterial diameter produced by chronic decreases in blood flow are endothelium-dependent. Science, 1986. 231(4736): p. 405-7.

22. Segal, S.S., Integration and modulation of intercellular signaling underlying blood flow control. Journal of vascular research, 2015. 52(2): p. 136-157.

23. Fisher, S.A., Vascular smooth muscle phenotypic diversity and function. Physiological genomics, 2010. 42(3): p. 169-187.

24. Fine, A. and R.H. Goldstein, The effect of transforming growth factor-beta on cell proliferation and collagen formation by lung fibroblasts. Journal of Biological Chemistry, 1987. 262(8): p. 3897-3902.

25. Doetschman, T., et al., Transforming growth factor beta signaling in adult cardiovascular diseases and repair. Cell and tissue research, 2012. 347(1): p. 203-223.

26. Ignotz, R.A. and J. Massague, Transforming growth factor-beta stimulates the expression of fibronectin and collagen and their incorporation into the extracellular matrix. Journal of Biological Chemistry, 1986. 261(9): p. 4337-4345.

27. Vasile, E., et al., Differential expression of thymosin β-10 by early passage and senescent vascular endothelium is modulated by VPF/VEGF: evidence for senescent endothelial cells in vivo at sites of atherosclerosis. The FASEB Journal, 2001. 15(2): p. 458-466.

28. Ylikorkala, A., et al., Vascular abnormalities and deregulation of VEGF in Lkb1-deficient mice. Science, 2001. 293(5533): p. 1323-1326.

29. Jeremy, J.Y., et al., Nitric oxide and the proliferation of vascular smooth muscle cells. Cardiovascular research, 1999. 43(3): p. 580-594.

30. Vanhoutte, P.M., et al., Endothelial dysfunction and vascular disease. Acta physiologica, 2009. 196(2): p. 193-222.

31. Bulckaen, H., et al., Low-dose aspirin prevents age-related endothelial dysfunction in a mouse model of physiological aging. American journal of physiology. Heart and circulatory physiology, 2008. 294(4): p. H1562-70.

32. Klöß, S., A. Bouloumié, and A. Mülsch, Aging and chronic hypertension decrease expression of rat aortic soluble guanylyl cyclase. Hypertension, 2000. 35(1): p. 43-47.

33. Csiszar, A., et al., Aging-induced phenotypic changes and oxidative stress impair coronary arteriolar function. Circulation research, 2002. 90(11): p. 1159-1166.

34. Daiber, A., et al., Targeting vascular (endothelial) dysfunction. British journal of pharmacology, 2016.

35. Wagenseil, J.E. and R.P. Mecham, Vascular extracellular matrix and arterial mechanics. Physiological reviews, 2009. 89(3): p. 957-989.

36. Avolio, A., et al., Regulation of arterial stiffness: cellular, molecular and neurogenic mechanisms. Artery Research, 2011. 5(4): p. 122-127.

37. O'rourke, M.F. and J. Hashimoto, Mechanical factors in arterial aging: a clinical perspective. Journal of the American College of Cardiology, 2007. 50(1): p. 1-13.

38. Cheng, J.K. and J.E. Wagenseil, Extracellular matrix and the mechanics of large artery development. Biomechanics and modeling in mechanobiology, 2012. 11(8): p. 1169-1186.

39. Driessen, N., et al., A computational model for collagen fibre remodelling in the arterial wall. Journal of theoretical biology, 2004. 226(1): p. 53-64.

40. Holzapfel, G.A., T.C. Gasser, and R.W. Ogden, A new constitutive framework for arterial wall mechanics and a comparative study of material models. Journal of elasticity and the physical science of solids, 2000. 61(1-3): p. 1-48.

41. Qiu, H., et al., Mechanism of gender-specific differences in aortic stiffness with aging in nonhuman primates. Circulation, 2007. 116(6): p. 669-676.

42. Nichols, W. and M. O'Rourke, McDonald's Blood Flow in Arteries 5th edn (London: Arnold). 2005.

43. Karnik, S.K., et al., A critical role for elastin signaling in vascular morphogenesis and disease. Development, 2003. 130(2): p. 411-423.

44. Kamenskiy, A., et al., Patient demographics and cardiovascular risk factors differentially influence geometric remodeling of the aorta compared with the peripheral arteries. Surgery, 2015. 158(6): p. 1617-1627.

45. Guo, X. and G.S. Kassab, Variation of mechanical properties along the length of the aorta in C57bl/6 mice. American Journal of Physiology-Heart and Circulatory Physiology, 2003. 285(6): p. H2614-H2622.

46. Kamenskiy, A.V., et al., Age and disease-related geometric and structural remodeling of the carotid artery. Journal of vascular surgery, 2015. 62(6): p. 1521-1528.

47. Latham, R.D., et al., Regional wave travel and reflections along the human aorta: a study with six simultaneous micromanometric pressures. Circulation, 1985. 72(6): p. 1257-1269.

48. Mitchell, G.F., Arterial stiffness and wave reflection: biomarkers of cardiovascular risk. Artery research, 2009. 3(2): p. 56-64.

49. McDonald, D., Regional pulse-wave velocity in the arterial tree. Journal of applied physiology, 1968. 24(1): p. 73-78.

50. Mithieux, S.M. and A.S. Weiss, Elastin. Advances in protein chemistry, 2005. 70: p. 437-461.

51. Clark, J.M. and S. Glagov, Transmural organization of the arterial media. The lamellar unit revisited. Arteriosclerosis, Thrombosis, and Vascular Biology, 1985. 5(1): p. 19-34.

52. Jacob, M.P., Extracellular matrix remodeling and matrix metalloproteinases in the vascular wall during aging and in pathological conditions. Biomedicine & pharmacotherapy, 2003. 57(5): p. 195-202.

53. Zaragoza, C., et al., Nitric oxide regulates matrix metalloprotease-13 expression and activity in endothelium. Kidney international, 2002. 61(3): p. 804-808.

54. Upchurch, G.R., et al., Nitric oxide inhibition increases matrix metalloproteinase–9 expression by rat aortic smooth muscle cells in vitro. Journal of vascular surgery, 2001. 34(1): p. 76-83.

55. Tronc, F., et al., Role of Matrix Metalloproteinases in Blood Flow–Induced Arterial Enlargement. Arteriosclerosis, thrombosis, and vascular biology, 2000. 20(12): p. e120-e126.

56. Lu, P., et al., Extracellular matrix degradation and remodeling in development and disease. Cold Spring Harbor perspectives in biology, 2011. 3(12): p. a005058.

57. O'Sullivan, S., et al., Nitric oxide-matrix metaloproteinase-9 interactions: biological and pharmacological significance--NO and MMP-9 interactions. Biochim Biophys Acta, 2014. 1843(3): p. 603-17.

58. Briones, A.M., S.M. Arribas, and M. Salaices, Role of extracellular matrix in vascular remodeling of hypertension. Current opinion in nephrology and hypertension, 2010. 19(2): p. 187-194.

59. McNulty, M., et al., Collagen type-I degradation is related to arterial stiffness in hypertensive and normotensive subjects. Journal of human hypertension, 2006. 20(11): p. 867-873.

60. Greenwald, S., Ageing of the conduit arteries. The Journal of pathology, 2007. 211(2): p. 157-172.

61. Rachev, A. and K. Hayashi, Theoretical study of the effects of vascular smooth muscle contraction on strain and stress distributions in arteries. Annals of biomedical engineering, 1999. 27(4): p. 459-468.

62. Li, D.Y., et al., Elastin is an essential determinant of arterial morphogenesis. Nature, 1998. 393(6682): p. 276-280.

63. Milewicz, D.M., et al., Genetic variants promoting smooth muscle cell proliferation can result in diffuse and diverse vascular diseases: evidence for a hyperplastic vasculomyopathy. Genetics in Medicine, 2010. 12(4): p. 196-203.

64. Harvey, A., A.C. Montezano, and R.M. Touyz, Vascular biology of ageing—Implications in hypertension. Journal of molecular and cellular cardiology, 2015. 83: p. 112-121.

65. Mattace-Raso, F.U., et al., Arterial stiffness and risk of coronary heart disease and stroke. Circulation, 2006. 113(5):

p. 657-663.

66. Quinn, U., L.A. Tomlinson, and J.R. Cockcroft, Arterial stiffness. JRSM cardiovascular disease, 2012. 1(6): p. 18.

67. Christensen, K.L., Reducing pulse pressure in hypertension may normalize small artery structure. Hypertension, 1991. 18(6): p. 722-727.

68. Hickson, S.S., et al., The relationship of age with regional aortic stiffness and diameter. JACC: Cardiovascular Imaging, 2010. 3(12): p. 1247-1255.

69. Scuteri, A., et al., Longitudinal Perspective on the Conundrum of Central Arterial Stiffness, Blood Pressure, and AgingNovelty and Significance. Hypertension, 2014. 64(6): p. 1219-1227.

70. Franklin, S.S., et al., Hemodynamic patterns of age-related changes in blood pressure. Circulation, 1997. 96(1): p. 308-315.

71. Gates, P.E. and D.R. Seals, Decline in large elastic artery compliance with age: a therapeutic target for habitual exercise. British journal of sports medicine, 2006. 40(11): p. 897-899.

72. Van Bortel, L. and J. Spek, Influence of aging on arterial compliance. Journal of human hypertension, 1998. 12(9).

73. Guala, A., C. Camporeale, and L. Ridolfi, Compensatory effect between aortic stiffening and remodelling during ageing. PloS one, 2015. 10(10): p. e0139211.

74. Sugawara, J., et al., Age-associated elongation of the ascending aorta in adults. JACC: Cardiovascular Imaging, 2008. 1(6): p. 739-748.

75. Schmidt-Trucksäss, A., et al., Structural, functional, and hemodynamic changes of the common carotid artery with age in male subjects. Arteriosclerosis, thrombosis, and vascular biology, 1999. 19(4): p. 1091-1097.

76. Fitch, J.M., et al., Organization of collagen types I and V in the embryonic chicken cornea: monoclonal antibody studies. Proceedings of the National Academy of Sciences, 1984. 81(9): p. 2791-2795.

77. Glagov, S., et al., Mechanical functional role of non-atherosclerotic intimal thickening. Frontiers of medical and biological engineering: the international journal of the Japan Society of Medical Electronics and Biological Engineering, 1992. 5(1): p. 37-43.

78. Papaioannou, T.G. and C. Stefanadis, Vascular wall shear stress: basic principles and methods. Hellenic J Cardiol, 2005. 46(1): p. 9-15.

79. Chiu, J.-J. and S. Chien, Effects of disturbed flow on vascular endothelium: pathophysiological basis and clinical perspectives. Physiological reviews, 2011. 91(1): p. 327-387.

80. Asmar, R., M. O'Rourke, and M. Safar, Arterial stiffness and pulse wave velocity clinical applications. 1999: Éditions scientifiques et médicales Elsevier.

81. Michel, J., et al., Effect of chronic ANG I-converting enzyme inhibition on aging processes. II. Large arteries. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 1994. 267(1): p. R124-R135.

82. Hass, G.M., Elastic tissue. Arch. Path., 1939. 27: p. 334.

83. Duca, L., et al., Matrix ageing and vascular impacts: focus on elastin fragmentation. Cardiovascular research, 2016. 110(3): p. 298-308.

84. McClelland, R.L., et al., Distribution of coronary artery calcium by race, gender, and age. Circulation, 2006. 113(1): p. 30-37.

85. Alford, P.W., J.D. Humphrey, and L.A. Taber, Growth and remodeling in a thick-walled artery model: effects of spa-

tial variations in wall constituents. Biomechanics and modeling in mechanobiology, 2008. 7(4): p. 245-262.

86. Shanahan, C.M., Mechanisms of vascular calcification in CKD—evidence for premature ageing? Nature Reviews Nephrology, 2013. 9(11): p. 661-670.

87. Nilsson, P.M., M.H. Olsen, and S. Laurent, Early Vascular Aging (EVA): New Directions in Cardiovascular Protection. 2015: Academic Press.

88. Fujimoto, D., Aging and cross-linking in human aorta. Biochemical and biophysical research communications, 1982. 109(4): p. 1264-1269.

89. Safar, M.E. and P. Lacolley, Disturbance of macro-and microcirculation: relations with pulse pressure and cardiac organ damage. American Journal of Physiology-Heart and Circulatory Physiology, 2007. 293(1): p. H1-H7.

90. Schlatmann, T.J. and A.E. Becker, Histologic changes in the normal aging aorta: implications for dissecting aortic aneurysm. The American journal of cardiology, 1977. 39(1): p. 13-20.

91. Hayashi, K. and E. Hirayama, Age-related changes of wall composition and collagen cross-linking in the rat carotid artery–In relation with arterial mechanics. Journal of the Mechanical Behavior of Biomedical Materials, 2017. 65: p. 881-889.

92. Wheeler, J.B., et al., Relation of murine thoracic aortic structural and cellular changes with aging to passive and active mechanical properties. Journal of the American Heart Association, 2015. 4(3): p. e001744.

93. Graham, H.K., et al., Localised micro-mechanical stiffening in the ageing aorta. Mechanisms of ageing and development, 2011. 132(10): p. 459-467.

94. Qiu, H., et al., Short communication: vascular smooth muscle cell stiffness as a mechanism for increased aortic stiffness with agingnovelty and significance. Circulation research, 2010. 107(5): p. 615-619.

95. Hong, Z., et al., Vascular smooth muscle cell stiffness and adhesion to collagen I modified by vasoactive agonists. PloS one, 2015. 10(3): p. e0119533.

96. Lakatta, E.G., The reality of aging viewed from the arterial wall. Artery research, 2013. 7(2): p. 73.

97. Zhang, J., et al., Extracellular Matrix Disarray as a Mechanism for Greater Abdominal Versus Thoracic Aortic Stiffness With Aging in PrimatesSignificance. Arteriosclerosis, thrombosis, and vascular biology, 2016. 36(4): p. 700-706.

98. Benetos, A., et al., Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral arteries. Arteriosclerosis, Thrombosis, and Vascular Biology, 1993. 13(1): p. 90-97.

99. Wang, R., et al., Differential mechanical response and microstructural organization between non-human primate femoral and carotid arteries. Biomechanics and modeling in mechanobiology, 2014. 13(5): p. 1041-1051.

100. Armentano, R., et al., Effects of hypertension on viscoelasticity of carotid and femoral arteries in humans. Hypertension, 1995. 26(1): p. 48-54.

101. Gaballa, M.A., et al., Large artery remodeling during aging. Hypertension, 1998. 32(3): p. 437-443.

102. Cox, R.H., Effects of age on the mechanical properties of rat carotid artery. American Journal of Physiology-Heart and Circulatory Physiology, 1977. 233(2): p. H256-H263.

103. Li, Z., et al. REMODELING OF THE RAT AORTIC-WALL DURING AGING. in FASEB JOURNAL. 1995. FEDERATION AMER SOC EXP BIOL 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998.

104. Lakatta, E.G., M. Wang, and S.S. Najjar, Arterial aging and subclinical arterial disease are fundamentally intertwined at macroscopic and molecular levels. Medical Clinics of North America, 2009. 93(3): p. 583-604.

105. O'Rourke, M.F., Arterial aging: pathophysiological principles. Vascular Medicine, 2007. 12(4): p. 329-341.

106. Virmani, R., et al., Effect of aging on aortic morphology in populations with high and low prevalence of hypertension and atherosclerosis. Comparison between occidental and Chinese communities. The American journal of pathology, 1991. 139(5): p. 1119.

107. Hartley, M.C., et al., Evaluation of the diameter of the proximal descending thoracic aorta with age: implications for thoracic aortic stent grafting. Annals of vascular surgery, 2009. 23(5): p. 639-644.

108. Lakatta, E.G., et al., Human aging: changes in structure and function. Journal of the American College of Cardiology, 1987. 10(2): p. 42A-47A.

109. Kamenskiy, A.V., et al., Biaxial mechanical properties of the human thoracic and abdominal aorta, common carotid, subclavian, renal and common iliac arteries. Biomechanics and modeling in mechanobiology, 2014. 13(6): p. 1341-1359.

110. McVeigh, G.E., et al., Age-related abnormalities in arterial compliance identified by pressure pulse contour analysis. Hypertension, 1999. 33(6): p. 1392-1398.

111. Kamenskiy, A.V., et al., Effects of age on the physiological and mechanical characteristics of human femoropopliteal arteries. Acta biomaterialia, 2015. 11: p. 304-313.

112. Kamenskiy, A.V., et al., Passive biaxial mechanical properties and in vivo axial pre-stretch of the diseased human femoropopliteal and tibial arteries. Acta biomaterialia, 2014. 10(3): p. 1301-1313.

113. van der Heijden-Spek, J.J., et al., Effect of age on brachial artery wall properties differs from the aorta and is gender dependent. Hypertension, 2000. 35(2): p. 637-642.

114. Corretti, M.C., et al., Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. Journal of the American College of Cardiology, 2002. 39(2): p. 257-265.

115. Mitchell, G.F., et al., Local shear stress and brachial artery flow-mediated dilation. Hypertension, 2004. 44(2): p. 134-139.

116. Benjamin, E.J., et al., Clinical correlates and heritability of flow-mediated dilation in the community. Circulation, 2004. 109(5): p. 613-619.

117. Mackay, E., et al., Structural basis for the changing physical properties of human pulmonary vessels with age. Thorax, 1978. 33(3): p. 335-344.

118. Hayashi, K., et al., Mechanical properties of human cerebral arteries. Biorheology, 1979. 17(3): p. 211-218.

119. Moritake, K., et al., Experimental Study on Quantitative Flow Measurement by a Doppler Flowmeter with a Sound-spectrograph. Neurological research, 1981. 3(1): p. 363-380.

120. Atkinson, J., Age-related medial elastocalcinosis in arteries: mechanisms, animal models, and physiological consequences. Journal of applied physiology, 2008. 105(5): p. 1643-1651.

121. Giallauria, F., et al., Arterial stiffness and bone demineralization: the Baltimore longitudinal study of aging. American journal of hypertension, 2011. 24(9): p. 970.

122. Persy, V. and P. D'Haese, Vascular calcification and bone disease: the calcification paradox. Trends in molecular medicine, 2009. 15(9): p. 405-416.

123. Dao, H.H., et al., Evolution and modulation of age-related medial elastocalcinosis: impact on large artery stiffness and isolated systolic hypertension. Cardiovascular research, 2005. 66(2): p. 307-317.

124. Micheletti, R.G., et al., Calcification of the internal elastic lamina of coronary arteries. Modern Pathology, 2008. 21(8): p. 1019-1028.

125. Amann, K., Media calcification and intima calcification are distinct entities in chronic kidney disease. Clinical Journal of the American Society of Nephrology, 2008. 3(6): p. 1599-1605.

126. Karwowski, W., et al., The mechanism of vascular calcification–a systematic review. Medical Science Monitor, 2011. 18(1): p. RA1-RA11.

127. Johnson, R.C., J.A. Leopold, and J. Loscalzo, Vascular calcification. Circulation research, 2006. 99(10): p. 1044-1059.

128. Tesauro, M., et al., Arterial ageing: from endothelial dysfunction to vascular calcification. Journal of Internal Medicine, 2017.

129. Friedman, M.H., A biologically plausible model of thickening of arterial intima under shear. Arteriosclerosis, Thrombosis, and Vascular Biology, 1989. 9(4): p. 511-522.

130. Stary, H., Macrophages, macrophage foam cells, and eccentric intimal thickening in the coronary arteries of young children. Atherosclerosis, 1987. 64(2-3): p. 91-108.

131. Lakatta, E.G., Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises. Circulation, 2003. 107(3): p. 490-497.

132. Peacock, A.J., R. Naeije, and L.J. Rubin, Pulmonary circulation: diseases and their treatment. 2016: CRC Press.

133. Glagov, S., et al., Hemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries. Archives of pathology & laboratory medicine, 1988. 112(10): p. 1018-1031.

134. Heckenkamp, J. and G.M. Lamuraglia, Intimal hyperplasia, arterial remodeling, and restenosis: an overview. Perspectives in Vascular Surgery and Endovascular Therapy, 1999. 11(2): p. 71-94.

135. Davies, M. and P.O. Hagen, Pathobiology of intimal hyperplasia. British Journal of Surgery, 1994. 81(9): p. 1254-1269.

136. Qiu, J., et al., Biomechanical regulation of vascular smooth muscle cell functions: from in vitro to in vivo understanding. Journal of The Royal Society Interface, 2014. 11(90): p. 20130852.

137. Rensen, S., P. Doevendans, and G. Van Eys, Regulation and characteristics of vascular smooth muscle cell phenotypic diversity. Netherlands Heart Journal, 2007. 15(3): p. 100-108.

138. Hayoz, D., et al., Conduit artery compliance and distensibility are not necessarily reduced in hypertension. Hypertension, 1992. 20(1): p. 1-6.

139. Gimbrone Jr, M.A., Endothelial dysfunction and the pathogenesis of atherosclerosis, in Atherosclerosis V. 1980, Springer. p. 415-425.

140. Dzau, V.J. and G.H. Gibbons, Introduction: Vascular Remodeling: Mechanisms and Implications. Journal of cardiovascular pharmacology, 1993. 21: p. S1-S5.

141. Lee, H.-Y. and B.-H. Oh, Aging and arterial stiffness. Circulation Journal, 2010. 74(11): p. 2257-2262.

142. Schiffrin, E.L., Reactivity of small blood vessels in hypertension: relation with structural changes. State of the art lecture. Hypertension, 1992. 19(2 Suppl): p. II1.

143. Folkow, B., Physiological aspects of primary hypertension. Physiological reviews, 1982. 62(2): p. 347-504.

144. Mulvany, M. and C. Aalkjaer, Structure and function of small arteries. Physiological reviews, 1990. 70(4): p. 921-

961.

145. Lee, D.L., R.C. Webb, and L. Jin, Hypertension and RhoA/Rho-kinase signaling in the vasculature. Hypertension, 2004. 44(6): p. 796-799.

146. Heerkens, E.H., A.S. Izzard, and A.M. Heagerty, Integrins, vascular remodeling, and hypertension. Hypertension, 2007. 49(1): p. 1-4.

147. Brozovich, F.V., et al., Mechanisms of vascular smooth muscle contraction and the basis for pharmacologic treatment of smooth muscle disorders. Pharmacological reviews, 2016. 68(2): p. 476-532.

148. Staiculescu, M.C., et al., Prolonged vasoconstriction of resistance arteries involves vascular smooth muscle actin polymerization leading to inward remodelling. Cardiovascular research, 2013. 98(3): p. 428-436.

149. Heagerty, A.M., E.H. Heerkens, and A.S. Izzard, Small artery structure and function in hypertension. Journal of cellular and molecular medicine, 2010. 14(5): p. 1037-1043.

150. Ohanian, J., et al., Age-related remodeling of small arteries is accompanied by increased sphingomyelinase activity and accumulation of long-chain ceramides. Physiological reports, 2014. 2(5): p. e12015.

151. Moreau, P., L.V. d'Uscio, and T.F. Lüscher, Structure and reactivity of small arteries in aging. Cardiovascular research, 1998. 37(1): p. 247-253.

152. Feihl, F., et al., Hypertension and microvascular remodelling. Cardiovascular research, 2008.

153. Allen, S.P., S.S. Wade, and R.L. Prewitt, Myogenic tone attenuates pressure-induced gene expression in isolated small arteries. Hypertension, 1997. 30(2): p. 203-208.

154. Rizzoni, D. and E. Agabiti-Rosei, Structural abnormalities of small resistance arteries in essential hypertension. Internal and emergency medicine, 2012. 7(3): p. 205-212.

155. Rizzoni, D., et al., Relationship between media-to-lumen ratio of subcutaneous small arteries and wall-to-lumen ratio of retinal arterioles evaluated noninvasively by scanning laser Doppler flowmetry. Journal of hypertension, 2012. 30(6): p. 1169-1175.

156. Mitchell, G.F., Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. Journal of Applied Physiology, 2008. 105(5): p. 1652-1660.

157. Sutera, S.P. and R. Skalak, The history of Poiseuille's law. Annual Review of Fluid Mechanics, 1993. 25(1): p. 1-20.

158. Mathiassen, O.N., et al., Small artery structure is an independent predictor of cardiovascular events in essential hypertension. Journal of hypertension, 2007. 25(5): p. 1021-1026.

159. Rizzoni, D., et al., Prognostic significance of small-artery structure in hypertension. Circulation, 2003. 108(18): p. 2230-2235.

160. Tschudi, M.R., et al., Effect of age on kinetics of nitric oxide release in rat aorta and pulmonary artery. Journal of Clinical Investigation, 1996. 98(4): p. 899.

161. Harazny, J.M., et al., Increased wall: lumen ratio of retinal arterioles in male patients with a history of a cerebrovascular event. Hypertension, 2007. 50(4): p. 623-629.

162. Laurant, P., M. Adrian, and A. Berthelot, Effect of age on mechanical properties of rat mesenteric small arteries. Canadian journal of physiology and pharmacology, 2004. 82(4): p. 269-275.

163. Stefanadis, C., et al., Effect of vasa vasorum flow on structure and function of the aorta in experimental animals. Circulation, 1995. 91(10): p. 2669-2678.

164. Cheung, N., et al., Aortic distensibility and retinal arteriolar narrowing. Hypertension, 2007. 50(4): p. 617-622.

165. Liao, D., et al., Relationship between carotid artery stiffness and retinal arteriolar narrowing in healthy middle-aged persons. Stroke, 2004. 35(4): p. 837-842.

166. Hamburg, N.M., et al., Cross-sectional relations of digital vascular function to cardiovascular risk factors in the Framingham Heart Study. Circulation, 2008. 117(19): p. 2467-2474.

167. O'callaghan, C.J. and B. Williams, Mechanical strain–induced extracellular matrix production by human vascular smooth muscle cells. Hypertension, 2000. 36(3): p. 319-324.

168. Kanda, K. and T. Matsuda, Mechanical stress-induced orientation and ultrastructural change of smooth muscle cells cultured in three-dimensional collagen lattices. Cell Transplantation, 1994. 3(6): p. 481-492.

169. Kulik, T.J. and S.P. Alvarado, Effect of stretch on growth and collagen synthesis in cultured rat and lamb pulmonary arterial smooth muscle cells. Journal of cellular physiology, 1993. 157(3): p. 615-624.

170. Owens, G.K., Role of mechanical strain in regulation of differentiation of vascular smooth muscle cells. Circulation research, 1996. 79(5): p. 1054-1055.

171. Intengan, H.D., et al., Resistance artery mechanics, structure, and extracellular components in spontaneously hypertensive rats. Circulation, 1999. 100(22): p. 2267-2275.

172. Martinez-Lemus, L.A., et al., αvβ3-and α5β1-integrin blockade inhibits myogenic constriction of skeletal muscle resistance arterioles. American Journal of Physiology-Heart and Circulatory Physiology, 2005. 289(1): p. H322-H329.

173. Mogford, J.E., et al., Vascular smooth muscle αvβ3 integrin mediates arteriolar vasodilation in response to RGD peptides. Circulation Research, 1996. 79(4): p. 821-826.

174. Na, S., et al., Time-dependent changes in smooth muscle cell stiffness and focal adhesion area in response to cyclic equibiaxial stretch. Annals of biomedical engineering, 2008. 36(3): p. 369-380.

175. Sun, Z., et al., Extracellular matrix-specific focal adhesions in vascular smooth muscle produce mechanically active adhesion sites. American Journal of Physiology-Cell Physiology, 2008. 295(1): p. C268-C278.

176. Flavahan, N.A., et al., Imaging remodeling of the actin cytoskeleton in vascular smooth muscle cells after mechanosensitive arteriolar constriction. American Journal of Physiology-Heart and Circulatory Physiology, 2005. 288(2): p. H660-H669.

177. Cipolla, M.J. and G. Osol, Vascular smooth muscle actin cytoskeleton in cerebral artery forced dilatation. Stroke, 1998. 29(6): p. 1223-1228.

178. Cipolla, M.J., Control of cerebral blood flow. 2009.

179. Boudier, H.S., et al., The microcirculation and hypertension. Journal of hypertension. Supplement: official journal of the International Society of Hypertension, 1992. 10(7): p. S147-S156.

180. Jonk, A.M., et al., Microvascular dysfunction in obesity: a potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. Physiology, 2007. 22(4): p. 252-260.

181. Levy, B., et al., Microcirculation in hypertension. Circulation, 2001. 104(6): p. 735-740.

182. Verhave, J.C., et al., Elevated pulse pressure is associated with low renal function in elderly patients with isolated systolic hypertension. Hypertension, 2005. 45(4): p. 586-591.

183. Loutzenhiser, R., A. Bidani, and L. Chilton, Renal Myogenic Response. Circulation research, 2002. 90(12): p. 1316-1324.

184. Fesler, P., et al., Pulse pressure is an independent determinant of renal function decline during treatment of essential hypertension. Journal of hypertension, 2007. 25(9): p. 1915-1920.

185. Wong, T., et al., Retinal microvascular changes and MRI signs of cerebral atrophy in healthy, middle-aged people. Neurology, 2003. 61(6): p. 806-811.

186. Vernooij, M., et al., Prevalence and risk factors of cerebral microbleeds The Rotterdam Scan Study. Neurology, 2008. 70(14): p. 1208-1214.

187. Mitchell, G.F., et al., Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility–Reykjavik study. Brain, 2011. 134(11): p. 3398-3407.

188. Vermeer, S.E., et al., Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke, 2002. 33(1): p. 21-25.

189. Van Swieten, J., et al., Periventricular lesions in the white matter on magnetic resonance imaging in the elderly. Brain, 1991. 114(2): p. 761-774.

190. Vermeer, S.E., et al., Silent brain infarcts and the risk of dementia and cognitive decline. New England Journal of Medicine, 2003. 348(13): p. 1215-1222.

191. Brown, W.R. and C.R. Thore, Review: cerebral microvascular pathology in ageing and neurodegeneration. Neuropathology and applied neurobiology, 2011. 37(1): p. 56-74.

192. Sonntag, W.E., et al., Decreases in cerebral microvasculature with age are associated with the decline in growth hormone and insulin-like growth factor 1. Endocrinology, 1997. 138(8): p. 3515-3520.

193. Cook, J.J., et al., Age-related alterations in the arterial microvasculature of skeletal muscle. Journal of gerontology, 1992. 47(3): p. B83-B88.

194. Scuteri, A., et al., Arterial stiffness is an independent risk factor for cognitive impairment in the elderly: a pilot study. Journal of hypertension, 2005. 23(6): p. 1211-1216.

195. Uzu, T., et al., Cerebral microvascular disease predicts renal failure in type 2 diabetes. Journal of the American Society of Nephrology, 2010. 21(3): p. 520-526.

196. Kurella, M., et al., Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. Journal of the American Society of Nephrology, 2005. 16(7): p. 2127-2133.

197. Murray, C.J. and A.D. Lopez, Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. The Lancet, 1997. 349(9064): p. 1498-1504.

198. Group, S.R., A randomized trial of intensive versus standard blood-pressure control. N Engl J Med, 2015. 2015(373): p. 2103-2116.

199. Roy, C.S., The elastic properties of the arterial wall. The Journal of physiology, 1881. 3(2): p. 125-159.

200. Chirinos, J.A., Arterial stiffness: basic concepts and measurement techniques. Journal of cardiovascular translational research, 2012. 5(3): p. 243-255.

201. Wilkinson, I.B. and C.M. McEniery, Arterial stiffness, endothelial function and novel pharmacological approaches. Clinical and experimental pharmacology and physiology, 2004. 31(11): p. 795-799.

202. Franklin, S.S., et al., Is pulse pressure useful in predicting risk for coronary heart disease? Circulation, 1999. 100(4): p. 354-360.

203. Wilkinson, I.B., et al., Nitric oxide regulates local arterial distensibility in vivo. Circulation, 2002. 105(2): p. 213-217.

204. Hayashi, K., et al., Stiffness and elastic behavior of human intracranial and extracranial arteries. Journal of biomechanics, 1980. 13(2): p. 175181-179184.

205. Cowan, D.B. and B.L. Langille, Cellular and molecular biology of vascular remodeling. Current opinion in lipidology, 1996. 7(2): p. 94-100.

206. Touyz, R.M., F. Tabet, and E.L. Schiffrin, Redox - dependent signalling by angiotensin II and vascular remodelling in hypertension. Clinical and Experimental Pharmacology and Physiology, 2003. 30(11): p. 860-866.

207. Joannides, R., et al., Role of nitric oxide in the regulation of the mechanical properties of peripheral conduit arteries in humans. Hypertension, 1997. 30(6): p. 1465-1470.

208. Wilkinson, I.B., et al., Inhibition of basal nitric oxide synthesis increases aortic augmentation index and pulse wave velocity in vivo. British journal of clinical pharmacology, 2002. 53(2): p. 189-192.

209. Latson, T.W., et al., Effect of nitroglycerin on aortic impedance, diameter, and pulse-wave velocity. Circulation research, 1988. 62(5): p. 884-890.

210. Ben-Shlomo, Y., et al., Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. Journal of the American College of Cardiology, 2014. 63(7): p. 636-646.

211. Vlachopoulos, C., K. Aznaouridis, and C. Stefanadis, Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. Journal of the American College of Cardiology, 2010. 55(13): p. 1318-1327.

212. Weber, T., et al., Arterial stiffness, wave reflections, and the risk of coronary artery disease. Circulation, 2004. 109(2): p. 184-189.

213. London, G.M., et al., Arterial wave reflections and survival in end-stage renal failure. Hypertension, 2001. 38(3): p. 434-438.

214. Blacher, J., et al., Impact of aortic stiffness on survival in end-stage renal disease. Circulation, 1999. 99(18): p. 2434-2439.

215. Meaume, S., et al., Aortic pulse wave velocity predicts cardiovascular mortality in subjects> 70 years of age. Arteriosclerosis, thrombosis, and vascular biology, 2001. 21(12): p. 2046-2050.

216. Cruickshank, K., et al., Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance. Circulation, 2002. 106(16): p. 2085-2090.

217. Laurent, S., et al., Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension, 2001. 37(5): p. 1236-1241.

218. Laurent, S. and P. Boutouyrie, Arterial stiffness and stroke in hypertension. CNS drugs, 2005. 19(1): p. 1-11.

219. Najjar, S.S., et al., Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. Journal of the American College of Cardiology, 2008. 51(14): p. 1377-1383.

220. Dernellis, J. and M. Panaretou, Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. Hypertension, 2005. 45(3): p. 426-431.

221. Takase, H., et al., Brachial-ankle pulse wave velocity predicts increase in blood pressure and onset of hypertension. American journal of hypertension, 2011. 24(6): p. 667.

222. Kaess, B.M., et al., Aortic stiffness, blood pressure progression, and incident hypertension. Jama, 2012. 308(9): p. 875-881.

223. Manisty, C.H. and A.D. Hughes, Meta - analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure, and augmentation index. British journal of clinical pharmacology, 2013. 75(1): p. 79-92.

224. Shorr, R. and G. Somes, Can Diastolic Blood Pressure be Excessively Lowered in the Treatment of Isolated Systolic Hypertension? Journal of clinical hypertension (Greenwich, Conn.), 2000. 2(2): p. 134-137.

225. Abad-Pérez, D., et al., Effect of oral nitrates on pulse pressure and arterial elasticity in patients aged over 65 years with refractory isolated systolic hypertension: study protocol for a randomized controlled trial. Trials, 2013. 14(1): p. 388.

226. Mallareddy, M., C.R. Parikh, and A.J. Peixoto, Effect of Angiotensin - Converting Enzyme Inhibitors on Arterial Stiffness in Hypertension: Systematic Review and Meta - Analysis. The Journal of Clinical Hypertension, 2006. 8(6): p. 398-403.

227. Ong, K.-T., et al., Aortic stiffness is reduced beyond blood pressure lowering by short-term and long-term antihypertensive treatment: a meta-analysis of individual data in 294 patients. Journal of hypertension, 2011. 29(6): p. 1034-1042.

228. Böhm, M., et al., Cardiovascular protection: a breakthrough for high-risk patients. European Heart Journal Supplements, 2009. 11(suppl F): p. F19-F26.

229. Mancia, G., Defining blood pressure goals: is it enough to manage total cardiovascular risk? Journal of Hypertension, 2009. 27: p. S3-S8.

230. Mancia, G., Cardiac and vascular protection: the potential of ONTARGET. The Medscape Journal of Medicine, 2008. 10(Supp): p. S7.

231. Thuillez, C. and V. Richard, Targeting endothelial dysfunction in hypertensive subjects. Journal of human hypertension, 2005. 19: p. S21-S25.

232. C Rizos, E., A. P Agouridis, and M. S Elisaf, The effect of statin therapy on arterial stiffness by measuring pulse wave velocity: a systematic review. Current vascular pharmacology, 2010. 8(5): p. 638-644.

233. Mizuguchi, Y., et al., Impact of statin therapy on left ventricular function and carotid arterial stiffness in patients with hypercholesterolemia. Circulation Journal, 2007. 72(4): p. 538-544.

234. Plantinga, Y., et al., Supplementation with vitamins C and E improves arterial stiffness and endothelial function in essential hypertensive patients. American journal of hypertension, 2007. 20(4): p. 392-397.

235. Schnider, S.L. and R. Kohn, Glucosylation of human collagen in aging and diabetes mellitus. Journal of Clinical Investigation, 1980. 66(5): p. 1179.

236. Corman, B., et al., Aminoguanidine prevents age-related arterial stiffening and cardiac hypertrophy. Proceedings of the National Academy of Sciences, 1998. 95(3): p. 1301-1306.

237. Brownlee, M., et al., Aminoguanidine prevents diabetes-induced arterial wall protein cross-linking. Science, 1986. 232: p. 1629-1633.

238. Li, Y.M., et al., Prevention of cardiovascular and renal pathology of aging by the advanced glycation inhibitor aminoguanidine. Proceedings of the National Academy of Sciences, 1996. 93(9): p. 3902-3907.

239. Ailawadi, G., et al., Smooth muscle phenotypic modulation is an early event in aortic aneurysms. The Journal of thoracic and cardiovascular surgery, 2009. 138(6): p. 1392-1399.

240. Andreeva, E.R., I.M. Pugach, and A.N. Orekhov, Subendothelial smooth muscle cells of human aorta express macrophage antigen in situ and in vitro. Atherosclerosis, 1997. 135(1): p. 19-27.

241. Lacolley, P., et al., The vascular smooth muscle cell in arterial pathology: a cell that can take on multiple roles. Cardiovascular research, 2012. 95(2): p. 194-204.

242. Lowe, H., B. James, and L. Khachigian, A novel model of in-stent restenosis: rat aortic stenting. Heart, 2005. 91(3): p. 393-395.

243. Muller, D.W., S.G. Ellis, and E.J. Topol, Experimental models of coronary artery restenosis. Journal of the American College of Cardiology, 1992. 19(2): p. 418-432.

244. Pasterkamp, G., D.P. de Kleijn, and C. Borst, Arterial remodeling in atherosclerosis, restenosis and after alteration of blood flow: potential mechanisms and clinical implications. Cardiovascular research, 2000. 45(4): p. 843-852.

245. Pasterkamp, G., Z.S. Galis, and D.P. De Kleijn, Expansive arterial remodeling: location, location, location. Arteriosclerosis, thrombosis, and vascular biology, 2004. 24(4): p. 650-657.

246. Lelong, D. and M. Logak, Pathogenesis of spontaneous cervico-cerebral artery dissection. A hypothesis and a review of the literature. Medical hypotheses, 2004. 62(3): p. 453-457.

247. Aiello, V.D., et al., Morphology of the internal elastic lamina in arteries from pulmonary hypertensive patients: a confocal laser microscopy study. Modern pathology, 2003. 16(5): p. 411-416.

248. Kapadia, M.R., et al., Nitric oxide and nanotechnology: a novel approach to inhibit neointimal hyperplasia. Journal of vascular surgery, 2008. 47(1): p. 173-182.

249. Ahanchi, S.S., N.D. Tsihlis, and M.R. Kibbe, The role of nitric oxide in the pathophysiology of intimal hyperplasia. Journal of vascular surgery, 2007. 45(6): p. A64-A73.

250. Pober, J.S. and W.C. Sessa, Evolving functions of endothelial cells in inflammation. Nature Reviews Immunology, 2007. 7(10): p. 803-815.

251. Ohtsu, H., et al., Angiotensin II signal transduction through small GTP-binding proteins. Hypertension, 2006. 48(4): p. 534-540.

252. Heeneman, S., J.C. Sluimer, and M.J. Daemen, Angiotensin-converting enzyme and vascular remodeling. Circulation research, 2007. 101(5): p. 441-454.

253. Rakugi, H., et al., Induction of angiotensin converting enzyme in the neointima after vascular injury. Possible role in restenosis. Journal of Clinical Investigation, 1994. 93(1): p. 339.

254. Rakugi, H., et al., Potential importance of tissue angiotensin-converting enzyme inhibition in preventing neointima formation. Circulation, 1994. 90(1): p. 449-455.

255. Wilson, D.P., et al., Angiotensin II receptor antagonists prevent neointimal proliferation in a porcine coronary artery organ culture model. Cardiovascular research, 1999. 42(3): p. 761-772.

256. Yamada, T., et al., Angiotensin II receptor blocker inhibits neointimal hyperplasia through regulation of smooth muscle–like progenitor cells. Arteriosclerosis, thrombosis, and vascular biology, 2007. 27(11): p. 2363-2369.

257. Schwartz, R.S., N.A. Chronos, and R. Virmani, Preclinical restenosis models and drug-eluting stents: still important, still much to learn. Journal of the American College of Cardiology, 2004. 44(7): p. 1373-1385.

258. Faxon, D. Angiotensin Converting Enzyme-Inhibition And Restenosis-The Final Results Of The Marcator Trial. In Circulation. 1992. Amer Heart Assoc 7272 Greenville Avenue, Dallas, Tx 75231-4596.

259. Serruys, P., et al., Does the new angiotensin converting enzyme inhibitor cilazapril prevent restenosis after percutaneous transluminal coronary angioplasty? Results of the MERCATOR study: a multicenter, randomized, double-blind placebo-controlled trial. Circulation (Baltimore), 1992. 86(1): p. 100-110.

260. Avolio, A., D. Jones, and M. Tafazzoli-Shadpour, Quantification of alterations in structure and function of elastin in the arterial media. Hypertension, 1998. 32(1): p. 170-175.

261. Wagenseil, J.E. and R.P. Mecham, Elastin in large artery stiffness and hypertension. Journal of cardiovascular translational research, 2012. 5(3): p. 264-273.

262. Nakashima, Y., Y. Shiokawa, and K. Sueishi, Alterations of elastic architecture in human aortic dissecting aneurysm. Laboratory investigation; a journal of technical methods and pathology, 1990. 62(6): p. 751-760.

263. Le, V.P., et al., Decreased aortic diameter and compliance precedes blood pressure increases in postnatal development of elastin-insufficient mice. American Journal of Physiology-Heart and Circulatory Physiology, 2011. 301(1): p. H221-H229.

264. Martyn, C. and S. Greenwald, A hypothesis about a mechanism for the programming of blood pressure and vascular disease in early life. Clinical and Experimental Pharmacology and Physiology, 2001. 28(11): p. 948-951.

265. Wang, L., et al., Coronary artery calcification and myocardial perfusion in asymptomatic adults: the MESA (Multi-Ethnic Study of Atherosclerosis). Journal of the American College of Cardiology, 2006. 48(5): p. 1018-1026.

266. Iribarren, C., et al., Calcification of the aortic arch: risk factors and association with coronary heart disease, stroke, and peripheral vascular disease. Jama, 2000. 283(21): p. 2810-2815.

267. Jeziorska, M., C. McCollum, and D. Woolley, Observations on bone formation and remodelling in advanced atherosclerotic lesions of human carotid arteries. Virchows Archiv, 1998. 433(6): p. 559-565.

268. Son, B.-K., et al., Statins protect human aortic smooth muscle cells from inorganic phosphate-induced calcification by restoring Gas6-Axl survival pathway. Circulation research, 2006. 98(8): p. 1024-1031.

269. Cowell, S.J., et al., A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. New England Journal of Medicine, 2005. 352(23): p. 2389-2397.

270. Bellamy, M.F., et al., Association of cholesterol levels, hydroxymethylglutaryl coenzyme-A reductase inhibitor treatment, and progression of aortic stenosis in the community. Journal of the American College of Cardiology, 2002. 40(10): p. 1723-1730.

271. Novaro, G.M., et al., Effect of hydroxymethylglutaryl coenzyme a reductase inhibitors on the progression of calcific aortic stenosis. Circulation, 2001. 104(18): p. 2205-2209.

272. Rosenhek, R., et al., Statins but not angiotensin-converting enzyme inhibitors delay progression of aortic stenosis. Circulation, 2004. 110(10): p. 1291-1295.

273. Rajamannan, N.M., et al., Atorvastatin inhibits hypercholesterolemia-induced cellular proliferation and bone matrix production in the rabbit aortic valve. Circulation, 2002. 105(22): p. 2660-2665.

274. Abedin, M., Y. Tintut, and L.L. Demer, Vascular calcification. Arteriosclerosis, thrombosis, and vascular biology, 2004. 24(7): p. 1161-1170.

275. Proudfoot, D. and C.M. Shanahan, Biology of calcification in vascular cells: intima versus media. Herz, 2001. 26(4): p. 245-251.

276. Chen, N.X., et al., High glucose increases the expression of Cbfa1 and BMP-2 and enhances the calcification of vascular smooth muscle cells. Nephrology Dialysis Transplantation, 2006. 21(12): p. 3435-3442.

277. Taki, K., et al., Oxidative stress, advanced glycation end product, and coronary artery calcification in hemodialysis patients. Kidney international, 2006. 70(1): p. 218-224.

278. Dao, H.H., et al., Pharmacological prevention and regression of arterial remodeling in a rat model of isolated systolic hypertension. Journal of hypertension, 2002. 20(8): p. 1597-1606.

279. Schafer, A., et al., Eplerenone improves vascular function and reduces platelet activation in diabetic rats. Journal of Physiology and Pharmacology, 2010. 61(1): p. 45.

280. Gkizas, S., et al., Aldosterone receptor blockade inhibits degenerative processes in the early stage of calcific aortic stenosis. European journal of pharmacology, 2010. 642(1): p. 107-112.

281. Johnson, R., J. Leopold, and J. Loscalzo, Vascular Calcification: Pathobiological Mechanisms and Clinical Implications (vol 99, pg 1044, 2006). CIRCULATION RESEARCH, 2009. 105(6): p. E8-E8.

282. Block, G.A., et al., Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney international, 2005. 68(4): p. 1815-1824.

283. Budoff, M.J., et al., Diabetes and progression of coronary calcium under the influence of statin therapy. American heart journal, 2005. 149(4): p. 695-700.

284. Jeon, G.-H., et al., Association between serum estradiol level and coronary artery calcification in postmenopausal women. Menopause, 2010. 17(5): p. 902-907.

285. Jono, S., et al., Parathyroid hormone–related peptide as a local regulator of vascular calcification. Arteriosclerosis, thrombosis, and vascular biology, 1997. 17(6): p. 1135-1142.

286. Avolio, A., Arterial stiffness. Pulse, 2013. 1(1): p. 14-28.

287. Osol, G., et al., Myogenic tone, reactivity, and forced dilatation: a three-phase model of in vitro arterial myogenic behavior. American Journal of Physiology-Heart and Circulatory Physiology, 2002. 283(6): p. H2260-H2267.

288. Jackson, W.F., Ion channels and vascular tone. Hypertension, 2000. 35(1): p. 173-178.

289. Nelson, M., et al., Calcium channels, potassium channels, and voltage dependence of arterial smooth muscle tone. American Journal of Physiology-Cell Physiology, 1990. 259(1): p. C3-C18.

290. Davis, M.J., M.A. Hill, and L. Kuo, Local regulation of microvascular perfusion. Comprehensive Physiology, 2011.

291. Gui, P., et al., Integrin receptor activation triggers converging regulation of Cav1. 2 calcium channels by c-Src and protein kinase A pathways. Journal of Biological Chemistry, 2006. 281(20): p. 14015-14025.

292. Wu, X., et al., Regulation of the L-type calcium channel by α5β1 integrin requires signaling between focal adhesion proteins. Journal of Biological Chemistry, 2001. 276(32): p. 30285-30292.

293. McCarron, J., et al., Myogenic contraction by modulation of voltage-dependent calcium currents in isolated rat cerebral arteries. The Journal of Physiology, 1997. 498(Pt 2): p. 371.

294. Wu, X. and M.J. Davis, Characterization of stretch-activated cation current in coronary smooth muscle cells. American Journal of Physiology-Heart and Circulatory Physiology, 2001. 280(4): p. H1751-H1761.

295. Welsh, D.G., et al., Swelling - activated cation channels mediate depolarization of rat cerebrovascular smooth muscle by hyposmolarity and intravascular pressure. The Journal of Physiology, 2000. 527(1): p. 139-148.

296. Hill, M.A., et al., Therapeutic potential of pharmacologically targeting arteriolar myogenic tone. Trends in pharmacological sciences, 2009. 30(7): p. 363-374.

297. Sandow, S.L. and C.E. Hill, Incidence of myoendothelial gap junctions in the proximal and distal mesenteric arteries of the rat is suggestive of a role in endothelium-derived hyperpolarizing factor-mediated responses. Circ Res, 2000. 86(3): p. 341-6.

298. Hansen, P.B., J.G. De Mey, and P.M. Vanhoutte, Endothelium-dependent hyperpolarizations in health and disease. Acta Physiol (Oxf), 2017. 219(1): p. 97-99.

299. Feletou, M., R. Kohler, and P.M. Vanhoutte, Nitric oxide: orchestrator of endothelium-dependent responses. Ann Med, 2012. 44(7): p. 694-716.

300. Leung, S.W. and P.M. Vanhoutte, Endothelium-dependent hyperpolarization: age, gender and blood pressure, do they matter? Acta Physiol (Oxf), 2017. 219(1): p. 108-123.

301. Chennupati, R., et al., Endothelium-dependent hyperpolarization-related relaxations diminish with age in murine saphenous arteries of both sexes. Br J Pharmacol, 2013. 169(7): p. 1486-99.

302. Nakashima, M., et al., Endothelium-dependent hyperpolarization caused by bradykinin in human coronary arteries. J Clin Invest, 1993. 92(6): p. 2867-71.

303. Urakami-Harasawa, L., et al., Importance of endothelium-derived hyperpolarizing factor in human arteries. J Clin Invest, 1997. 100(11): p. 2793-9.

304. Mantelli, L., S. Amerini, and F. Ledda, Roles of nitric oxide and endothelium-derived hyperpolarizing factor in vasorelaxant effect of acetylcholine as influenced by aging and hypertension. J Cardiovasc Pharmacol, 1995. 25(4): p. 595-602.

305. Meininger, G.A. and J.P. Trzeciakowski, Combined effects of autoregulation and vasoconstrictors on hindquarters vascular resistance. American Journal of Physiology-Heart and Circulatory Physiology, 1990. 258(4): p. H1032-H1041.

306. Knot, H.J. and M.T. Nelson, Regulation of arterial diameter and wall [Ca^{2+}] in cerebral arteries of rat by membrane potential and intravascular pressure. The Journal of physiology, 1998. 508(1): p. 199-209.

307. Hill, M.A., et al., Invited review: arteriolar smooth muscle mechanotransduction: Ca^{2+} signaling pathways underlying myogenic reactivity. Journal of Applied Physiology, 2001. 91(2): p. 973-983.

308. Kotecha, N. and M.A. Hill, Myogenic contraction in rat skeletal muscle arterioles: smooth muscle membrane potential and Ca^{2+} signaling. American Journal of Physiology-Heart and Circulatory Physiology, 2005. 58(4): p. 1326-1334.

309. Knot, H.J. and M.T. Nelson, Regulation of membrane potential and diameter by voltage-dependent K^+ channels in rabbit myogenic cerebral arteries. American Journal of Physiology-Heart and Circulatory Physiology, 1995. 269(1): p. H348-H355.

310. Hill, M.A. and G.A. Meininger, Calcium entry and myogenic phenomena in skeletal muscle arterioles. American Journal of Physiology-Heart and Circulatory Physiology, 1994. 267(3): p. H1085-H1092.

311. Bao, R., et al., A close association of RyRs with highly dense clusters of $Ca2^+$-activated Cl^- channels underlies the activation of STICs by Ca^{2+} sparks in mouse airway smooth muscle. The Journal of general physiology, 2008. 132(1): p. 145-160.

312. Yang, Y., et al., Heterogeneity in function of small artery smooth muscle BKCa: involvement of the β1- subunit. The Journal of physiology, 2009. 587(12): p. 3025-3044.

313. Jackson, W.F. and K.L. Blair, Characterization and function of $Ca2^+$-activated K^+ channels in arteriolar muscle cells. American Journal of Physiology-Heart and Circulatory Physiology, 1998. 274(1): p. H27-H34.

314. Otsuka, T., et al., Administration of the Rho-kinase inhibitor, fasudil, following nitroglycerin additionally dilates the site of coronary spasm in patients with vasospastic angina. Coronary artery disease, 2008. 19(2): p. 105-110.

315. Ge, Y., et al., Impaired myogenic constriction of the renal afferent arteriole in a mouse model of reduced βENaC expression. American Journal of Physiology-Renal Physiology, 2012. 302(11): p. F1486-F1493.

316. Moore, L.C. and D. Casellas, Tubuloglomerular feedback dependence of autoregulation in rat juxtamedullary afferent arterioles. Kidney international, 1990. 37(6): p. 1402-1408.