Novel Contributors and Mechanisms of Cellular Senescence in Hypertension-Associated Premature Vascular Aging

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Hypertension has been described as a condition of premature vascular aging, relative to actual chronological age. In fact, many factors that contribute to the deterioration of vascular function as we age are accelerated in hypertension. Nonetheless, the precise mechanisms that underlie the aged phenotype of arteries from hypertensive patients and animals remain elusive. Cellular senescence is an age-related physiologic process in which cells undergo irreversible growth arrest. Although controlled senescence negatively regulates cell proliferation and promotes tissue regeneration, uncontrolled senescence can contribute to disease pathogenesis by presenting the senescence-associated secretory phenotype, in which molecules such as proinflammatory cytokines, matrix metalloproteases, and reactive oxygen species are released into tissue microenvironments. This review will address and critically evaluate the current literature on the role of cellular senescence in hypertension, with particular emphasis on cells types that mediate and modulate vascular function and structure.

Keywords: blood pressure; cellular senescence; hypertension; vascular aging.

doi:10.1093/ajh/hpz052

PREMATURE VASCULAR AGING IN HYPERTENSION

Our desire to reverse (or at least delay) the aging process has long been the focus of biomedical research and homeopathic medicine. However, whether the lifespan of an individual organism relates to the longevity of its constituent cells, tissues, and organs is still obscure. In this sense, plants present a unique perspective in the search for a definitive answer to this most fundamental question. For example, deciduous trees are mostly made up of dead tissues; the canopy is renewed and discarded every year, root systems turn over, and reproduction takes place repeatedly over decades, centuries or even millennia.[1] This phenomenon is regulated by senescence and presents a clear disconnect between the lifespan of the whole and the parts. Given that senescence is an important physiologic process to control cell proliferation and rejuvenate tissues and organs in humans, this disassociation could also be present in the process of human pathophysiology, including cardiovascular diseases.

Generally, the increase in cardiovascular events as we age is attributable to the natural decline in organ function.[2] Within the context of hypertension, age is considered a major risk factor and the prevalence of hypertension increases with age, irrespective of biological sex.[3] In hypertension however, the decline in vascular function and aged phenotype are premature in their onset and particularly pronounced.[4,5] As a result, vascular age determination, as opposed to chronological age per se, has now been introduced into clinical guidelines for cardiovascular disease prevention.[6] Nonetheless, what precisely defines vascular aging is broad and can encompass many of the vascular maladaptations presented in hypertensive patients and animals, including:

1) Hypercontractility: Defects in the regulation of vascular smooth muscle cell calcium (e.g., increased calcium entry and storage, impaired intracellular calcium buffering capacity, and decreased calcium extrusion) and a switch in the abundance of endothelium-derived provasoconstrictive factors relative to provasodilatory factors.
2) Stiffening and remodeling: Changes in vascular distensibility and cross-section area due to calcification, actin polymerization, fibrosis, and extracellular matrix deposition.
3) Inflammation and oxidative stress: Immune cell and non-immune cell exacerbated generation of proinflammatory cytokines, chemokines, adhesion molecules, and reactive oxygen species (ROS) relative to proresolving factors such as lipoxins, resolvins, and protectins.

Therefore, hypertension is a condition of vascular aging and the factors that contribute to the deterioration of vascular function as we age are accelerated in hypertension[4,5] (Figure 1). Nonetheless, identification of these age-associated factors and their mechanisms remain elusive.

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Initially submitted February 6, 2019; date of first revision March 25, 2019; accepted for publication April 10, 2019; online publication April 15, 2019.

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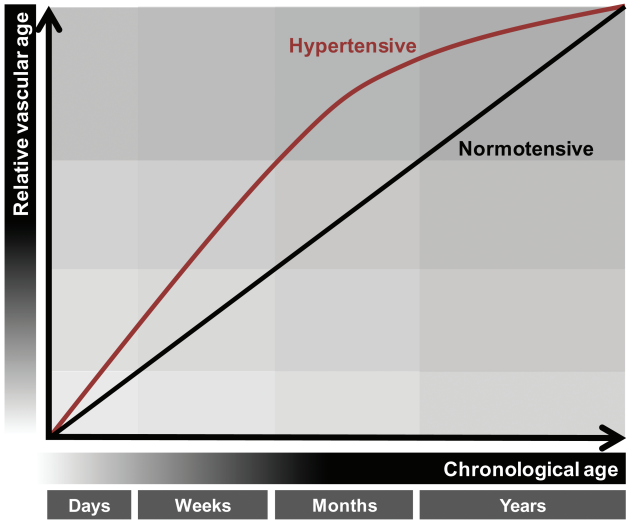

Figure 1. Relative vascular age is accelerated in hypertension. For any given chronological age, a hypertensive patient or animal has an increased vascular age, compared with an age-matched normotensive control. The definition of vascular age encompasses a broad range of phenotypes that can refined into taxonomies such as hypercontractility, stiffening and remodeling, and inflammation and oxidative stress.

CELLULAR SENESCENCE IS AN AGE-ASSOCIATED PHYSIOLOGIC PROCESS

Cellular senescence is a conserved mechanism among somatic cell types that induces irreversible cell-cycle arrest in response to excessive or prolonged stress or replicative exhaustion. Evolutionarily, senescence is a protective mechanism to prevent the transmission of genomic defects to the next generation. Moreover, controlled senescence actually promotes tissue regeneration and function via the recruitment of immune cells and clearance of senescent cells.[7,8] However, aged tissues or tissues from diseased animals are not able to efficiently complete this sequence of events, thereby resulting in the accumulation of senescent cells.[7]

The number of stimuli that trigger senescence is constantly increasing and specific mechanisms of vascular cell senescence in the context of hypertension or prohypertensive stimuli will be discussed later in this review. Broadly, senescent stimuli can be classified into either damage-induced senescence (e.g., DNA damage and telomere alterations, epigenetic depression of the cyclin-dependent kinase inhibitor 2A locus, ROS, oncogenic signaling/tumor suppressor inactivation) or developmentally programmed senescence (e.g., developmental cues, polyploidization, and cell fusion).[9] These triggers generally result in the activation of p53 and convergence on the cyclin-dependent kinase inhibitors p15, p16, p21, and p27. The inhibition of cyclin-dependent kinase–cyclin complexes causes proliferative arrest, and the crucial component responsible for the implementation of senescence is the hypophosphorylated form of retinoblastoma (Rb) protein.[10]

One specific means by which senescent cells can contribute to the development and/or maintenance of pathophysiology is by mediation of inflammation and oxidative stress. Upon the onset of senescence, senescent cells develop heightened secretory activity known as the senescence-associated secretory phenotype (SASP).[11] This phenotype is characterized by the secretion of proinflammatory cytokines and chemokines, ROS, growth factors, proteases, plasminogen activator inhibitor-1, but never anti-inflammatory or proresolving factors, into the local tissue environment.[11] Although the SASP pattern may vary according to cell type, as well as the particular stress or damage that induces senescence,[12] physiologically, this proinflammatory/pro-oxidative milieu signals the recruitment of phagocytes to infiltrate tissues and clear out the senescent cells. Thus, the mitostatic effect of uncontrolled senescence is counterbalanced by the effects of the SASP and this can contribute to the pathophysiology of disease. In fact, this phenomenon is already known to occur in endothelial cells[13] and vascular smooth muscle cells[14]; thus, it is logical to hypothesize that senescent cells contribute to vascular inflammation in hypertension (Figure 2). Nonetheless, determining whether senescence primarily drives pathophysiology or is a secondary bystander is difficult.

Although understanding the mechanistic relationship between senescence and pathophysiology is a focus of great interest, there is already evidence supporting the therapeutic approach of targeting senescence for the treatment and reversal of disease.[15,16] Agents that prevent the activation of specific mechanisms of senescence, such as those involving telomerase, DNA-damage repair machinery, cell-cycle checkpoint kinases, and tumor suppressors, are all known to reduce indices of pathophysiology.[15,16]

CELLULAR SENESCENCE IS A WIDESPREAD PHENOTYPE IN HYPERTENSION

Although senescence has been linked with age for many years,[17,18] only recently was it reported that the removal of senescent cells does indeed delay chronological and premature aging, increase lifespan, and rejuvenate organ function,[19–21] including the vasculature[22] and kidneys.[20] Nonetheless, our understanding of senescence in hypertension-associated end-organ dysfunction, beyond phenotypic recognition, is far from complete. Almost all forms of experimental hypertension and hypertensive patients show cellular senescence in various organs as an indicator of end-organ damage. To the best of our knowledge, Table 1 presents a list of investigations that reported senescence in an established experimental model of hypertension or after exposure to prohypertensive stimuli. Overall, these studies generally indicate a pressure-dependent association between increased cellular senescence and hypertension,[23,24] with angiotensin II being the predominant prosenescence factor.[25] Furthermore, antihypertensive therapy has been shown to reduce indices of senescence.[24] Nonetheless, it currently unknown if removal of senescent cells does indeed lower (or prevent) hypertension.

VASCULAR CELL SENESCENCE CAN MEDIATE THE AGING PHENOTYPE

It is well established that a host of prohypertensive stimuli can cause senescence of vascular cells and induce many

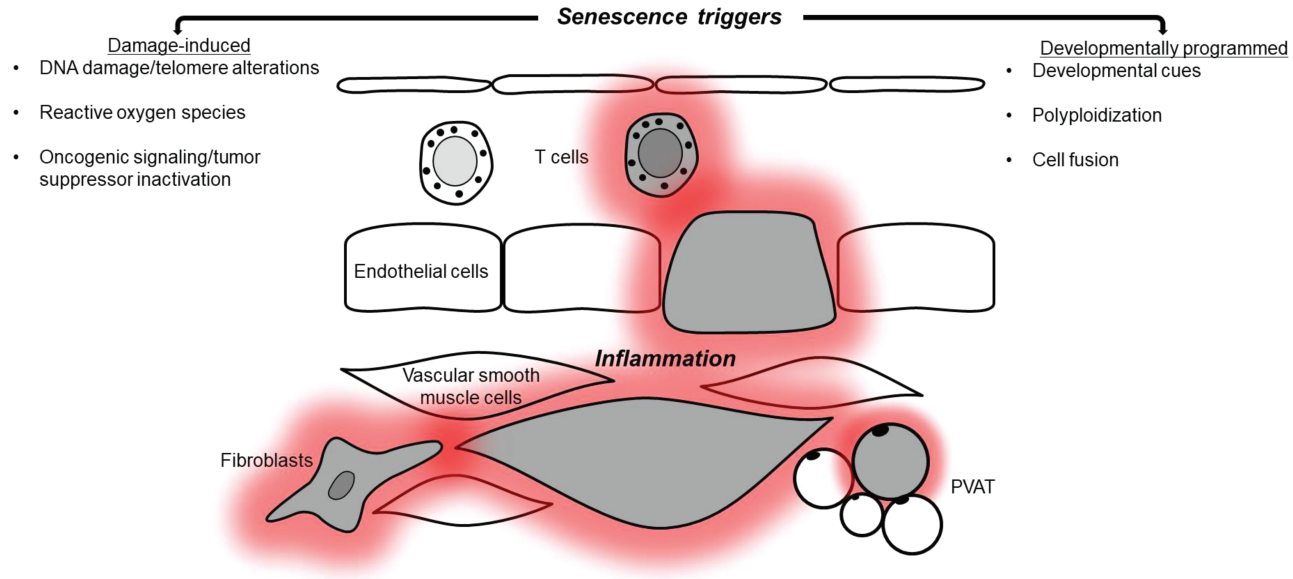

Figure 2. The senescence-associated secretory phenotype from endothelial cells and vascular smooth muscle cells, as well as T cells, fibroblasts, and perivascular adipose tissue (PVAT) synergize to cause vascular wall inflammation and dysfunction, driving the development and/or maintenance of hypertension.

of the vascular aging phenotypes defined earlier. Table 2 presents a compilation of seminal investigations that reported senescent vascular cells mediating a characteristic of the aged phenotype. Studies that demonstrated an association, but not causality, between a vascular aging phenotype and senescence were not surveyed in this list due to an overabundance of literature.

From these investigations, it is possible to extrapolate that senescence of vascular cells contributes to the aged phenotype and probably contributes to the maintenance of hypertension. This collection of basic science literature supports the observations that the onset of senescence is dependent on relative age (as opposed to chronological age) and appears earlier in patients with longer exposure to a cardiovascular disease risk factors, particularly hypertension.[46]

BEYOND VASCULAR SENESCENCE IN HYPERTENSION

Hypertension is a complex condition that is driven by multiorgan dysfunction. In addition to endothelial cells and vascular smooth muscle cells of the vasculature, perivascular adipose tissue (PVAT), the kidneys, the brain, and the immune system have well-defined roles in facilitating increases in blood pressure, and recently, gut dysbiosis has also been revealed to contribute. Therefore, cellular senescence in these other organs and cell types could also contribute to the pathogenesis of hypertension-associated premature vascular aging.

Perivascular adipose tissue

Analogous to the SASP, PVAT is well known to secrete a variety of factors ranging from adipokines, gaseous molecules, and angiotensin 1–7 to ROS, proinflammatory cytokines, and angiotensin II.[94] Given the close proximity of PVAT to cells of the vasculature, paracrine cross-talk can easily occur, and this can influence vascular function. Generally, PVAT from healthy animals secretes anticontractile factors,[95] whereas PVAT from hypertensive animals not only loses this anticontractile phenotype,[96] but it also generates of hyper-contractile factors.[97,98] Nonetheless, the mechanisms underlying this phenotypic switch are still being revealed. Recently, it was observed that adipose tissue senescence, via mineralocorticoid receptor activation, contributed to increased arterial contractile responses.[74] This illustrates that senescent PVAT can mediate premature vascular aging by promoting hypercontractility.

Kidneys

As indicated in Table 1, renal senescence is present in aldosterone, angiotensin II, and deoxycorticosterone acetate models of hypertension, as well as human hypertensive patients. Uncontrolled senescence would not only affect renal function, but also probably contribute to the high frequency of end-stage renal disease in the elderly adults.[99,100]

Brain

Most of the literature on cellular senescence in the brain has focused on its ability to mediate neurodegeneration.[101,102] Hypertension has also been established to cause and contribute to neurodegeneration.[103,104] Therefore, it is plausible that the 2 phenomena are not mutually exclusive and that increased neuronal senescence in hypertension could be an underlying factor. Furthermore, while it is unlikely that senescent neurons drive increases sympathetic tone, we hypothesize that the SASP of other senescent brain cells (e.g., glial cells or neural stem cells) could propagate inflammation in surrounding (non-senescent) tissues that could then

Table 1. Investigations that reported senescence using established experimental models of hypertension or prohypertensive stimuli

Experimental model of hypertension		Tissue/cell type	Reference
Aldosterone		Kidney	26
		VSMCs	27
Angiotensin II		Aorta	28
		Endothelial cells	29
		EPCs	30–35
		Endothelial cells	36
		Kidney	24,37
		Myocardium	38
		VSMCs	25,39–41,
Dahl Salt-sensitive rats		Aorta	42
		Myocardium	43,44
		VSMCs	45
Deoxycorticosterone acetate rats		Coronary arteries	24
		Kidney	24
		Myocardium	24
Human patient samples		Endothelial cells	46
		EPCs	47
		Kidney	24,48
		Leukocytes	48
		VSMCs	28,49,50
Nitric oxide inhibition		Aorta	51
		EPCs	52
		Endothelial cells	53,54
Spontaneously hypertensive rats		Aorta	55,56
		EPCs	35,47,57,58
		Microvascular endothelial cells	59
		Myocardium	60
Miscellaneous	Senescence inducer		
	Activated Ras	VSMCs	61
	Hydrogen peroxide	Endothelial cells	62,63
	Indoxyl sulfate	VSMCs	45
	Tert-butyl hydroperoxide or L-buthionine-[S,R]-sulphoximine	Endothelial cells	64
	Tumor necrosis factor α	Endothelial cells	65

Abbreviations: EPC, endothelial progenitor cell; VSMC, vascular smooth muscle cell.

mediate neurogenic hypertension. Beyond neurons, it has been observed that angiotensin II induces senescence in astrocytes via ROS.[105] The downstream effects of astrocyte senescence on hypertension could be far reaching given their multifunctional role in brain homeostasis (e.g., blood–brain barrier integrity, extracellular ion balance, and inflammation).

T cells

Uncontrolled immune system activation, including monocytes/macrophages,[106] natural killer cells,[107] dendritic cells,[108] T cells,[109] and γ-δ T cells,[110] has been well ascribed in the pathogenesis of hypertension. In particular, T cells have been the focus of a great deal of research.[111] Nonetheless, what precisely activates T cells to mediate inflammation and further increases in blood pressure has yet to be fully elucidated. It has been observed that immunosenescent ($CD28^{null}$ and $CD57^{+}$) cytotoxic T cells are increased in patients with hypertension.[112] An outstanding question that remained from this study was whether senescent T cells present a heightened production of cytokine and chemokines (SASP), beyond their normal proinflammatory capacity. Moreover, whether these other immune cells involved in the development and/or maintenance of hypertension (i.e.,

Table 2. Seminal investigations that reported senescence mediated a phenotype of vascular aging

	Vascular age phenotype	Tissue/cell type	Model	Reference
Hypercontractility	Endothelial vasoactive factors	Aorta	Senescence-accelerated mice	66,67
		Mesenteric resistance arteries	Senescence-accelerated mice + Western diet	68
		Endothelial cells	Replicative senescence	69
		Endothelial cells	Telomere inhibition-induced senescence	70
		Endothelial cells	Replicative senescence	71–73
	Other	PVAT	Obese (db/db) mice	74
Stiffening and remodeling	Actin polymerization	Endothelial cells	Replicative senescence	75
		Endothelial cells	Replicative senescence	76,77
		VSMCs	Replicative senescence	78
	Calcification	Aorta	Hypercholesterolemic mice	22
		VSMCs	Replicative senescence	79–81
	Fibrosis	Aortic valves	Senescence-accelerated mice	82
		Fibroblasts	Replicative senescence or ionizing radiation-induced senescence	83,84
	ECM deposition	Endothelial cells	Replicative senescence	76,85,86
Inflammation and oxidative stress	Cytokines and chemokines	Endothelial cells	Replicative senescence	13
		VSMCs	Activated Ras-induced senescence	61
		VSMCs	Replicative senescence and bleomycin-induced senescence	14
	Cell adhesion	Endothelial cells	Replicative senescence	87
		Endothelial cells	Replicative senescence	69
		Endothelial cells	Telomere inhibition	70
	Impaired resolution	Fibroblasts	Bleomycin or ionizing radiation	88
		Myofibroblasts	Bleomycin	89
	ROS	Endothelial cells	Replicative senescence	90
		Endothelial cells	Replicative senescence	91,92
		Pulmonary artery endothelial cells	Replicative senescence	93

Abbreviations: ECM, extracellular matrix; PVAT, perivascular adipose tissue; ROS, reactive oxygen species; VSMC, vascular smooth muscle cell.

monocytes/macrophages, dendritic cells, or γ-δ T cells) present a senescent phenotype has not been reported. On the other hand, it has been observed that senescent natural killer cells can promote vascular remodeling and angiogenesis,[113] thus demonstrating the evolutionarily conserved function of senescence on vascular homeostasis.[7,8]

Gut

Gut dysbiosis has recently come to prominence as a novel mediator of organs important for the control of blood pressure.[114] Therefore, it is obvious that hypertension-associated dysbiosis is associated with hypertension-associated premature vascular aging.[30] Importantly however, alterations in the composition and diversity of microbiota via gut senescence have been revealed as a mechanistic cause of disease.[115] We hypothesize that this gut senescence mechanism also exists in hypertension, accelerating the decline in vascular function. Supporting this idea are the observations that longevity in mice is promoted by a probiotic-induced suppression of colonic senescence[116] and that decreased gut microbial diversity promotes a physiologic decline in organ function that cannot be solely attributed to chronological aging per se.[117] Nonetheless, direct evidence of a gut senescence-vascular axis in hypertension remains to be confirmed.

NOVEL MECHANISMS UNDERLYING VASCULAR SENESCENCE IN HYPERTENSION

In hypertension, cells of the vasculature are continually exposed to stress and damage from autocrine, paracrine, and endocrine sources. Therefore, novel mechanisms of senescence in hypertension are vast. Nonetheless, we wish to highlight autophagy, endoplasmic reticulum stress and proteotoxicity, and telomere uncapping as 3 potentially novel prosenescence mechanisms of particular relevance to the hypertension field.

Autophagy is the evolutionarily conserved catabolic process essential for both maintaining homeostasis via the removal of damaged proteins and organelles and to provide micronutrients during times of stress.[118] Importantly, autophagy has also been implicated as a modulator of longevity,[119] and it is also known that its induction can extend lifespan.[120] Therefore, it is tempting to suggest that a decline in autophagy contributes to aged phenotype of the vasculature associated with hypertension. This notion is supported by studies that showed an upregulation of autophagy reversed several phenotypes of vascular aging in old mice[121,122] and our own studies observing that spontaneously hypertensive rats have decreased autophagic activity in resistance arteries.[123] Precisely how autophagy induction reduces the aged vascular phenotype is the focus of intense research,[124–126] and only one original investigation has demonstrated that upregulation of autophagy decreases vasculature senescence.[127] Right now our understanding is centered on the premise that the accumulation of dysfunctional and decaying organelles and misfolded proteins leads to a state of oxidative stress that subsequently quenches nitric oxide bioavailabilty[121,122] (Figure 3) and also uncouples endothelial nitric oxide synthase.[128] Nonetheless, given the close association of autophagy with metabolism and energy homeostasis, we hypothesize that upregulation of autophagy imparts influence on metabolic sensors (e.g., AKT and AMPK) and thereby can modulate vascular function through these mechanisms.

Although organelle recycling and protein misfolding is an inevitable consequence of normal cellular function, the unfolded protein response and multiple proteostasis systems are devoted to the refolding, repair, or clearance of damaged proteins, including autophagy.[129] However, when the unfolded protein response and proteostasis systems do not function effectively, dysfunctional organelles accumulate and misfolded proteins are vulnerable to aggregation.[130] In hypertension, our group has previously revealed that alleviation of endoplasmic reticulum stress and the unfolded protein response lowers blood pressure and improves vascular function and structure in hypertensive rats.[131,132] However, the proteotoxicity that occurs as a consequence of endoplasmic reticulum stress is only beginning to emerge in hypertension[133,134] and nothing is currently known about its contribution to vascular senescence in hypertension.

Telomeres are protective structures present at the ends of chromosomes important for preventing genome instability. It is well established that cellular senescence can be triggered by telomere shortening,[135] and a number of reviews have focused on the contribution of telomere shortening to vascular cell senescence and cardiovascular disease,[136,137] including hypertension.[138] However, there is increasing evidence that the exposure of chromosome ends, or "telomere uncapping," is more pathophysiologically relevant.[139] This is supported with evidence demonstrating that vascular telomere uncapping and senescence are linked to hypertension independently of mean telomere length, and telomere uncapping is associated with hypertension to a greater degree than mean telomere length.[140] Furthermore, it has been observed that telomeric repeat-binding factor 2 (a protein that plays a central role in telomere maintenance and protection against end-to-end fusion of chromosomes) deletion leads to telomere uncapping, increased senescence signaling, elevated blood pressure, and impaired endothelium-dependent vasodilation.[141] Overall, these investigations reveal that arterial telomere uncapping is an important inducer of senescence within the context of hypertension-associated premature vascular aging and telomere uncapping contributes to the development and maintenance of high blood pressure. Nonetheless, telomere uncapping does not necessarily apply to other organ systems involved in the pathogenesis of hypertension.

CONCLUSION

Age is not considered to be a modifiable risk factor for cardiovascular disease such as physical inactivity, dietary excess, or smoking. Unfortunately though, it outranks all those, as a predictor of clinical events.[142] Age is a major risk factor for hypertension,[3] and premature aging (relative actual chronological age) is commonly observed in the vasculature of

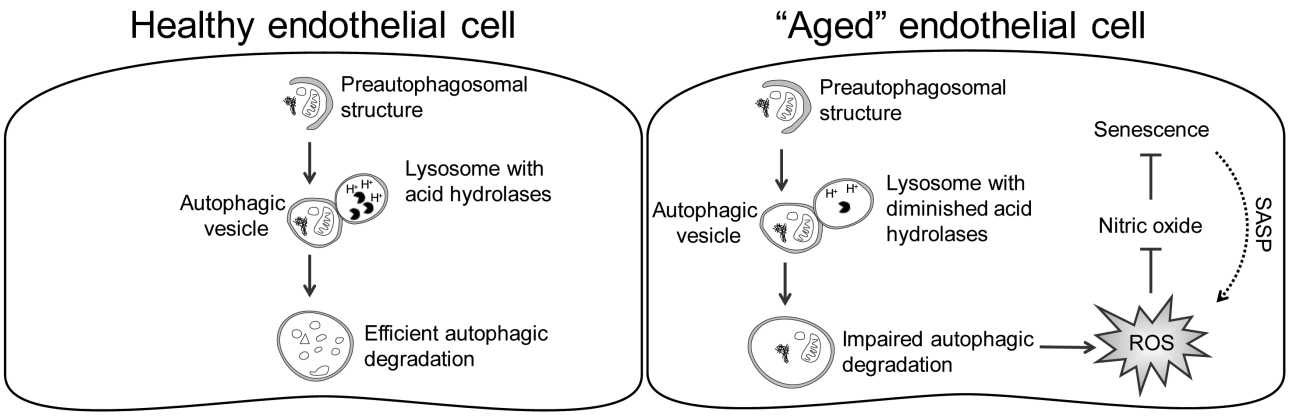

Figure 3. Autophagy is able to prevent the aged phenotype in endothelial cells. Efficient degradation of dysfunctional organelles and misfolded protein aggregates prevents their accumulation and the induction of oxidative stress, which subsequently reduces nitric oxide bioavailability. Inefficient recycling of cellular waste occurs in both chronological aging and premature aging associated with cardiovascular diseases. Abbreviations: ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype.

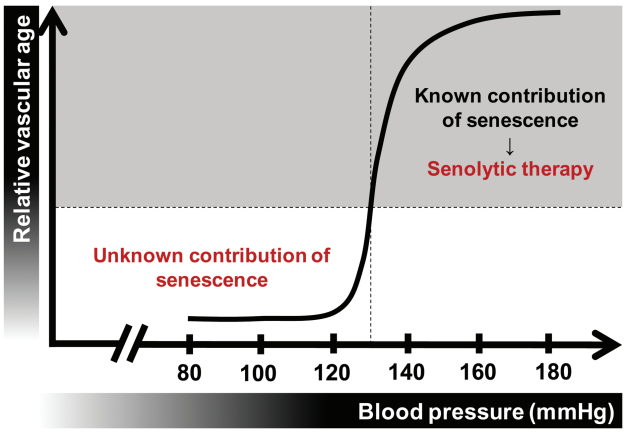

Figure 4. Our current understanding of senescence in hypertension-associated vascular aging, beyond phenotypic recognition, is far from complete. Most of the literature indicates a pressure-dependent association between increased cellular senescence and hypertension. However, there are no current studies demonstrating whether senescence can mediate increases in blood pressure, nor if removal of senescent cells (senolytic therapy) can lower blood pressure and improve vascular function in arteries from hypertensive animals.

hypertensive animals.[4,5] Nonetheless, the factors and molecular mechanism underlying this phenotype remain elusive. Senescence is age-associated phenomenon important for homeostasis.[7] However, if senescence becomes excessive and uncontrolled, it could contribute to the genesis and/or maintenance of hypertension via acceleration of relative vascular age.[46] Enhancing our understanding of cellular senescence, beyond phenotypic recognition, could further refine the vascular age determination as a prognostic and diagnostic index of cardiovascular disease risk, as well as offer an alternative therapeutic target to hypertensive patients resistant to all currently available treatments (Figure 4).

ACKNOWLEDGMENT

This work was supported by the American Heart Association (18POST34060003) and National Institutes of Health (K99GM118885, PO1HL134604, and R01HL143082).

DISCLOSURE

The authors declared no conflict of interest.

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