

## Oxidative Stress, Inflammation, and Vascular Aging in Hypertension

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Age-related decline in function is a physiological phenomenon occurring in all organ systems. However, acceleration and early occurrence of this process are observed in cardiovascular pathologies, including hypertension.<sup>1,2</sup> In the vascular system, this is characterized by progressive pathological remodeling with stiffening,<sup>3</sup> typically associated with extracellular matrix (ECM) alterations in collagen and elastin.<sup>4</sup> This is, in part, dependent on cellular senescence and growth arrest.<sup>5</sup> Although hypertension and atherosclerosis are associated with accumulation of cellular senescence markers in the vascular wall, these conditions are often associated with vascular dysfunction rather than simple loss of proliferative capacity.<sup>6</sup> For example, risk factors for cardiovascular disease, such as hypertension, smoking, hyperlipidaemia, or diabetes mellitus are associated with accelerated decline of vascular function.<sup>2</sup> This is why vascular age determination has been introduced in key clinical guidelines for cardiovascular prevention, to indicate to the patient how their lifestyle contributes to the acceleration of vascular function deterioration.<sup>7</sup>

Oxidative stress and inflammation, key mechanisms of endothelial dysfunction and arterial damage, link these risk factors to vascular disease, arterial stiffness, and aging. These underlie macro- and microangiopathy, renal dysfunction, cardiac ischemia, and cognitive decline (Figure). Several novel pathways regulating these mechanisms of accelerated vascular aging have been elucidated in recent issues of *Hypertension* and are further discussed in the present Best Papers in *Hypertension* review.

### Vascular Aging and Remodeling in Hypertension

Hypertension is inherently associated with accelerated vascular aging,<sup>8</sup> and, therefore, it sheds light on vascular remodeling occurring with age.<sup>1</sup> Early vascular aging—a term introduced in the context of premature development of vascular stiffness and remodeling by Nilsson et al<sup>2,9,10</sup>—is a key feature of hypertension.<sup>1</sup> Oxidative and inflammatory mechanisms with reactive oxygen species (ROS) overproduction have been implicated in this process as demonstrated by clinical studies, such as MOBILIZE (maintenance of balance, independent living, intellect, and zest in the elderly), which demonstrated

in ≈700 participants—an association between plasma levels of oxidative stress-regulated inflammatory marker—soluble vascular cell adhesion molecule-1 and mobility impairment.<sup>11</sup> This may provide a valuable biomarker and indicates that the interface of oxidation and inflammation might translate into vital clinical outcomes.<sup>12</sup>

Key features of hypertension that are essential in vascular aging that contribute to vascular stiffening are fibrosis, perivascular inflammation, and vascular calcification.<sup>13</sup> Hypertension increases both vascular smooth muscle cell (VSMC) stiffness and VSMC adhesion, which are further augmented with aging.<sup>14</sup> Histological measures of aortic collagen and elastin are predominantly changed by aging rather than by hypertension,<sup>14</sup> whereas blood pressure (BP) elevation is linked to a reversible activation of procontractile signaling in VSMCs.<sup>15</sup> Hypertensive aged mice show accelerated development of endothelial dysfunction, increased vascular ROS, and elevated endothelial ET-1 (endothelin-1) expression. These mechanisms are mediated, in part, by the induction of smooth muscle-specific Galpha12/Galalpha13, Galphaq/Galalpha11.<sup>15</sup>

Vascular calcification, regulated by bone morphogenetic proteins (BMP) and other proteins, is an important hallmark of accelerated vascular aging and has been observed in isolated systolic hypertension in older patients. BMP signaling is, therefore, central to molecular processes underlying vascular damage. For example, BMP6 induces osteogenic and chondrogenic transcription factors Runx2 and Msx2, in a redox-dependent fashion.<sup>16</sup> It also promotes recruitment of inflammatory cells into the vascular wall to promote vascular disease.<sup>17</sup> In contrast, BMP7 attenuates left ventricular remodeling under pressure overload.<sup>18</sup> The importance of BMP in vascular and cardiac damage in hypertension is further supported by studies demonstrating that BMP inhibition attenuates vascular inflammation and calcification.<sup>17</sup>

Vascular stiffening occurring with age is a good example of the interplay between oxidative stress and inflammation.<sup>19,20</sup> Both of these processes increase with aging. An increase in inflammatory cytokines and chemokines leads to infiltration of T cells and macrophages, which contribute to tissue injury.<sup>21</sup> Cytokines, such as interferon- $\gamma$ , interleukin 17, or tumor necrosis factor- $\alpha$ , increase oxidative stress in VSMCs

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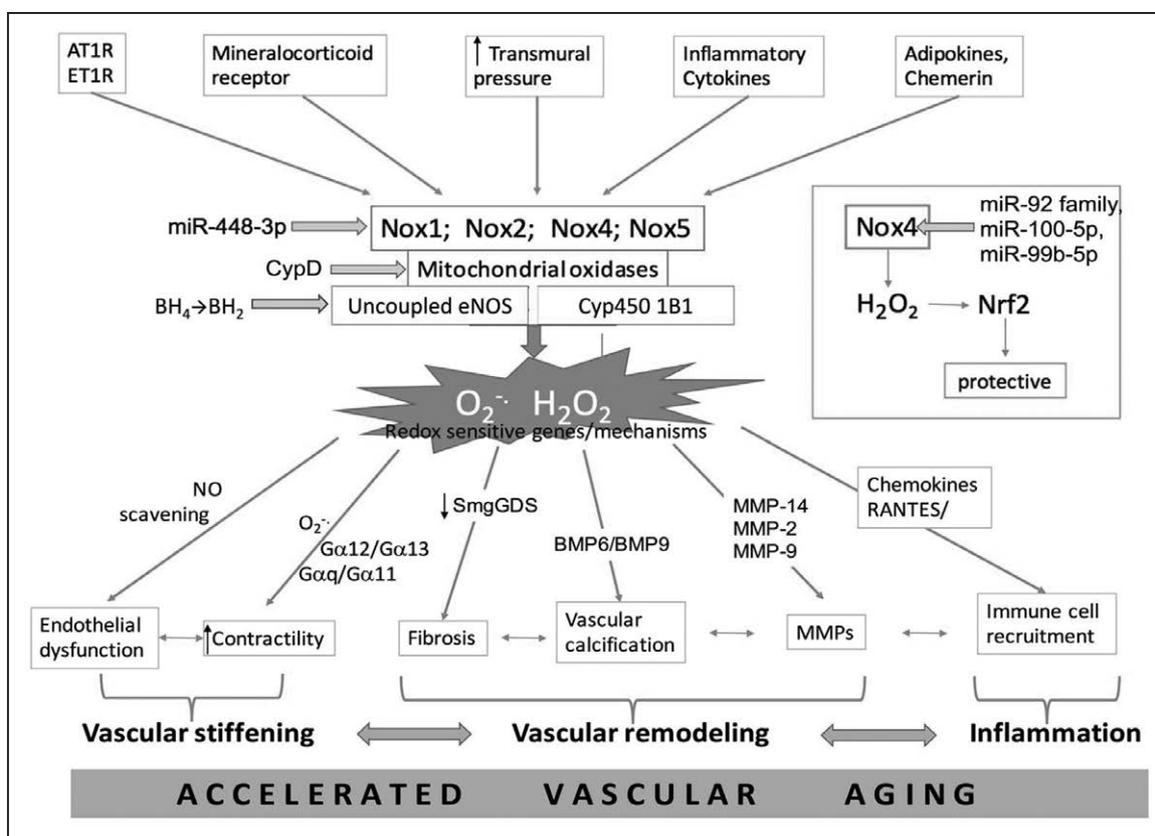
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**Figure.** Central role of oxidative stress in accelerated vascular aging in hypertension. AT1R indicates angiotensin II receptor type 1; BH<sub>2</sub>, dihydrobiopterin; BH<sub>4</sub>, tetrahydrobiopterin; BMP, bone morphogenic protein; CypD, cyclophilin D; eNOS, endothelial NO synthase; ET1R, endothelin 1 receptor; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; MMP, matrix metalloproteinase; Nox, NADPH oxidase; O<sub>2</sub><sup>•-</sup>, superoxide anion; RANTES, regulated on activation, normal T cell expressed and secreted chemokine; and SmgGDS, GTP-binding protein dissociation stimulator.

and endothelium.<sup>22</sup> Perivascular fibrosis is greatly dependent on immune cells because it is prevented in RAG1<sup>-/-</sup> mice lacking mature T and B cells.<sup>21</sup> This process, although inflammatory in its nature, seems to be initiated by oxidative stress. In line with this, therapies which are known to reduce oxidative stress, such as mineralocorticoid antagonists, or angiotensin-converting enzyme inhibitors, are known to improve vascular stiffness acceleration.<sup>23</sup> One of the key novel mechanisms linking oxidative stress to fibrosis involves small GTP-binding protein dissociation stimulator. Its upregulation by statins results in Rac1 degradation and reduced oxidative stress<sup>24</sup> and may reduce cardiac and possibly vascular fibrosis.

Accelerated aging in hypertension is observed in both the micro- and macrocirculation, with important cross talk between large vessels and microvasculature.<sup>25</sup> Increased BP, attributed to dysfunction and remodeling of small arterioles, plays a role in inducing arterial stiffness.<sup>25,26</sup> As discussed above, oxidative stress and inflammation are essential components affecting both micro- and macrovascular function, initiating a vicious circle between increased BP, vascular remodeling, stiffness, and continued hypertension and its atherosclerotic complications.<sup>15,25,26</sup>

### Oxidative Stress and Accelerated Aging

The role of superoxide anion (O<sub>2</sub><sup>•-</sup>), produced by the nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, in

vascular disease is widely accepted.<sup>27,28</sup> Various homologues of the enzyme may serve different functions in physiology and pathology.<sup>27,29-31</sup> Therefore, a need for specific targeting and the search for novel NADPH oxidase (Nox) inhibitors continues.<sup>32,33</sup> Recent studies in *Hypertension* have identified novel regulators of Nox function, including chemokines, such as chemerin—a pathological adipokine. Chemerin, through Nox activation and redox-sensitive mitogen-activated protein kinase signaling, exerts proapoptotic, proinflammatory, and proliferative effects in human vascular cells.<sup>34</sup> These processes promote VSMC transformation with vascular calcification and have been linked to impaired NO formation and homoarginine.<sup>35</sup> NO can inhibit NADPH oxidases.<sup>36</sup> Gao et al demonstrated a potentially important practical application of this observation to explain the mechanism by which dietary nitrate reduces BP. They showed that inorganic nitrate and nitrite attenuate reactivity of the renal microcirculation and BP responses to angiotensin II by modulating Nox activity and NO bioavailability.<sup>37</sup> In a model of oxidative stress (SOD1<sup>-/-</sup>), abnormal angiotensin II-mediated arteriolar contractions were normalized by nitrite with Nox oxidases as a possible target.<sup>37</sup>

Nrf2 (nuclear factor E2-related factor 2) and Rho kinases are also important regulators of vascular dysfunction linked to Nox activity in aging. In models of diabetes mellitus-induced accelerated vascular aging and erectile dysfunction, Nrf2-Nox interaction, is key, as Nrf2 downregulation increases Nox1

(NADPH oxidase 1)-derived ROS and consequently impairs vascular function.<sup>38</sup> In this setting, Nrf2 activator, Nox1, and Rho kinase inhibitors normalized vascular function,<sup>38</sup> indicating that Nrf2 is clearly vasoprotective. Similarly, Nrf2 down-regulation has been observed in arteries from stroke-prone spontaneously hypertensive rats,<sup>39</sup> which contributes to redox-sensitive vascular dysfunction in hypertension. Angiotensin II increased nuclear accumulation of Nrf2 in VSMCs from Wistar Kyoto rats, with blunted effects in stroke-prone spontaneously hypertensive rats.<sup>39</sup> Nrf2 activators blocked angiotensin II-induced ROS generation. Although pathogenic oxidative stress in human vasculature and the heart is primarily caused by Nox enzymes, Nox4-knockout mice have shown clearly that this homologue of oxidase may be protective in most pathological conditions.<sup>30,40</sup> Nox4<sup>-/-</sup> leads to increased vascular inflammation, vascular hypertrophy, and endothelial dysfunction, which translates into greater susceptibility to the development of atherosclerosis.<sup>30,41</sup> Nox4 downregulation is also critically linked with the development of VSMC senescent phenotype characterized by lower proliferation and pro-inflammatory cytokines and matrix metalloproteinase (MMP) secretion.<sup>42</sup> We are now beginning to understand the mechanisms of this protective effect.<sup>40</sup> A recent study published in *Hypertension* showed that in mice with cardiac-specific overexpression of Nox4, Nrf2 deletion significantly attenuated their protective phenotype during chronic pressure overload. Nox4-Nrf2 is an important endogenous protective pathway that limits mitochondrial damage and apoptosis-inducing factor-related cell death in the heart under hemodynamic overload.<sup>43</sup> In contrast to that, salt sensitive SS/Nox4<sup>-/-</sup> rats exhibit a significant reduction of salt-induced hypertension compared with SS rats, which was accompanied by a reduction of albuminuria, tubular casts, and glomerular injury. Interestingly Nox4<sup>-/-</sup> rats showed lower Nox2, p67phox, and p22phox in the renal cortex indicating potential differential regulation or interaction between NADPH oxidase homologues.<sup>44</sup> This demonstrates complexity of the role of Nox4 in the regulation of vascular function and disease. Possible mechanisms linked to cardiovascular protection related to Nox4 may be linked to microRNA (miRNAs) expression. Kriegel et al have systematically identified endogenous miRNAs in endothelial cells that regulate genes relevant to hypertension. They reported significant suppression of the abundance of mRNA encoded by Nox4 by the miR-92 family, miR-100-5p, and miR-99b-5p. Inhibition of the miRNAs targeting Nox4 mRNA increased hydrogen peroxide release from endothelial cells.<sup>45</sup> Nox2 expression can in turn be regulated by miR-448-3p. Downregulation of miR-448-3p leads to the increase in expression of Ncf1 gene and p47phox protein, as well as substantial increases in Nox2-derived ROS production.<sup>46</sup> This is important because these miRNAs may not only be important in understanding pathophysiology of oxidative stress in vascular dysfunction and aging but may serve as valuable potential biomarkers.<sup>47,48</sup>

Although NADPH oxidases have received considerable attention, other sources of oxidative stress should not be forgotten. In particular, mitochondrial ROS generation in the context of aging is important. It has been challenging to study mitochondrial ROS production because of the complexity of

the process of their generation and the abundance of mitochondrial ROS scavenging and protection mechanisms.<sup>49</sup> Thus, the regulation of mitochondrial O<sub>2</sub><sup>-</sup> generation and the antihypertensive potential of targeting the mitochondria are still poorly defined. Interestingly, angiotensin II and cytokines cooperatively induce cyclophilin D-dependent mitochondrial O<sub>2</sub><sup>-</sup> production in hypertension.<sup>50</sup> This has shown a common oxidative stress downstream mechanism linking oxidation and inflammation to hypertension. Targeting cyclophilin D decreases mitochondrial O<sub>2</sub><sup>-</sup>, improves vascular relaxation, and reduces hypertension.<sup>50</sup>

Cytochrome P450 1B1 is another source of ROS, which may be important in vascular pathobiology of hypertension and atherosclerosis. It contributes to VSMC growth and hypertension, as well as to vascular aging characteristic of elastin breaks and vascular infiltration of macrophages and T lymphocytes.<sup>51</sup>

Endothelial NO synthase (eNOS) uncoupling is also a characteristic feature of accelerated vascular aging in diabetes mellitus, hypertension and is induced by oxidation of tetrahydrobiopterin and loss of this important eNOS cofactor.<sup>52</sup> This process is initiated by O<sub>2</sub><sup>-</sup> from Nox enzymes or mitochondrial oxidases and is, in part, regulated by cytokines from inflammatory monocytes,<sup>53</sup> as discussed below.

Although prooxidant mechanisms are important, an imbalance between prooxidant and antioxidant mechanisms is key in human vascular aging.<sup>54</sup> Interestingly Fibroblast growth factor 21 exerts protective effects, preventing cardiac hypertrophy development through regulation of genes involved in antioxidant pathways, including mitochondrial uncoupling proteins (Ucp2 and Ucp3) and superoxide dismutase, thus, preventing ROS production and preventing pathological remodeling.<sup>55</sup>

### Mineralocorticoid Receptors in the Regulation of Oxidative Stress and Vascular Aging

It has been known for many years that the effects of aldosterone and mineralocorticoid receptor (MR) activation on the vasculature are mediated by oxidative stress. The importance of MR blockade is highlighted by its clinical benefits in resistant hypertension.<sup>56</sup> The past few years have advanced the understanding of mechanisms involved in vascular comorbidities. First, an important clinical pharmacological study by Arnold et al<sup>57</sup> demonstrated that MR activation plays a role in the hypertension of autonomic failure, which can be considered a feature of vascular aging.<sup>1</sup> Inappropriate MR activation contributes to human hypertension, independently of canonical mineralocorticoid effects. It provided rationale for the use of eplerenone in those patients.<sup>57</sup> Such aberrant MR activation is observed in relation to hypertensive target-organ damage, for example, in heart failure,<sup>58</sup> a key mechanism involves the small GTPase Rac1 activation and increased Nox4 gene induction and ROS overproduction, which in the context of pressure-overload heart failure is pathogenic rather than protective.<sup>58</sup> MR is, therefore, a key therapeutic target for cardiac and renal target-organ damage in hypertension and may prevent diastolic dysfunction and heart failure development.<sup>59,60</sup> Indeed, MR knockout prevents development of diet-induced diastolic dysfunction.<sup>61</sup> Interestingly, some effects of aldosterone seem to involve angiotensin type 1a receptors. This

is evident in aldosterone-induced vascular injury, which is prevented by angiotensin type 1a receptor knockout mice and by the angiotensin type 1a receptor antagonist losartan.<sup>62</sup> Angiotensin type 1a receptor is required for MR stimulation to induce vascular remodeling and inflammation and endothelial dysfunction.<sup>62</sup> Interestingly, leptin induces hypertension and endothelial dysfunction via aldosterone-dependent mechanisms. Chronic leptin receptor antagonism reduced aldosterone levels. Furthermore, chronic leptin and MR blockade reduced BP and improved endothelial function in both leptin-sensitized and obese hyperleptinemic female mice.<sup>63</sup> Endothelial MR is essential in the development of not only endothelial dysfunction and hypertension but in mediating hypertensive cardiac injury and dysfunction.<sup>64,65</sup> These phenomena suggest that MR blockade may provide a key strategy to delay and prevent features of cardiovascular aging. Even low, subpressor doses of the MR antagonist, spironolactone prevented aortic and femoral artery stiffening in female mice fed a high-fat/high-sugar western diet,<sup>66</sup> which is particularly important taking into account that vascular stiffening is the main feature of vascular aging.<sup>1</sup>

### Inflammatory Mechanisms of Hypertension Are Linked to Oxidative Stress

Increasing evidence shows an important relationship between inflammation and hypertension.<sup>17,67–70</sup> Oxidative stress is central in the pathology both as an initiator of vascular and renal inflammation and the consequence of inflammatory responses and cytokines.<sup>71–73</sup> This is particularly important, in light of the role of immunosenescent T cells in hypertension and the susceptibility of T cells to changes associated with aging.<sup>74</sup> They are characterized by loss of CD28 marker and appearance of CD57 and functionally produce tumor necrosis factor- $\alpha$  and interferon- $\gamma$ , which affect vascular changes.<sup>75</sup> While early studies have shown that T cells are key in hypertension,<sup>76,77</sup> recent clinical studies indicate that their role is related to a close interaction with other elements of innate, cellular, and humoral immunity.<sup>76</sup> In particular, B cells seem to be essential in hypertension, and their lack is associated with diminished vascular oxidative stress.<sup>78</sup>

Obesity is related to particularly high immune activation that may contribute to hypertension both nonspecifically through cytokines and adipocytokines, as well as through more specific mechanisms. For example, a novel role for Fc $\gamma$ RIIB in the pathogenesis of obesity-induced hypertension, independent of processes regulating adiposity, and it may entail an IgG-induced attenuation of eNOS function. Approaches targeting Fc $\gamma$ RIIB may potentially offer new means to treat hypertension in obese individuals.<sup>79</sup> Although antibodies seem to be important, B cells may exert their effects through B-cell specific contribution to cytokine production, such as tumor necrosis factor- $\alpha$ ,<sup>80</sup> which has been shown to be prohypertensive and proatherosclerotic. Role of macrophages in hypertension and atherosclerosis is evident<sup>67,81</sup> and closely linked to NADPH oxidases, which are abundant within both monocytes and macrophages.<sup>82</sup> Nox2 NADPH oxidase mediates M1/M2 polarization and regulates their participation in vascular damage, inflammation, and fibrosis.<sup>83,84</sup> The interaction between tumor

necrosis factor- $\alpha$ -like weak inducer of apoptosis (Tnfsf12) regulates vascular damage by stimulating ROS production in an Nox2-dependent manner in macrophages and can, therefore, promote accelerated vascular aging<sup>85</sup> and cognitive impairment.<sup>86</sup>

There is increasing interest in unraveling the mechanisms of activation of immune cells in the vascular wall. Increased oxidative stress in dendritic cells leads to increased capacity for antigen presentation, which involved Nox2 and isolevuglandins, which increase the ability of dendritic cells to drive T-cell proliferation.<sup>76,87</sup> Pattern recognition receptors, such as TLR4, have recently been implicated in the regulation of antigen presenting cell function in hypertension. This activates inflammatory signaling through My88D and activation of nuclear factor- $\kappa$ B, important in cardiac and renal damage and potentially in the development of high BP.<sup>88,89</sup> Moreover, adipokines, such as resistin, may induce hypertension in a TLR4-dependent manner.<sup>90</sup> A recent study in *Hypertension* demonstrated that TLR4-dependent activation of toll-interleukin receptor domain-containing adaptor protein-inducing interferon- $\beta$  contribute angiotensin II-induced hypertension and cardiac hypertrophy. At the same time, MyD88-dependent pathway can paradoxically inhibit prohypertensive responses.<sup>91</sup>

Inflammation and oxidative stress are important for microvascular dysfunction. This is especially important in conditions associated with small vessel disease of the brain and cognitive impairment—a key clinical consequence of vascular aging. This prompted *Hypertension* to publish a key statement,<sup>92</sup> on the difference between vascular dementia and Alzheimer disease and articles on the impact of hypertension on exacerbating Alzheimer disease through reduced NO bioavailability and eNOS and nNOS activity.<sup>93</sup> Importantly, microvascular dysfunction leading to cognitive impairment is dependent on Nox2 activation in macrophages infiltrating perivascular space in the brain.<sup>86</sup> This seems to be a predominant mechanism for NO decrease and neurovascular unit impairment,<sup>86</sup> emphasizing key interactions between oxidation and inflammation in cognitive dysfunction pathology.

New molecules are emerging as important mediators regulating oxidation and inflammation in the vasculature and heart, including osteoprotegerin, that may act through reduction in apoptosis and preservation of the matrix structure. Although osteoprotegerin can affect vascular function, its cardiac effects seem to be direct and independent of effects on the vasculature.<sup>94</sup> Recent vascular transcriptomic analysis has shown that the *SPHK1* gene (sphingosine phosphate kinase 1) involved in sphingosine-1-phosphate generation is highly affected in hypertensive vasculature in response to angiotensin II<sup>95</sup>. This is important because it seems to modulate NO release, Nox activity, vascular contraction, and inflammation.<sup>95</sup> All of these are essential in accelerated vascular aging in hypertension.

Vascular remodeling depends to a large extent on MMPs, which degrade collagen and elastin and could possibly counteract fibrosis. Their inhibition effectively retards/alleviates arterial structural remodeling, decreases stiffness, and improves vascular endothelial function in animal models.<sup>96</sup> This is because MMPs create a proinflammatory

microenvironment that shifts the phenotypes of endothelial cells and VSMCs toward secretory, migratory, proliferative, and senescent phenotype. Mechanistically, the effects of MMPs are mediated by ROS. Importantly MMP genes are redox sensitive and are regulated by increased Nox activity. This is how MMPs promote arterial remodeling in aging, hypertension, and atherosclerosis.<sup>96</sup> MMPs and tissue inhibitors of metalloproteinases, such as TIMP-2, play protective role by suppressing MMP-dependent monocyte/macrophage vascular accumulation.<sup>97</sup> In particular, MMP-9 has been implicated in inflammatory senescence signature.<sup>98</sup> Pathological remodeling of the ECM can be also regulated by novel factors important in vascular disease, such as Fibulin-5. *FBLN5* mediates cell-ECM interactions and elastic fiber assembly and is critical for ECM remodeling. These mechanisms seem to involve epigenetic regulation in a SOX9/HDAC-dependent mechanism.<sup>99</sup> Necrotic VSMCs induce inflammation in macrophages and monocytes, thus, affecting vascular remodeling.<sup>100</sup> In summary, senescent vascular wall cells are skewed toward a secretory phenotype that promotes chronic ECM degradation and perivascular inflammation,<sup>6</sup> key features of aging vasculature.

### Conclusions and Clinical Perspective

Recent advances in hypertension research have unraveled novel oxidative and inflammatory mechanisms of vascular dysfunction that underlie accelerated vascular aging in hypertension and associated cardiovascular diseases.<sup>101</sup> The clinical consequences encompass microvascular dysfunction in the brain, heart, and systemically, as well as accelerated development of atherosclerosis and cardiovascular risk. Development of novel specific inhibitors of NADPH oxidases, which would not interfere with Nrf2- or Nox4-dependent cardiovascular protective mechanisms are needed. Nanotechnologies may bring novel therapeutic approaches to combat both oxidative stress and inflammation in cardiovascular disease.<sup>102</sup> Recent developments in the understanding of early vascular aging (Figure) may lead to novel biomarker discovery based on selected markers of oxidant stress, miRNAs, and inflammatory molecules.

In summary, vascular aging is closely linked, pathogenically and phenotypically, to hypertension in the clinical setting. At the same time, increased BP per se promotes accelerated vascular aging, which predisposes to target-organ complications. Therefore, accelerated vascular aging constitutes an important diagnostic and therapeutic target and as such several clinical studies are now ongoing to (1) identify biomarkers of accelerated vascular aging, (2) establish predictive value of vascular stiffness, and (3) enable vascular aging prevention and treatment.<sup>1,14</sup> Potential therapeutic strategies tested to date include AT1R blockers, HMG-CoA reductase inhibitors, calcium channel blockers, anticoagulants, testosterone, or even estradiol. It is, however, unlikely that a single drug regimen will be sufficient. Composite interventions, including exercise, cognitive training, and most importantly, active risk factor management, apart from possible pharmacological targeting, will likely be needed to prevent and ameliorate the vascular aging phenomenon of hypertension.

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None.

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