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Vascular Smooth Muscle Remodeling in Conductive and Resistance Arteries in Hypertension: VSMC in hypertension

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Abstract

Cardiovascular disease is a leading cause of death worldwide and accounts for greater than 17.3 million deaths per year, with an estimated increase in incidence to 23.6 million by 2030 [1]. Cardiovascular death represents 31% of all global deaths [2] - with stroke, heart attack, and ruptured aneurysms predominantly contributing to these high mortality rates. A key risk factor for cardiovascular disease is hypertension. Although treatment or reduction in hypertension can prevent the onset of cardiovascular events, existing therapies are only partially effective. A key pathological hallmark of hypertension is increased peripheral vascular resistance due to structural and functional changes in large (conductive) and small (resistance) arteries. In this review, we discuss the clinical implications of vascular remodeling, compare the differences between vascular smooth muscle cell (VSMC) remodeling in conductive and resistance arteries, discuss the genetic factors associated with VSMC function in hypertensive patients, and provide a prospective assessment of current and future research and pharmacological targets for the treatment of hypertension.

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I. Introduction

The arterial vascular wall contains multiple cellular components including endothelial cells, layers of vascular smooth muscle cells (VSMCs) and an extracellular matrix, and can be subdivided into three distinct layers or tunics: the tunica intima, tunica media and tunica externa. The innermost tunica intima is comprised of a single layer of endothelial cells, while the tunica externa is the outermost layer of the vessel wall and forms a sheath of connective tissue primarily comprised of collagen and elastin fibers. Between the intima and externa is the tunica media - the largest of the three layers and the site of key differences as we move down the arterial tree from large conducting vessels, to medium sized distributing vessels, and finally to resistance arteries. Conducting or elastic arteries (e.g. the aorta or carotid) have a tunica media with greater elastic than smooth muscle content, which facilitates vascular compliance in response to high pressure blood flow from the heart. In comparison, muscular distributing arteries such as the radial artery have decreased elastic material but higher smooth muscle content with contribute to increased contractility in these vessels [3,4]. Lastly, in resistance arteries, the tunica media lacks elastin and is made up of one to two layers of VSMCs.

In the healthy artery, changes in the extravascular environment, local signaling molecules, or hemodynamic demands, initiate structural and functional adaptations within the different cell types and layers of the vessel wall designed for blood pressure homeostasis. However, in disease states, these adaptive changes do not return to baseline levels but instead initiate pathological vascular alterations observed with cardiovascular disease. This maladaptive change is defined as “vascular remodeling”.

In hypertension, vascular remodeling involves changes to VSMCs in the vessel wall of both large and small arteries, as well as other cellular components of the vascular wall including endothelial cells [5,6], and elastin and collagen content [7,8]. Vascular remodeling is a heterogeneous process and differs depending on the vessel type and specific disease state or progression (**Figure 1**). For example, vascular remodeling may increase or decrease the arterial lumen diameter in processes defined as outward and inward remodeling respectively. Vessels that undergo eutrophic remodeling have no net change in vessel wall material or media cross-sectional area. Conversely, hypo- and hypertrophic remodeling result in a net decrease or increase in vessel cellular material, respectively. In larger conductive vessels, VSMCs primarily undergo hypertrophy, which results in an increased intima-media thickness and contributes to increased arterial stiffness and blood pulse wave pressure. By comparison, small resistance vessel remodeling may present as either eutrophic or hypertrophic remodeling, depending on the form of hypertension.

Mechanical forces on the blood vessel wall also greatly contribute to hypertensive vascular remodeling. Blood vessels respond to altered fluid shear stress and circumferential strain

through changes in vascular extracellular matrix composition, cellular secretion of endogenous growth factors and cytokines, and vascular sensitivity to circulating humoral factors. These dynamic changes are further regulated by temporal variables such as force duration, load, and force traits (e.g. cyclic stretch versus static strain) which cause differential responses on the vasculature. Disruption of the vascular-mechanical homeostasis may in fact initiate early pathways involved in pathological remodeling. The mechanobiological mechanisms that govern organ, tissue, and cell level changes in organisms, and how these structures adapt to mechanical insults, is an area of intense research interest and is too large for the scope of this vascular specific review. Extensive data exists and is expertly reviewed by others [9,10].

In this review article, we discuss the clinical relevance of vascular remodeling, emphasizing the relationship between current hypertensive drugs and the reversal of remodeling. Next, we outline the functional and structural alterations to VSMCs in both large and small arteries, highlighting similarities and differences in the pattern and mechanisms of remodeling. We examine genome-wide association data to address the genomic underpinnings of VSMC remodeling in hypertension, and lastly, assess future research areas and drug targets for treating hypertension.

II. Clinical Relevance

Clinical studies in patients with cardiovascular diseases find correlations between vascular remodeling and cardiovascular disease progression [11–13]. These findings extend from cardiovascular disease in general, to hypertension specifically, as vascular remodeling, particularly in the small arteries, is a hallmark of disease progression in hypertension and is highly correlated with disease severity [14,15]. Therefore, improved understanding of the pathological mechanisms of vascular remodeling holds high relevance for the clinical consequences and treatment of hypertension. In **Table 1**, we provide a comprehensive summary of the features of a number of clinical studies that investigate the clinical relationship between hypertension and vascular remodeling.

a. Conductive Artery Remodeling in Clinical Hypertension

In larger conductive arteries, vessel remodeling in hypertension is characterized by increased intima-media thickness, which contributes to overall increased vessel wall thickness [16]. Conductive wall thickening and hypertrophy during hypertension ultimately lead to increased vessel stiffness and decreased arterial compliance, which could negatively impact myocardial work capacity and coronary perfusion [17]. The changes observed in large arteries during hypertension are similar to those seen as a consequence of physiological aging in elderly patients [18,19] leading to one theory that increased blood pressure accelerates age-related alterations to large arteries [20–22].

In this regard, a cross-sectional study of elderly patients with at least one risk factor for cardiovascular disease showed an association between carotid arterial stiffness, high average systolic blood pressures and high visit-to-visit systolic blood pressure [23]. In another clinical study, increased aortic stiffness (measured by pulse wave velocity) correlated significantly with negative end organ effects in the heart and kidney in patients with mild hypertension [24].

Specifically, pulse wave velocity correlated with changes in left ventricular mass and wall thickness, left atrial diameter, and negatively with creatinine clearance, indicative of renal function decline. These findings have been reported in several other studies investigating structural and functional changes in the heart [25–27] and kidney [28] of hypertensive patients with increased arterial stiffness.

b. Resistance Artery Remodeling in Clinical Hypertension

The smaller diameter arteries of the resistance vasculature play a vital role in the control of systemic blood pressure. As such, resistance arteries are particularly vulnerable to vascular remodeling during hypertension and small artery changes have been well-correlated with clinical disease progression and severity [29]. Numerous groups report an increased media-to-lumen (M/L) ratio in small subcutaneous resistance arteries collected during a gluteal biopsy [30,31]. More recently developed non-invasive techniques, including microscopic and clinical analysis of the retinal vascular bed, confirm findings of increased M/L ratio and highlight novel non-invasive tools for diagnosing pathophysiological vascular changes in hypertension [32,33].

Hypertensive patients have significantly increased wall-to-lumen ratio in retinal arterioles compared to normotensive controls as measured using scanning laser Doppler flowmetry [32]. Similarly, hypertensive patients with advanced microvascular retinal damage (retinopathy) have a higher incidence of left atrial enlargement, reduced left ventricular ejection fraction, and consequently congestive heart failure [33]. Comparison of resistance arteries from the forearm and coronary microvasculatures suggests that these two parameters are remodeled in parallel in untreated patients with mild hypertension [34]. These findings provide examples of non-invasive determination of changes to resistance arteries in hypertension and support the clinical significance of small artery remodeling in hypertension. These techniques may also be useful to clinically assess whether vascular remodeling can be reversed by effective treatment of hypertension.

c. Clinical Interventions and Vascular Remodeling

Treatment for individuals with hypertension currently includes a multipronged approach including pharmacological antihypertensive agents and/or lifestyle changes in both diet and exercise. The five major classes of antihypertensive drugs (β-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II (Ang II) receptor blockers (ARB) and calcium-channel blockers (CCBs)) [35] all promote blood pressure lowering, but have different effects on vascular remodeling depending on their mechanisms of action. Specifically, a comprehensive review of the literature shows that drugs that target vessel dilation are typically more successful in correcting resistance artery remodeling than those that primarily manipulate cardiac output [36–39].

Clinical studies have shown that drugs targeting the renin-angiotensin-aldosterone system (RAAS), specifically the synthesis of Ang II (ACE inhibitors) or the binding of the ligand to its receptor (ARBs), are beneficial in reversing conductive vascular remodeling due to hypertension. For example, the ACE inhibitor (ACE-I) perindopril significantly decreases vessel thickness in the conductive radial artery in hypertensive patients after 9 months of

treatment [40]. In another randomized cross-over study, patients were treated with the ARB valsartan, the ACE inhibitor captopril or a combination of both [41]. Both single and combination treatments decreased brachial artery pulse wave velocity, an indirect measure of arterial wall stiffness [41]. An 8 week treatment with the ARB irbesartan decreased radial, but not carotid, artery wall thickness with no correlation to degree of blood pressure lowering or the levels of circulating RAAS circulating hormones [42]. In support of a role for VSMC remodeling, the authors hypothesize that these heterogeneous findings are due to differences in vessel wall structure as the radial artery has a higher proportion of VSMCs to extracellular matrix than the carotid [42]

Pharmacological agents blocking the RAAS have similar beneficial effects on remodeling in the resistance vasculature. Treatment with the direct renin inhibitor aliskiren, in concert with the ARB valsartan, significantly improved small artery remodeling in hypertensive patients, as assessed by retinal arteriole structure [43]. The works of Thybo et al. and Schiffrin and colleagues similarly report that in clinical studies ACE-Is [38,44,45] and ARBs [46,47], but not β-blockers, improved resistance vasculature structure. These data support the notion that the RAAS is a relevant and important clinical target for reversing vascular remodeling in the conductive and resistance vasculature. Many of these studies show a 2–3 mmHg lowering of systolic blood pressure in patients treated with ACE-Is or ARBs compared to those treated with β-blockers or other classes, raising the question of whether a direct effect of RAAS or the level of blood pressure (with implied direct effect of mechanical stretch) is responsible for vascular remodeling.

The beneficial effects of RAAS blockade in reversing large and small artery vascular remodeling are recapitulated in animal models of hypertension. Treatment with the ACE-I perindopril decreased aortic wall thickness in two-kidney, one-clip hypertensive rats, by reversing VSMC hypertrophy without altering vessel collagen content [48]. In a comparison between low dose or high dose ACE-I quinapril versus hydralazine, both doses of quinapril was more effective in lowering aortic collagen content in the spontaneously hypertensive rats (SHRs), despite less effective blood pressure lowing with low dose quinapril compared to hydralazine [49]. Lastly, the ARB losartan is superior to the CCB amlodipine at improving vascular remodeling in prehypertensive stroke-prone spontaneously hypertensive (SHRSP) rats [50]. Taken together, these studies suggest a dominant role of the RAAS in vascular remodeling in hypertension.

Cardiovascular training is also an effective treatment against hypertension and vascular remodeling, likely attributable in part to attenuating the RAAS. Spontaneously hypertensive rats (SHRs) that engaged in moderate exercise training over 12 weeks had lower blood pressure and ACE expression, and attenuated aortic remodeling [51]. Hypertensive patients with decreased capillary area and capillary lumen area had an improvement in both parameters following aerobic exercise training [52]. The beneficial effects of aerobic exercise training and pharmaceutical interventions on remodeling demonstrate a clinical relevance of vascular remodeling in the pathology and cardiovascular consequences of hypertension.

III. Conductive Artery Remodeling

Vascular smooth muscle cells (VSMC) in conductive arteries maintain vessel tone and structure by balancing forces between vasoconstrictive and vasodilatory signals, and regulate the production of extracellular matrix. Yet, the adaptations of conductive arterial VSMCs to rising intravascular pressure have not been particularly well studied in the literature. Included in this section are several seminal works that have expanded our current understanding of the structural changes and signaling pathways involved in vascular remodeling in large conductive arteries during hypertension.

a. Structural and Functional Changes of Large Arteries and VSMCs in Hypertension

The conductive (or elastic) arteries of the vascular system are critically important in regulating pulse wave pressures generated by the left ventricle during a heart cycle. Conductive arteries are located closest to the heart and their large lumen, high content of elastic fibers, and low compliance allows for regulation of the pulse wave pressures generated by the contractile motions of the heart, a feature known as the Windkessel effect. During hypertension, large elastic artery remodeling is characterized by a decrease in arterial compliance and an increase in wall thickness, due to an increase in intima-media thickness in the range of 15–40% [3].

Studies in patients with untreated essential hypertension show that local pulse pressure is correlated with overall wall thickening and increased intima-media thickness in the common carotid artery, a representative conductive artery [53]. Similarly, aortic stiffening is associated with increased blood pressure in a longitudinal community-based cohort study of the relationship between arterial stiffening and incidence of hypertension [54]. Medium sized distal muscular arteries are also remodeled during hypertension, and present with increased intima-media thickness but no overall changes in vessel or lumen diameter [53,55]. In contrast to the correlation in conductive arteries, there is no significant relationship between local pulse pressure and intima-media thickness in the distal radial artery [3,53]. This highlights a key difference in remodeling in proximal elastic arteries (such as the carotid) compared to distal medium sized arteries like the radial artery, likely due to differences in their structural composition as briefly discussed earlier in this review.

The increased lumen in proximal elastic arteries during hypertension is typically attributed to the breakdown of elastin fibers in response to increased pulsatile strength [56]. Simultaneously, hypertension is also thought to increase collagen deposition in large vessels and it is hypothesized that the alteration of the elastin/collagen ratio is a significant contributor to increased arterial stiffness. However, data from patients with essential hypertension, as well as rodent models of hypertension, show conflicting findings where arterial wall thickening does not always result in enhanced arterial stiffness or a change in elastin/collagen ratio [55,57–60]. This suggests that remodeling is not uniform in all large vessels and that other variables are at play. For example, other extracellular matrix proteins such as fibronectin and integrins may be involved in the structural changes in conductive arteries in hypertension [58,59]. This demonstrates that our current understanding of potential (mal)adaptive cellular and molecular mechanisms that contribute to essential hypertension

are limited by the relatively small cohorts of human studies and the inherent limitations of animal models.

In light of this, new tools are being applied to the field to better understand the cellular mechanisms contributing to hypertension. For example, Sehgel et al. measured stiffness of aortic VSMCs using atomic force microscopy and an *in vitro* reconstituted aortic tissue model in SHRs that have increased blood pressure and aortic stiffness and in normotensive Wistar Kyoto rats (WKYs), to define the direct contribution of VSMCs to increased conductive artery stiffness [61]. The authors also show that SHR aortic VSMCs exhibit increased cellular stiffness due to the increased expression of contractile proteins including phosphorylated myosin light chain and myosin light chain kinase. These alterations in VSMC stiffness are also present due to physiological aging, and vessel and cell stiffness are amplified when hypertension and aging are both present [62]. Researchers have also identified a role for apoptosis or programmed cell death in hypertension-induced remodeling in conductive vessels. SHRs [63] and deoxycorticosterone acetate–salt induced hypertensive rats [64] have increased apoptosis in the aorta or isolated aortic VSMCs compared to control animals/cells. Sharifi et al. hypothesize that increased apoptosis may be a countermeasure against cellular hypertrophy during hypertension [64].The molecular mechanisms responsible for these cellular changes are not yet fully defined but the findings presented above begin to provide evidence for direct changes in VSMCs in conductive arteries during hypertension.

Further evidence for direct changes to VSMCs is presented in the *in vitro* culture system studies by Leung et al. (1976) where cells are plated on matrix and exposed to cyclic stretch [65]. Rabbit aortic VSMCs, cultured on elastin membranes, increased their production of collagen after exposure to a cyclic stretch paradigm[65]. Cyclic stretch also induces significant changes in smooth muscle myosin protein and mRNA expression [66]. This effect appeared to be dependent on the extracellular matrix as stretch-induced myosin expression was only present when VSMCs were plated on collagen type 1 or laminin, but not when cells were plated on fibronectin. Thus, cyclic stretch combined with signals from the extracellular matrix seems critical for the regulation of smooth muscle myosin activity [66]. Although these studies do not address the molecular pathways between cyclical stretch and protein synthesis, they begin to address the effects of mechanical strain on conductive VSMCs and highlight the need for further investigation in the area of VSMC-extracellular matrix interaction.

Recently, a relationship between senescence (aging) of VSMCs and hypertension has emerged. *Klotho* is a recently discovered anti-aging gene and its expression typically decreases with age. However, a study of elderly hypertensive, elderly non-hypertensive and non-elderly hypertensive patients by Su et al. showed that non-elderly hypertensive patients had lower circulating levels of Klotho protein than elderly non-hypertensive patients [67]. Further, Klotho protein in elderly hypertensive patients was the lowest among all groups [67]. The decreased circulating levels of Klotho in non-elderly hypertensive patients suggest a role of cell senescence in vascular remodeling in hypertension. In support of this, middle-aged heterozygous Klotho$^{+/-}$ mice have increased aortic stiffness (measured by pulse wave velocity) and aldosterone levels compared to age-match wild-type littermate controls [68]. Hu et al. have proposed that Klotho decreases phosphate uptake in VSMCs, thus decreasing

vascular calcification [69]. Additional studies modulating Klotho protein levels show positive effects with increased Klotho (or negative effects with decreased Klotho) but do not specifically investigate changes to VSMCs [70–73].

b. Signaling and Neurohumoral Pathways

VSMC and vessel function in conductive arteries are typically self-regulated via internal signaling pathways. In addition, conductive arteries are subject to peripheral nervous system oversight via well-defined neurohumoral pathways. In this section, we will discuss alterations in intrinsic signaling pathways related to VSMC function, as well as changes in the peripheral nervous system regulation of conductive artery function, during hypertension.

As previously mentioned, the RAAS is a major therapeutic target for reducing blood pressure and reversing vascular remodeling in hypertension. This is partially because VSMCs in conductive arteries have altered reactivity to RAAS signaling components during hypertension. For example, cultured aortic VSMCs from SHRs have enhanced activation of MAP kinase in response to Ang II, compared to normotensive WKYs [74]. Treatment of cultured VSMCs from the pulmonary artery of hypertensive patients with Ang II also induces cell proliferation via the Ang II Type 1 receptor (AT_1R) [75]. Several studies have shown that the interaction of aldosterone with the VSMC-mineralocorticoid receptor (MR) promotes pathways that contribute to development of large artery stiffness [76–79]. In patients with primary hyperaldosteronism, arterial wall stiffness is increased as measured by pulse wave velocity [78] and ultrasonography [79]. Supporting this, Galmiche et al. show that VSMC-MR knockout mice are protected against changes in arterial stiffness following aldosterone/salt challenge, by preventing the induction of changes in extracellular matrix proteins such as fibronectin and α5-integrin [76].

The handling of intra and extracellular calcium (Ca^{2+}) is an important mechanism by which VSMCs control arterial lumen diameter and blood flow. A clear dysfunction in Ca^{2+} handling during hypertension was established as early as the 1960s and 70s [80,81]. Femoral artery strips collected from SHRs, renal hypertensive, and deoxycorticosterone acetate (DCA) hypertensive rats required higher concentrations of Ca^{2+} to produce a maximal vasoconstriction in response to KCl than normotensive rats [81]. Since then, subsequent studies have firmly established that VSMCs in hypertensive patients have enhanced reactivity to Ca^{2+} compared to cells from normotensive human and animals [82–87]. Interestingly, alterations in multiple intracellular signaling components are implicated in Ca^{2+} sensitivity in hypertensive VSMCs. These include increased expression and sensitivity of IP_3 receptors [88,89], altered Rho-kinase signaling [90], enhanced phospholipase C activity [85], abnormal expression and function of plasma membrane Ca^{2+} [91,92] and K+ channels [93], and hypoxia [94].

Sympathetic nerve activity is long known to play a vital role in the regulation of cardiovascular function. Unsurprisingly, increased sympathetic nerve activity is associated with hypertension in animal models with increased blood pressure [95] and cellular changes in VSMCs response to neurohumoral factors have been reported. Isolated thoracic aorta from SHRs have an increased endothelium-independent contractile response to noradrenaline and phenylephrine, compared to normotensive controls [96]. Further, cultured aortic VSMCs and

intact rat aorta are sensitive to noradrenergic-induced VSMC proliferation [97]. Noradrenergic-induced cell proliferation, in conjunction with increased sympathetic nerve activity in hypertension, suggests that altered SNS activity may directly impact VSMCs structure and reactivity in hypertension.

Beyond the signaling pathways discussed above, transgenic mouse models with VSMC specific targeting have been used to identify additional signaling molecules and pathways that are critical to the proper regulation of blood pressure. In **Table 2**, we have summarized seminal studies describing gene targets that can increase or decrease blood pressure when specifically deleted from smooth muscle cells. Included among them are G_{12}-G_{13} and their primary effector leukemia associated Rho-GEF (LARG) [98], the antioxidant/antiaging protein SIRT1 [99], PPAR-γ [100,101] and the mineralocorticoid receptor (MR) [102].

c. Inflammatory Pathways

Vascular inflammation is a key feature in the development of cardiovascular diseases, including hypertension, and the infiltration of inflammatory cells such as T cells and macrophages into large conductive arteries is a hallmark feature of hypertension in animal models [103,104]. A series of studies using genetic knockout animals and the adoptive transfer of immune cells provide compelling evidence for a role for vascular inflammation in the development of hypertension. For example, the injection of immunosuppressive regulatory T cells (T_{regs}) [105] or T and B cell deficiency ($Rag^{-/-}$) [106] are both protective against Ang II induced hypertension, while the adoptive transfer of T cells into $Rag^{-/-}$ mice is sufficient to produce a full hypertensive response to Ang II [106]. However, a more recent study reported that this Ang II resistance in $Rag^{-/-}$ mice has been lost, and is independent of T cells, suggesting genetic drift can influence the effect of vascular inflammation in hypertension [107]. The signaling of individual pro-inflammatory cytokines is also implicated in hypertension pathology where increased concentrations of the pro-inflammatory cytokine IL-17 is observed in hypertensive mice and in smooth muscle cells from hypertensive patients, and $IL\text{-}17^{-/-}$ mice are resistant to sustained hypertension following Ang II infusion [108]. Treatment with small hairpin RNA against interleukin-6 (IL-6) is protective against vascular inflammation, vascular remodeling and increased blood pressure in a model of cold-induced hypertension [109].

Atherosclerosis is another cardiovascular disease that is closely associated with hypertension incidence and severity [110], and is characterized by loss of vessel wall elasticity and plaque formation in the intima. Inflammatory signaling and inflammation-induced vascular remodeling are thought to be key players in the pathology of atherosclerosis. As in hypertension, T_{reg} cells play a key role in disease progression as the depletion of T_{reg} cells promotes the development of atherosclerosis [111–113]. Important roles have also been identified for the cytokines IL-6 and IL-17 in the progression of atherosclerotic disease. IL-17/IL-17A/IL-17A receptor depletion in animals model of atherosclerosis decreased the systemic inflammation during disease progression but did not significantly decrease aortic plaque burden [114,115]. Differential findings exist for the role of IL-6 in atherosclerosis. Animals genetically lacking IL-6 in combination with ApoE deficient ($IL\text{-}6^{-/-}ApoE^{-/-}$[116] and $IL\text{-}6^{-/-}AprE^{+/-}$[117]) had enhanced atherosclerotic lesion formation in a high fat and

pathogen induced atheroscelorsis respectively [116,117]. Conversely, weekly IL-6 injections increased lesion size in both wild-type and *ApoE*$^{-/-}$ animals on high fat diet [118]. Taken together, these data from both human and animal models impressively demonstrate the multiple functions inflammatory signaling molecules can play in large artery remodeling in both hypertension and atherosclerosis, perhaps playing a role in parallel in disease development.

IV. Resistance Artery Remodeling

Small diameter (<250 μm) arteries in the peripheral vasculature are traditionally responsible for the regulation of blood pressure by controlling peripheral vascular resistance and blood flow. Structural and functional changes in these resistance arteries are a classic measure of cardiovascular pathology and disease progression. In this section, we discuss an extensive body of literature focused on resistance arterial VSMC changes during hypertension.

a. Structural and Functional of Resistance Arteries and VSMCs in Hypertension

Structural remodeling in the small arteries of the resistance vasculature is a hallmark of hypertension pathophysiology and is associated with increased risks of cardiovascular events [15]. In essential (idiopathic) hypertension, resistance arteries undergo inward eutrophic remodeling, which significantly increases the media/lumen ratio without a change in the media cross-sectional area [3,14,15,30,119–121]. In studies where resistance arteries were isolated from the subcutaneous fat of essential hypertensive patients, the rearrangement of VSMCs and extracellular matrix observed were characteristic of eutrophic remodeling, rather than VSMC hypertrophy and hyperplasia [15]. Alternatively, resistance arteries can undergo differential patterns of structural remodeling, depending on causative or modifying factors for hypertension. In hypertensive patients with diabetes mellitus or patients diagnosed with pulmonary hypertension, resistance arteries (from the systemic and pulmonary circulations respectively) undergo inward hypertrophic remodeling, which results in an increased media cross-sectional area and media/lumen ratio, typically due to VSMC hypertrophy or hyperplasia [119,121,122].

Hypertension-dependent structural changes in VSMCs are thought to have short-term protective, but long-term pathological, effects. For example, initial structural changes in forearm small arteries increased vascular resistance at maximal vasodilation in response to increased blood flow, so as to normalize wall stress [3]. On the other hand, long-term increases in vascular resistance lead to reductions in maximal dilation over time (such as reduced coronary flow reserve), reduced vascular perfusion, and impaired capillary rarefaction [3,15,123–125]. Furthermore, increased collagen levels did not correlate with increased stiffness during early stages of hypertension; yet, in later stages the vascular wall continues to compensate for elevated blood pressures by depositing more collagen and increasing wall stiffness [125]. These studies demonstrate that the temporal effects of vessel adaptations can differentially influence physiological outcomes.

Although intrinsic changes to the arterial wall influence blood pressure adaptation, circumferential wall stress (i.e. pressure forces) reciprocally impact vessel structure [126]. In vein graft experiments, exposure to high arterial pressure induced hypertrophic remodeling

to a similar level as those observed in secondary forms of hypertension [127–129]. This suggests a pressure dependent, but vessel independent contribution. These conclusions were reached when pressure reduction using antihypertensive drugs, such as β-blockers, failed to normalize artery structure or reduce peripheral resistance in humans [119,130]. These data suggest two things: 1. targeted reversal of resistance artery remodeling by simply lowering blood pressure in essential hypertension may fail due to pressure independent mechanisms, and 2. different etiologies of hypertension, either primary or secondary, should be treated differently as the main drivers for structural vessel changes may come from different mechanisms [131]. Importantly, the latter is a strategy that is already employed clinically.

Hypertensive patients, and animal models of essential hypertension, exhibit increased myogenic reactivity (the inherent constriction/dilation responses of VSMCs to changes in luminal pressure) which may contribute to inward remodeling in hypertension [3,132–134]. In line with this, current evidence exploring the role of ion channels in myogenic tone points to an important new role for their regulation of myogenic constriction in the development of hypertension [135–138]. Finally, the role of apoptosis in small artery remodeling is an emerging field of research where one hypothesis suggests that inward eutrophic remodeling is due to simultaneous inward growth of VSMC layers and cell death in the media periphery [139–141]. However, Dickhout et al. report decreased levels of apoptotic markers in their study of young prehypertensive SHRs [142]. These divergent findings demonstrate a need for further work to conclusively determine a role for apoptosis of VSMC in resistance artery remodeling.

Together, the structural and functional changes described above highlight the complex properties underlying vascular remodeling in the resistance vasculature in hypertension.

b. Signaling and Neurohumoral Pathways.

The cellular changes underlying differential VSMC remodeling patterns in hypertension (eutrophic or hypertrophic) have also been attributed to the differential activation of signaling pathways important for vasoconstriction, cellular migration, VSMC hypertrophy, apoptosis, and inflammation [3,15,143]. Imbalances between vasoconstrictive and vasodilatory intracellular signaling, or altered sensitivity to these signaling molecules, may contribute to the development and/or progression of hypertension. Here, we examine a number of key signaling pathways that are altered in resistance arteries during hypertension.

Altered responses to neurohumoral vasopressors have been well documented in studies of hypertensive humans who show some degree of vascular remodeling. It is unclear whether VSMCs become more sensitive to vasoconstrictor molecules such as norepinephrine, or if vasoconstriction pathways remain activated due to increased sympathetic nerve activity, as both events have been observed in hypertensive humans [144–150]. In humans, counter-regulatory vasodilatory events have also been tested using endothelium-independent agents, such as sodium nitroprusside (SNP), and were not different between control and hypertensive subjects [149,151]. Conversely, endothelial-dependent vasodilation by acetylcholine was impaired in hypertensive patients and animal models, but the amount of experimental variability in these observations may be a red-herring in interpreting the outcome of studies of VSMC function in hypertension [149,152,153]. Nonetheless, it remains

critically important to test the complex signaling pathways used to balance vasoconstriction and counteracting vasodilatory forces, which, under pathological conditions cause hyperconstriction, increased vascular resistance, and high blood pressure.

The RAAS plays a key angioadaptive role during hypertension [154], in part through the binding of Ang II to the AT_1R which results in vasoconstriction and the activation of cellular growth pathways mediated by tyrosine kinases [155]. In particular, c-Src acts as both a regulator of vasoconstriction and growth through transactivation of receptor tyrosine kinases [155–158], acting through mitogen activated protein kinases (MAPKs) which influence cell growth, apoptosis, and cell survival [154]. Treatment with antihypertensive drugs targeting the RAAS reverse pathologic VSMC phenotypes in resistance arteries, indicating that alterations in this key pathway can influence structural remodeling of VSMCs in resistance arteries [42,44,46,145,159,160].

Other signaling mediators influencing VSMCs during hypertension include aldosterone, endothelin 1 (ET-1), and NADPH which regulate hypertrophy, fibrosis, and inflammation of small arteries. Aldosterone infusion increases expression of ET-1, which directly induces hypertrophic remodeling of VSMCs [161–163]. These effects can be ameliorated by mineralocorticoid receptor antagonism [151,164]. Moreover, both aldosterone and Ang II induce NADPH oxidase activity in VSMCs, which causes ROS generation and concomitant activation of MAPKs, redox sensitive transcription factors (i.e. AP-1), inflammatory mediators, and matrix remodeling enzymes [125,165,166]. Because aldosterone is synthesized and secreted following Ang II stimulation of adrenal cortical cells via AT_1 receptor, imbalances in RAAS activation may have compounded negative effects as both aldosterone and Ang II increase blood pressure systemically, while also having direct effects on the vascular wall.

Sympathetic nerve innervation and purinergic signaling also have profound effects on VSMCs during hypertension. Neural-derived purinergic stimuli (ATP) regulate the beneficial short-term control of vascular tone, but may also drive long-term negative changes during small artery remodeling [167–169]. Clinical cases of hypertension typically present with enhanced sympathetic nerve activation [170], which has been shown to result in hypertrophic VSMC remodeling [169,171,172]. Moreover, local extracellular release of ATP and other purine nucleotides, which are derived from sympathetic nerve terminals, local immune cells, and adjacent VSMCs, can exert direct pathogenic changes on VSMCs [173–175] despite their normal functionality of coordinating minute-to-minute vasoconstriction events. In one study, sympathetic-driven vasoconstriction was increased in SHR, which was dependent upon ATP activation of purinergic receptors [176]. Further, mesenteric beds of SHR show potentiated responses to ATP compared to controls [177]. These observations demonstrate that hyper-stimulation of resistance arteries, due to increased sympathetic drive and purinergic signaling, directly promotes the progression of VSMCs remodeling changes observed in hypertension.

In contrast to the direct constrictive effects of neural-purinergic stimuli on vasoconstriction, ATP can also act as a mitogenic signal, stimulating both VSMC growth and proliferation in hypertensive models [178,179]. The effects of ATP and its metabolic breakdown products are

mediated by the direct binding of ligand to a diverse class of ionotropic and metabotropic cell surface receptors (e.g. G-protein coupled P2Y or cation channel P2X) [160]. Alterations in purinergic receptor subtypes, expression pattern, or abundance might also influence VSMC phenotypes during hypertension. In one study, proliferative VSMCs were correlated with increased expression of P2Y receptors, while differentiated contractile VSMCs primarily express $P2X_1$ receptors [180]. Together, this evidence establishes a novel neural-purinergic signaling nexus, which acts synergistically with other angioadaptive cellular pathways.

Phosphodiesterase 1 (PDE1) is a calcium/calmodulin dependent enzyme that hydrolyzes cyclic nucleotides such as cGMP and cAMP when intracellular Ca^{2+} is high [181]. These cyclic nucleotides play important secondary messenger roles in the vasodilatory effect of nitric oxide (NO) and impairment of their actions enables VSMC constriction. PDE1A is upregulated in VSMCs following stimulation with Ang II and transforming growth factor beta-1 (TGF-β1) [181,182], and is increased in animal models of pulmonary hypertension [183]. Treatment with PDE1 specific inhibitors improved endpoint measurements in animal models of cardiovascular disease [181–185]. Similarly, inhibition of PDE1A halted the progression of pulmonary arterial hypertension and reversed pulmonary artery remodeling and right heart hypertrophy [183].

Increased blood pressure in essential hypertension is often associated with obesity and increased whole body adiposity. Adipose tissue has gained recognition as an important endocrine organ, and adipokines (the primary signaling molecules released from adipocytes) have varying and important effects on VSMC function. Adiponectin is protective in the vasculature in part due to its anti-proliferative and anti-migratory effects on VSMCs [186]. In fact, hypoadiponectinemia (reduced circulating levels of adiponectin) is considered a risk factor for the development of hypertension and its consequent vascular remodeling [187]. Conversely, adipokines such as resistin [188,189], or treatment of VSMCs with adipocyte-conditioned media [190,191], promote the migration and/or proliferation of VSMCs in both human and animal models. Through the release of adipokines, and their direct signaling on VSMCs, the perivascular adipose tissue that is in direct contact with the vasculature can have significant effects on vascular remodeling during hypertension.

Here, we provided a comprehensive, but not exhaustive, examination of key pathways whose signaling is dysregulated in resistance arteries during hypertension (**Figure 1**).

V. Genetic Factors Underlying the Hypertensive Phenotype in VSMC

Adaptive changes in VSMCs resulting from high blood pressure are often underwritten by genetic factors [3,192,193]. The heritability of blood pressure phenotypes and the regulation of blood pressure by polygenic and monogenic traits reveal a strong influence of genetics on hypertension pathophysiology [194–197]. For example, offspring from hypertensive patients already have increased renal vascular resistance at an early age [14]. These changes influence the long-term maintenance of blood flow and cardiovascular homeostasis by VSMCs.

Genome wide association studies (GWAS) have become increasingly important in discerning candidate genes involved in modulating VSMC function during hypertension.

Within large hypertensive cohorts, GWAS have identified *ATP2B1,* a vascular calcium/calmodulin-dependent membrane ATPase, as a gene of interest in hypertension [198–202]. *Atp2b1* mRNA expression levels were elevated in aortic VSMCs of SHRs compared to the normotensive WKYs, suggesting that changes in *Atp2b* influence cellular calcium homeostasis [203]. Similarly, the *CSK* gene reached genome wide significance in hypertensive cohorts [199–202]. *CSK* encodes a cytoplasmic tyrosine kinase, which is directly involved in Ang II-dependent VSMC proliferation [204]. In another study, gene variants near the *GNAS-EDN3* alleles also reached genome wide significance in hypertensive cohorts [201,202]. *GNAS-EDN3* encodes the G-alpha subunit of G-protein receptor complexes and the vasoactive peptide endothelin 3, two proteins involved in vasoconstriction signaling pathways. Risk association scores for essential hypertension was found to be associated with SNPs in *TRIC-A*, a gene that encodes an intracellular monovalent cation channel involved in myogenic tone regulation [136].

Another gene family found to be involved in hypertension and playing a role in the VSMC are the phosphodiesterases (*PDEs*), discussed earlier in this review. In an Ang II rat model of hypertension, higher expression levels of PDE1A were correlated with decreased cyclic guanosine monophosphate homeostasis, which is associated with vasodilatory signaling pathways [181]. Further, *PDE1A* single nucleotide polymorphisms in humans were significantly associated with increased diastolic blood pressure and carotid intima-media thickening in genome-wide associated studies [184]. Recently, single gene variants in the *PDE3A* were identified as the primary cause of a rare autosomal dominant form of hypertension [205]. These gene variants encoded missense mutations in *PDE3A* resulting in gain of function mutations in protein kinase A/cyclic AMP signaling, increased cAMP-hydrolytic activity, and enhanced VSMC proliferation [206].

Non-coding genetic alterations (e.g. microRNAs) have also been shown to modulate VSMC function in hypertension. Mice lacking miR-143 and miR-145 exhibit reduced blood pressure, reduced VSMC migration, disorganized VSMC actin stress fibers, and reduced vascular tone [207]. In SHRs, up regulation of miR-130a was detected in remodeled superior mesenteric arteries and inhibition of miR-130a reduced VSMC proliferation *in vitro* [208]. Additionally, miR-133 expression was found to repress VSMC differentiation and proliferation by silencing the transcription factor SP-1 [209]. Lastly, the down regulation of Krüppel-like factor 4 (KLF4) by miR-146a was found to promote VSMC proliferation and neointimal hyperplasia in VSMCs [210]. These experiments focus on effects in large arteries and require validation in VSMCs of resistance arteries. Taken together, these studies highlight the importance of genetic factors in regulating VSMC remodeling and vascular homeostasis in hypertension [211].

VI. Look to the Future

Hypertension is a strong and independent predictor of risk and future incidence of cardiovascular events (e.g. stroke, myocardial infarction, end-organ damage) [15]. In particular, resistant hypertension pathologies are a persistent and growing problem, with an increasing number of patients unable to achieve adequate control their blood pressure despite taking three or more anti-hypertensive drugs, [212,213]. Thus, finding ways to prevent

hypertension progression by reversing vascular remodeling associated with hypertension is vital for global health. As discussed in this review, distinct hypertension etiologies cause differential vascular remodeling which depend on the type of pathology/origin, disease progression, and vessel type/size. An important goal for future research in vascular remodeling would be to find ways to more accurately characterize different classes of vascular remodeling phenotypes as defined above. Current research primarily focuses on remodeling within the resistance vasculature, since changes to resistance arteries are highly predictive of disease progression. However, the field would benefit from more detailed research on hypertension-dependent remodeling in the larger conductive arteries since maladaptive changes in conductive arteries (changes in vessel stiffness and increased pulse wave pressure/velocity) influence resistance vessels. Briefly alluded to earlier in this review, changes in medium-sized muscular arteries (skeletal and cardiac) in hypertension are also vastly understudied and may present a novel area for research in vascular remodeling in hypertension. Lastly, sex differences in regards to hypertension are becoming more apparent (as reviewed in [214]); it is likely that with further work, our view of SMC biology may change as research progresses in this area.

Although beyond the scope of this review, VSMC remodeling may be therapeutically targeted through improved endothelial cell function. Endothelial cells and VSMCs closely interact through direct cell-to-cell contact, and via soluble signaling molecules. Endothelial-dependent vasodilation is significantly impaired in hypertension and may contribute to VSMC remodeling. Thus, improvement of hypertensive-dependent endothelial dysfunction may in turn have beneficial effects on the VSMC. Vascular remodeling in hypertension involves changes in a wide host of signaling molecules and pathways (see **Table 2**). Thus, researchers have opportunities to target different pathways to reverse pathological vascular remodeling. The most effective therapeutic strategy likely requires a multivariable approach.

Lastly, reducing aberrant inflammatory and neurohumoral pathways to homeostatic levels in hypertension may also prove effective in reversing pathological VSMC remodeling, while simultaneously improving overall disease pathology. For example, therapeutic alterations in purinergic signaling would improve both inflammatory and neurohumoral pathways [148]. One interesting and potential novel target of the neural-purinergic axis in the peripheral vasculature is the ATP release channel Pannexin1 (Panx1). Panx1 has been shown to regulate small arterial VSMC constriction responses to NE and α1-adrenergic receptor stimulation with the NE mimetic phenylephrine. Recent evidence shows that inhibition of Panx1, either pharmacologically or genetically, significantly blunts adrenergic induced vasoconstriction and significantly reduces blood pressure in mice [175,215]. Another potential target is the gene collectrin (*Tmem27*), an amino acid transport regulator. Deletion of collectrin results in hypertension, augmented salt-sensitivity, and vascular remodeling [216]. Further evaluation of these and other targets may prove beneficial for treating essential hypertension and progression into resistant hypertension made worse by pathological vascular remodeling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

Ang II	Angiotensin II
ACE	Angiotensin converting enzyme
ACE-I	ACE inhibitor
ARB	Angiotensin receptor blocker/antagonist
CCB	Calcium channel blocker
ECM	Extracellular matrix
HT	Hypertension
RAAS	renin-angiotensin-aldosterone system
SHR	Spontaneously hypertensive rat
Panx	Pannexin
VSMCs	Vascular smooth muscle cells
WKY	Wistar Kyoto rat

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Highlights

- Structural and functional changes in large (conductive) and small (resistance) arteries accompany hypertension.
- There are important clinical implications of smooth muscle remodeling that are different in conductive and resistance arteries.
- This review discusses current and future research in smooth muscle remodeling, and how it could be a target for treatment of hypertension.

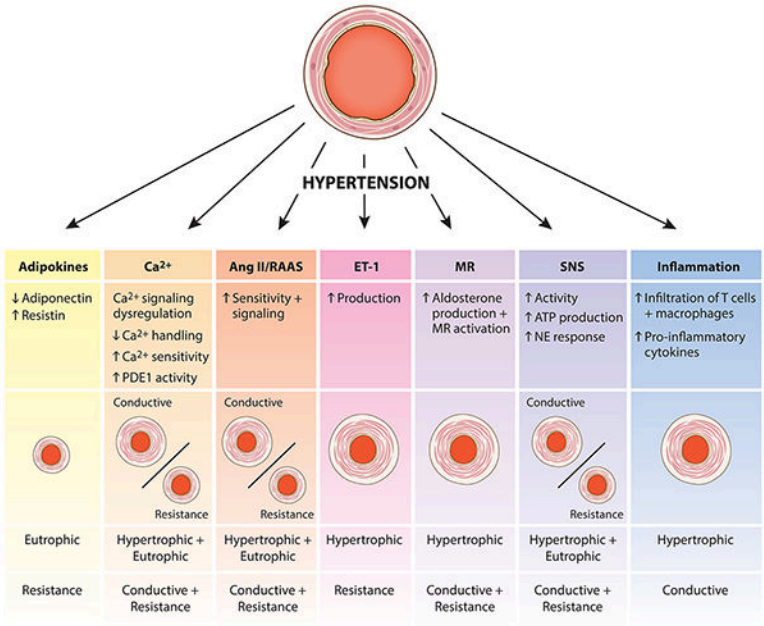

Figure 1:

Differential physiological effects on smooth muscle based arterial remodeling (conductive and resistance).

Table 1:

Basic properties of clinical studies referenced in manuscript

Age	Sex	Race	Cohort Size	Type of Hypertension	Reference
≥65	Female & Male	88.4% White, 11.6% Black	4476	65 years of age or older without known clinical cardiovascular disease; 40% with essential hypertension	11
54 (SD 5.8)	56.6% Female, 43.4% Male	74.5% White, 25.5% Black	12576	Normotensives from Atherosclerosis Risk in Communities (ARIC) Cohort	12
40–66	35% Female, 65% Male	Patients: 81% White, 19% Black; Controls: 74% White, 26% Black	86 (43 hypertensive, 43 normotensive)	Asymptomatic Hypertension	16
30–59 & 57–80	Undisclosed	Undisclosed	Undisclosed	Isolated Systolic Hypertension	17
40–75	55.9% Female, 44.1 Male	78% White, 22% Nonwhite	2845	Essential Hypertension	18
18–60+	51.5% Female, 48.5% Male	72.2% Non-Hispanic White, 10.9% Non-Hispanic Black, 7.2% Mexican American, 9.7% Other	14653	Essential Hypertension	21
≥70	74.7% Female, 25.3% Male	Japanese	164	Essential Hypertension	23
52±12.7	47.2% Female, 52.8% Male	Chinese	644	Mild Hypertension	24
74±9	56% Female, 44% Male	Japanese	211 (161 Hypertensive, 50 normotensive)	Essential Hypertension	25
42–74	38.2% Female, 61.8% Male	Undisclosed	424 (314 Hypertensive, 110 Normotensive)	Essential Hypertension	26
40–99	67% Female, 33% Male	Undisclosed	212	Isolated Systolic Hypertension	28
20–81	42.4% Female, 57.6% Male	Undisclosed	151 (128 Hypertensive, 23 Normotensive)	Essential Hypertension, Renovascular Hypertension, Primary Aldosteronism, Pheochromocytoma, NIDDM	29
Mean 51±4	27% Female, 73% Male	Undisclosed	30 (15 Hypertensive, 15 Normotensive)	Essential Hypertension	30
25–60	33% Female, 67% Male	Undisclosed	21 (14 Hypertensive, 7 Normotensive)	Essential Hypertension	31
18–65	100% Male	Undisclosed	50 (21 Hypertensive, 29 Normotensive)	Essential Hypertension	32
46–72	35.6% Female, 64.4% Male	Undisclosed	500	Essential Hypertension	33
25–70	40% Female, 60% Male	Undisclosed	66	Mild Essential Hypertension	34
35–65	32% Female, 68% Male	Undisclosed	50 (25 Hypertensive, 25 Normotensive)	Essential Hypertension	38
60–80	68.8% Female, 31.2% Male	Undisclosed	77	Essential Hypertension	40

Age	Sex	Race	Cohort Size	Type of Hypertension	Reference
27–72	Undisclosed	White	12	Essential Hypertension	[41]
26–67	27% Female, 73% Male	Undisclosed	55	Essential Hypertension	[42]
18–75	21% Female, 79% Male	White	114	Essential Hypertension	[43]
25–50	100% Male	Undisclosed	29 (17 Hypertensive, 12 Normotensive)	Mild Essential Hypertension	[44,45]
30–65	43% Female, 57% Male	Undisclosed	28 (19 Hypertensive, 9 Normotensive)	Mild Essential Hypertension	[46]
38–65	25% Female, 75% Male	Undisclosed	11	Essential Hypertension	[47]
Undisclosed	Undisclosed	Undisclosed	21 (10 Hypertensive, 11 Normotensive)	Essential Hypertension	[52]

Table 2:

Smooth muscle specific targeting of genes that regulate blood pressure in mice

Smooth muscle target protein	Cre or Promoter	Knockout or Overexpression	Hypertension or Hypotension	Resistance or Conductive arteries analyzed	Reference
Ang II Type 1A receptors	i) SM22-Cre ii) KISM22-Cre	i) KO ii) KO	i) No change ii) Hypotension	Conductive and resistance – aorta and mesenteric arteries	217,218
Arhgef1	SMMHC-CreER^{T2}	KO	Attenuates Ang II hypertension	Conductive – aorta	219
Atp2b1	SM22-Cre	KO	Hypertension	Conductive – femoral artery	220
Connexin 43	SMMHC-CreER^{T2}	KO	No Change	In vivo blood pressure only; carotid wire injury	221
COX2	SM22-Cre	KO	No change	Conductive – aorta	222
Dicer	SMMHC-CreER^{T2}	KO	Hypotension	Resistance – saphenous and mesenteric arteries	223
EGFR	SMMHC-CreER^{T2}	KO	Hypotension	Conductive – aorta	224
EPHB4	SMMHC-Cre	KO	Hypotension	Resistance – mesenteric arteries	225
Filamin A	SMMHC-CreER^{T2}	KO	Hypotension	Resistance arteries – caudal artery	226,137
G_{12}-G_{13}-LARG	SMMHC-CreER^{T2}	KO	Attenuates salt-induced hypertension	Conductive – aorta	98
Guanylyl cyclase-A	SM22-Cre	KO	No Change	Conductive and resistance – aorta, femoral, pulmonary, and renal arteries	227
NO-sensitive guanylyl cyclase	SMMHC-CreER^{T2}	KO	Hypertension	Conductive - aorta	228
IP_3R1, IP_3R2, IP_3R3	SMMHC-CreER^{T2}	KO (all 3 together)	No Change in Basal BP Attenuates Ang II hypertension	Conductive and resistance - aorta and mesenteric arteries	89
L-type Ca^{2+} channel $Ca_v1.2$	SM22-CreER^{T2}	KO	Hypotension	Conductive and resistance – aorta and tibialis	229
Mineralocorticoid receptor	SMactin-CreER^{T2}	KO	Hypotension	Resistance – mesenteric arteries	102
Myosin Light Chain Kinase (MLCK)	SM22-Cre	KO	Hypotension	Resistance – mesenteric arteries	230,231
Myosin phosphatase target subunit 1 (MYPT1)	SMα-actin promoter	KO	Hypertension	Resistance – mesenteric arteries	232
Na^+/Ca^{2+} exchanger	SMMHC-Cre	KO	Hypotension	Resistance – mesenteric arteries	233
Na^+-K^+-ATPase	SMα-actin promoter	OE	Hypotension	Conductive – aorta	234
Ndst1	SM22α-Cre	KO	No change	Conductive and resistance – aorta and thoracodorsal arteries	235
Nox1	SMMHC-Cre	OE	Potentiates Ang II hypertension	Conductive – aorta	236

Smooth muscle target protein	Cre or Promoter	Knockout or Overexpression	Hypertension or Hypotension	Resistance or Conductive arteries analyzed	Reference
Pannexin 1	SMMHC-CreER^{T2}	KO	Hypotension	Resistance – thoracodorsal artery	175
Piezo1	SM22α-Cre	KO	No change	Resistance arteries – caudal and rostral cerebellar artery	137
PPAR-γ	i) SM22-Cre ii) SMMHC promoter	i) KO ii) OE of inactive mutation	i) Hypotension ii) Hypertension	Conductive and resistance - aorta and cerebral	100,101
Rac1	SMMHC-CreER^{T2}	KO	Hypertension	Conductive and resistance – aorta and mesenteric arteries	237,238
SIRT1	SM22α promoter	OE	Attenuates hypertension	Conductive – aorta	99