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Mini-review

Oxidative stress and vascular stiffness in hypertension: A renewed interest for antioxidant therapies?☆

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ABSTRACT

Since the first successful launch of the Veterans Administration(VA) cooperative studies in the late 1960s, the increasing access to blood pressure lowering medications has significantly contributed to improving longevity and quality of life in hypertensive patients. Since then, insights into the pathogenesis of hypertension have shown a mechanistic role for reactive oxygen species (ROS) in all phases of disease progression, suggesting the potential utility of antioxidant therapies to counteract symptoms and, at the same time, treat a fundamental mechanism of the disease. Despite these progresses, hypertension still remains the main contributor to the global incidence of cardiovascular disease and the leading cause of morbidity and mortality worldwide. We here briefly review and update the role of ROS and ROS-dependent metalloproteinase activation in the maladaptive remodeling of the vascular wall in hypertension. Such understanding should provide new Potential sites of action for antioxidant therapies as an integrated therapeutic approach to hypertension and its consequences.

1. Introduction

The appreciation of "systemic arterial hypertension" as a clinical entity goes back to the early 1870s, when, a young underestimated British-Asian physician named Frederick Akbar Mahomed, operating at Guy's Hospital in London, having improved a rudimental sphygmomanometer, measured blood pressure (BP) in the general population and, for the first time, reported of high BP in individuals without kidney disease [1]. Mahomed's contribution has long been forgotten, and only recently re-evaluated as preparing the ground for the subsequent work by the Italian Scipione Riva-Rocci, who invented the BP cuff and the mercury manometer [2], and Nikolai Sergeivich Korotkoff, who introduced the auscultation of the artery below the cuff allowing the determination of diastolic BP [3] (Fig. 1). Although almost 150 years have elapsed from Mahomed's pioneering observations and despite the fact that a larger access to BP-lowering medications has increased longevity in hypertensive patients [4], hypertension still remains the main contributor to the global incidence of cardiovascular disease and a leading cause of morbidity and mortality worldwide [5]. For this reason, and as a consequence of recent studies showing benefits of more pronounced reduction of BP in the average hypertensive population, the recently released guidelines for the management of high BP in adults by the American College of Cardiology and American Heart Association Task Force, have redefined BP levels to define hypertension as sustained BP levels greater than 130/80 mmHg [6]. Accordingly, the World Health Organization (WHO) now estimates that the number of hypertensive adults will increase from 1 billion to 1.5 billion worldwide by 2025 [7]. Therefore, there is an urgent need to improve our knowledge on the complex pathogenesis of this clinical condition to meet the pressing demand for a more efficient clinical management of hypertensive patients [7].

2. Pathogenesis of hypertension: risk factors and arterial maladaptive remodeling

BP is the product of cardiac output and systemic vascular resistance [8]. It follows that hypertensive patients may experience an increased cardiac output, an increase in systemic vascular resistance, or both [6]. Under normal physiological conditions, the maintenance of normal BP requires the coordinated interplay of several regulatory neuro-humoral players, including the activities of the renin-angiotensin-aldosterone system (RAAS), natriuretic peptides, the endothelium and the sympathetic nervous system [6]. Over time, deviation from normal activity of any of these regulatory systems, if leading to persistent increase in BP,

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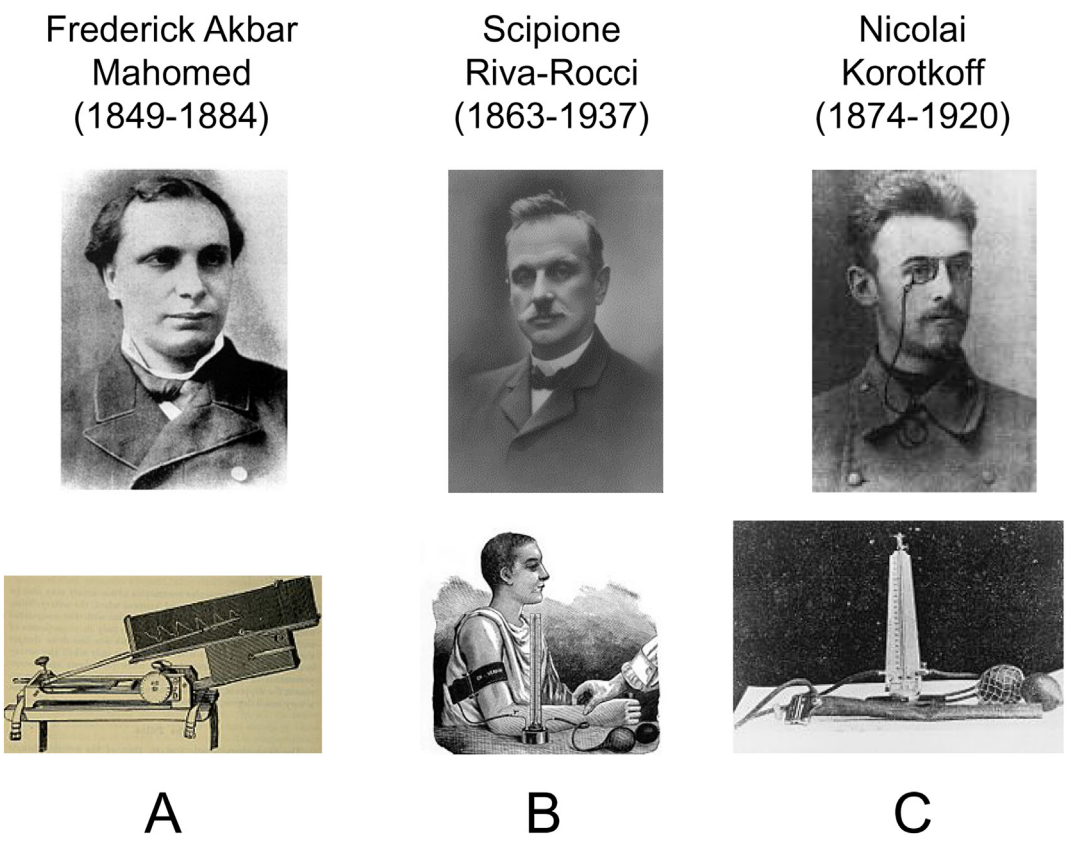

Fig. 1. Portraits of Frederick Akbar Mahomed (*left*), Scipione Riva-Rocci (*middle*) and Nicolai Korotkoff (right) and, below each portrait, the manometer used in their clinical practice (no copyright pending).

may result in target-organ damage, eventually affecting the heart, the kidneys, and the arteries, prompting atherosclerosis and cardiovascular events [6].

Several environmental risk factors including conditions of persistent psychosocial stress, imbalanced dietary sodium and potassium intake, a sedentary lifestyle, as well as overweight and obesity, are known to dynamically interact, within a predisposing genetic background, in determining the elevation of BP [9]. The hypertrophic adipose tissue releases several potential hypertensive molecules, such as free fatty acids, leptin, angiotensinogen, pro-inflammatory cytokines and reactive oxygen species (ROS) [10]. All these molecules increase BP affecting the vessel wall, the brain and the kidneys, leading to combinations of augmented vasoconstriction, reduced vasodilation, fluid retention, and/or increased vascular stiffness [11]. Aging is another critical factor constantly associated with the development of hypertension. The prevalence of high BP increases with age and, as such, hypertension is considered a typical condition of aging [12] (Fig. 2).

Biomechanically, hypertension associates with vascular remodeling and increased vascular stiffness, an array of structural, mechanical and functional changes occurring in the arterial walls primarily aimed at preserving normal blood flow and functions [13]. The vessel wall compliance depends on two major scaffolding proteins of the extracellular matrix (ECM), collagen and elastin, responsible for the structural strength and elasticity of the arterial vessels, respectively [14]. In the early phases of hypertension, “adaptive” vascular remodeling allows vessels to adapt to transient hemodynamic changes [15]. However, persistent and severe increases in BP leads to “hypertrophic maladaptive” remodeling of the arterial wall, histologically characterized by a significant increase in arterial wall thickness, increased cross sectional area and increased media-to-lumen ratio [16], while functionally arterial compliance is reduced [17] (Fig. 2). Biochemical features of “hypertrophic remodeling” include changes in collagen and elastin turnover, in favor of collagen deposition and increased collagen-to-elastin ratio [14,18]; a reduced production of the vasodilator and anti-inflammatory nitric oxide (NO); increased expression of pro-fibrotic and pro-inflammatory molecules, such as transforming growth factor (TGF)-β, monocyte adhesion molecules and cytokines; and increased expression and activity of matrix metalloproneinases (MMPs), all priming the shift of vascular smooth muscle cells (VSMCs) and endothelial cells towards more proliferative, hypertrophic and pro-inflammatory phenotypes [6] (Fig. 2).

3. Role of metalloproteinases in hypertension-related vascular remodeling

MMPs are a wide family of zinc-dependent endopeptidases involved in the irreversible remodeling of ECM in normal homeostasis and pathological conditions [19]. As such, they play crucial roles in developmental and regenerative process, including morphogenesis and organ regeneration, angiogenesis, wound healing, collateral artery formation and thrombus resolution [19]. Because of the importance of MMPs in initiating efficient matrix degradation, MMP expression and activity are tightly regulated. Not surprisingly, deregulation of their normal activity concurs to the pathogenesis of several vascular diseases, including atherosclerosis, aortic aneurysms, plaque rupture, restenosis after angioplasty [19] and – last but not least – arterial hypertension [20]. Serum concentrations of MMP-2, −9 and − 3 are increased in hypertensive patients [21,22], and are reduced upon antihypertensive treatments [22,23].

Most humoral factors associated with hypertension, including proinflammatory cytokines, growth factors, the vasoactive agents angiotensin (Ang)-II and endothelin (ET)-1, aldosterone and ROS have been shown to interfere with MMP expression and activity in both cellular and animal models of hypertension [20]. In situ zymography, a

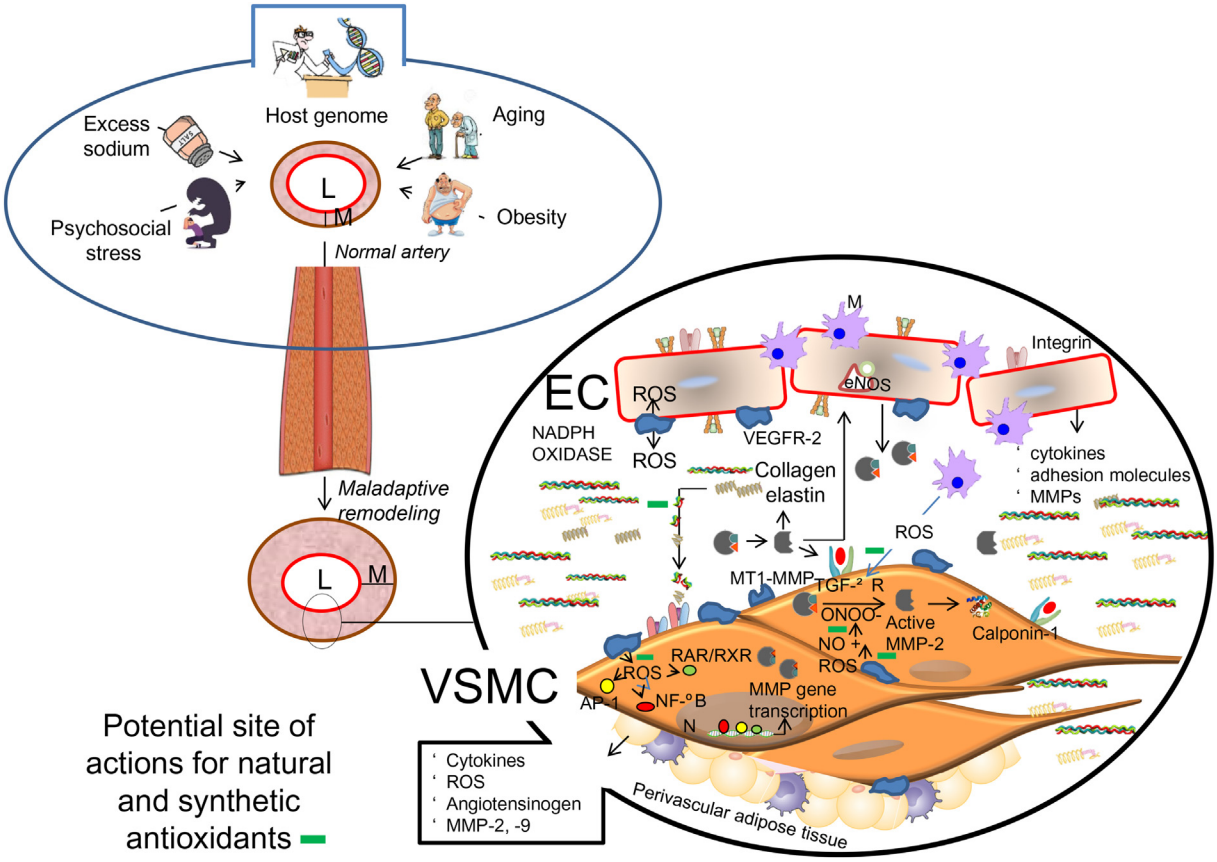

Fig. 2. Role of ROS and MMPs in the maladaptive vascular remodeling in hypertension. ROS and MT1-MMP activate MMP-2. Upon activation, MMP-2 degrades many ECM and non-ECM components. At the extracellular level, MMP-2 degrades collagen and elastin. The cleaved products of collagen bind the integrin receptors in VSMCs and activate focal adhesion kinase, in this way stimulating cell migration and proliferation. MMP-2 also activates the latent form of TGF-β, thus further sustaining VSMC transition to more proliferative, hypertrophic and pro-inflammatory phenotypes. At the intracellular level, the activation of MMP-2 by ROS contribute to proteolysis of calponin-1, thus sustaining both migration and proliferation of VSMCs. In endothelial cells, MMPs may cleave VEGFR-2 and eNOS, translating in vasoconstriction and capillary rarefaction. Through interference with these mechanisms, the use of antioxidants may alleviate hypertension-mediated vascular remodeling. Abbreviations: eNOS, endothelial nitric oxide synthase; MMP, matrix metalloproteinase; MT1-MMP, membrane type-1 matrix metalloproteinase; ROS, reactive oxygen species; $ONOO^-$, peroxynitrite; TGF-β, transforming growth factor β; VEGFR-2, vascular endothelial growth factor receptor 2; VSMC, vascular smooth muscle cells. EC, endothelial cells; M, monocyte/macrophages; N, nucleus.

laboratory technique that enables the direct localization of MMP activity in histological sections [24], when applied to vascular sections of hypertensive rats, has highlighted increased MMP activity in correspondence of the thickened intima of carotid arteries [25,26]. Correspondingly, chronic administration of pharmacological MMP inhibitors to hypertensive animals were shown to reduce BP [27] and curb both vascular fibrosis and arterial remodeling [28]. Although the pathogenic role of some MMPs, such as MMP-1, −8 -9 and − 14, has been conflicting, depending on the animal models and stage of hypertension progression [29,30], for other MMPs the causative role has been ascertained through elegant gene silencing experiments. For example, gene knockdown of MMP-2, −7 and − 12 were shown to prevent the rise in BP in mice treated with Ang-II and modulate hypertrophic remodeling [31,32]. Overall, these data demonstrate that prohypertensive signaling relies on transcriptional and posttranscriptional mechanisms connected to MMP gene expression, and suggest a functional prohypertensive role for MMPs, with potential implications as new therapeutic targets.

From a mechanistic standpoint, activated MMPs contribute to BP increase by degrading ECM and non-ECM protein components through extracellular and intracellular mechanisms. Extracellular activated MMPs, degrading collagen and elastin fibers, favor the unleashing of VSMCs from anchoring ECM proteins, allowing the VSMC shift from a contractile quiescent status to a hypertrophic and proliferative phenotype [33]. Furthermore, the binding of the same collagen cleavage products to VSMC integrin receptors triggers cell migration and proliferation and the synthesis of altered ECM components [34] (Fig. 2).

Among non-ECM extracellular targets of MMPs, there is TGF-β. MMP-2 activates latent TGF-β by cleavage of its inhibitor-associated peptide. Upon activation, by triggering the signaling pathway of *small mothers against decapentaplegic protein* (SMADs), TGF-β boosts VSMC migration and proliferation and the synthesis of collagen and fibronectin [35]. Additional extracellular targets of MMPs include cadherins [36], calcitonin gene-related peptide, adrenomedullin, β_2 adrenergic receptors and insulin receptors, the cleavage of which associates with potent pro-fibrotic and vasoconstrictor effects [34]. Some more specific endothelial targets of MMPs activity include the vasoconstrictor big ET-1 [37], the e-NOS cofactor heat shock protein (HSP)90 [38], and vascular endothelial growth factor receptor (VEGFR)-2, determining vasoconstriction and capillary rarefaction in spontaneous hypertensive rats, respectively [39]. Among the intracellular targets of MMPs are also calponins, smoothelin and caldesmon, the degradation of which has also been associated with increased VSMC proliferation, contraction, and the development of hypertension [40].

Although we are still far away from completely understanding the complicated pathogenetic mechanisms underlying arterial hypertension, common to all these processes is the increased levels of ROS. Excess ROS generation is observed in most tissue districts involved in hypertension, including the vascular wall, the kidney and the central nervous system [6].

4. Antioxidant therapies in human hypertension: A renewed interest?

The hypothesis of a relationship between ROS and hypertension goes back to the early 1960s, with the pioneering work by Romanowski, performed in normal and hypertensive rat with the prooxidant hydrogen peroxide (H_2O_2) [41]. Since then, interest in the prohypertensive role of ROS has grown relentlessly, to be suddenly boosted-up in the early 1990s, when Nakazono and coworkers showed that treatment of spontaneously hypertensive rats with superoxide dismutase (SOD) mimetics efficiently reduced BP [42]. Since then, each year hundreds of papers have been published on this topic, as shown by a PubMed search (http://www.ncbi.nlm.nih.gov/pubmed) that, interrogated with the key words "hypertension AND systemic blood pressure AND oxidative stress", retrieves a total of more than 1 thousand publications. The functional role of oxidative stress in hypertension has been successfully explored in various experimental models of hypertension, including genetic forms as well as endocrine-, surgical-, and diet-induced hypertension [43]. Hypertensive patients feature levels of plasma H_2O_2 significantly higher than normotensive subjects [44]. This can be the result of (a) a reduced activity and/or decreased content of antioxidant enzymes, including SOD, glutathione peroxidase, and catalase [45]; (b) the result of increased activity of ROS-producing enzymes, including xanthine oxidoreductase, uncoupled NO synthase (NOS) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases [46]. In animal models of hypertension, the knockout of gp91phox and p67phox, NADPH oxidase subunits, blunt the induction of hypertension [47]. Interestingly, in humans, prooxidative polymorphisms in the NADPH oxidase subunits have been associated with increased BP and atherosclerosis [48], while decreased levels of antioxidant molecules, including vitamins A, C, and E, have been demonstrated in hypertensive patients compared with normotensive controls [49].

At the cellular level, ROS affect many important processes in vascular homeostasis. They interact and neutralize the vasodilator NO, forming the more dangerous derivative peroxynitrite ($ONOO^-$) [50]; inactivate protein tyrosine phosphatases; increase intracellular free calcium concentration; and act as second messengers within redox-dependent signaling pathways, including p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK) 1/2, ERK5 and RhoA/Rho-associated protein kinase (ROCK). These mediators induce cell migration and proliferation, as well as the activation of redox-sensitive proinflammatory and proangiogenic transcription factors, including nuclear factor (NF)-κB, activator protein (AP)-1, retinoic acid receptor (RAR) and hypoxia-inducible factor (HIF)-1 [51]. Many of these redox-sensitive transcription factors are involved in the regulation of MMP gene expression [52]. As expected, in spontaneously hypertensive rats, vascular MMP-9 is co-expressed with NF-κB and AP-1, and down-regulated by antioxidants [53]. Of note, in VSMCs isolated from NADPH oxidase subunit p47phox (a) knockout mouse both ROS induction and MMP-2 expression are blunted [54], thus demonstrating that oxidative stress is an important upstream mediator of MMP expression [54].

In this issue of *Vascular Pharmacology*, Blascke de Mello et al. [55], besides confirming the increased expression of MMP-2 in the aorta of hypertensive mice, report a clear down-regulation of the anti-fibrotic protein calponin-1, and suggest that ROS, more specifically peroxynitrites, mediate the increased MMP-2 activity by acting at the post-transcriptional level, unmasking the catalytic site of MMP-2 via a non-proteolytic mechanism that involves the S-glutathiolation of a cysteine moiety in the inhibitory propeptide of MMP-2 [55]. At the same time, the acute administration of tempol, a synthetic antioxidant molecule, by reducing the level of vascular ROS, downregulated MMP-2 activity, restored the expression of calponin-1, and ameliorated the hypertrophic remodeling [55]. Although in this study a clear reduction of BP was not evident, likely due to the acute regimen of tempol exposure, these data are very interesting for at least two reasons:

1) they highlight the ability of tempol, even within brief period of treatment, to restore maladaptive remodeling of the vascular wall, thus suggesting its capacity to reduce BP when given chronically [56];
2) they produce evidence of additional levels of interference by ROS in the etiology of hypertension, going beyond the regulation of redox signaling pathways [57], in this way providing new potential sites of action for antioxidant therapies (Fig. 2).

In line with these results, many antihypertensive drugs currently adopted in clinical practice, including angiotensin-converting-enzyme (ACE) inhibitors, angiotensin (AT)1 receptor blockers, calcium antagonists and β-adrenergic blockers, besides reducing BP, show antioxidant effects and decrease the activity of several vascular MMPs [58]. Along these lines, decreased plasma levels of MMP-2 and -9 have been observed in hypertensive patients treated with losartan (but not with Ramipril) [59]. Similarly, in hypertensive mice losartan, nifedipine, nimodipine, nebivolol and metoprolol were all shown to reduce vascular oxidative stress and the expression of MMPs [60–62].

Overall, these data appear to pave the way for the general adoption of antihypertensive therapies based on natural/dietary antioxidant molecules. However, while in preclinical models of hypertension the administration of natural antioxidants was shown to be mostly successful in terms of BP regulation and vascular remodeling [63], clinical trials in humans have yielded discordant results [64]. In a recent meta-analysis, quercetin [65] and vitamin C [66] supplementations were proven useful in lowering BP, while other antioxidants, including the vitamin A derivative lycopene [67], vitamin D and vitamin E [68–70] yielded disappointing results. The reasons behind this lack of efficacy are not completely clear, and likely involve a combination of causes, including the interindividual variability in bioavailability and variable physiological responses to the consumption of these bioactive substances [71], the inclusion of patients without biochemical evidence of increased oxidative stress, ineffective dosing regimens, and the potential prooxidant capacity of some of these agents [43]. Therefore, if at this time inconclusive clinical evidence precludes clinicians to recommend antioxidants as antihypertensive therapies, fine mechanistic explorations, such as those produced by Blascke de Mello et al. [55] support the rationale for the future exploration of antioxidant pharmacotherapy in the recovery of arterial structural and functional damage, and in the promotion of vascular health. Future research challenges include a more complete functional characterization of vascular antioxidant targets, since this will aid identifying potential responders or non-responders among patients, and consequently tailor integrative co-adjuvant therapies to treat hypertension and its cardiovascular complications.

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