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Forum Editorial

Reactive Oxygen Species and Hypertension: A Complex Association

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THIS FORUM ISSUE of *Antioxidants & Redox Signaling* highlights the role of reactive oxygen species in hypertension. Although the association between free radicals and hypertension was suggested as early as 1960 (30), only in the past decade has an intense interest in the field developed, with the number of publications listed in PubMed with the key words "reactive oxygen species and hypertension" or "oxidative stress and hypertension" increasing from ≈20 in the 1980s to ≈200 in the 1990s to >1,500 in the 2000s (Fig. 1).

Hypertension affects 30% of adults in the Western world and is the leading cause of worldwide death and morbidity (3). Mechanisms leading to high blood pressure (BP) remain largely unknown. Among the many factors implicated in the pathophysiology of hypertension, compelling evidence indicates that reactive oxygen species may be important (21). This is due, in large part, to superoxide ($\bullet O_2^-$) excess (oxidative stress) and decreased nitric oxide (NO) bioavailability in the vasculature and kidneys and to cellular oxidative damage and redox-sensitive cardiovascular remodeling (11, 36).

In human hypertension, biomarkers of systemic oxidative stress, including levels of plasma thiobarbituric acid–reactive substances and 8-epi-isoprostanes, are elevated (8, 27). Factors contributing to increased oxidative stress in human hypertension include decreased antioxidant activity (SOD, catalase), reduced levels of ROS scavengers (vitamin E, glutathione), and activation of phagocytic (neutrophil, macrophage) and nonphagocytic (vascular, renal, cardiac) NAD(P)H oxidase (14, 25, 28, 33). In experimental models, convincing data indicate that oxidative stress plays a role in the pathophysiology of hypertension, particularly in angiotensin II (Ang II)–dependent forms of hypertension. This was first highlighted in a study by Rajagopalan *et al*. (26), in which it was shown that Ang II–mediated hypertension in rats increases vascular superoxide production *via* membrane NAD(P)H oxidase activation. Almost all models of hypertension display some form of oxidative excess (7, 35). Mice deficient in ROS-generating enzymes have lower blood pressure compared with wild-type counterparts, and Ang II infusion fails to induce hypertension in these mice (38). Moreover, experimental models with compromised antioxidant capacity develop hypertension (29). In cultured vascular smooth muscle cells (VSMCs) and isolated arteries from hypertensive rats and humans, NAD(P)H oxidase is upregulated, ROS production is enhanced, redox-dependent signaling is amplified, the thioredoxin system is downregulated, and antioxidant bioactivity is reduced (6, 34, 37). Accordingly, evidence at multiple levels supports a role for oxidative stress in the pathogenesis of hypertension.

Molecular processes underlying ROS-induced cardiovascular and renal changes involve activation of redox-sensitive signaling pathways (10, 22). Superoxide anion and H_2O_2 stimulate mitogen-activated protein kinases, tyrosine kinases, and transcription factors (NFB, AP-1, and HIF-1) and inactivate protein tyrosine phosphatases. ROS also increase $[Ca^{2+}]_i$ and upregulate protooncogene and proinflammatory gene expression and activity (20, 32). These phenomena occur through oxidative modification of proteins by altering key amino acid residues, by inducing protein dimerization, and by interacting with metal complexes such as Fe-S moieties. Changes in the intracellular redox state through glutathione and thioredoxin systems may also influence intracellular signaling events (5, 18).

Based on the extensive literature over the past decade, a strong belief now exists that oxidative stress is involved in the pathophysiology of hypertension. However, many unanswered questions still are asked. In particular, it is unclear (a) whether oxidative stress is a cause or a consequence of high blood pressure, (b) what tips the balance to a prooxidant state, (c) what regulates redox signaling pathways to become injurious *versus* protective, (d) what causes oxidative stress in hypertension, (e) whether oxidative damage of the vasculature or kidneys or both predisposes to hypertension, and (f) whether strategies targeting ROS may have therapeutic benefit in the management of patients with hypertension.

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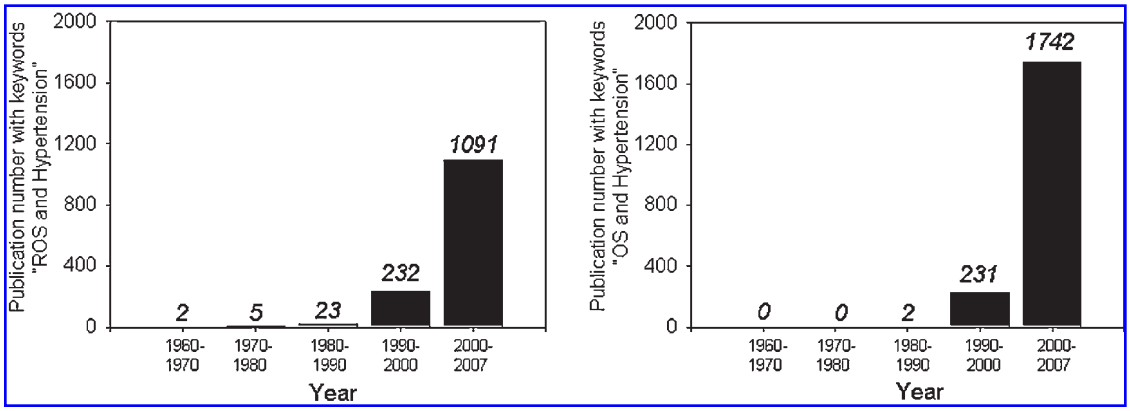

FIG. 1. Bar graphs demonstrate the number of papers with the key words "reactive oxygen species (ROS) and hypertension" and "oxidative stress (OS) and hypertension" published since 1960. Information was derived from PubMed, and articles in all languages were included. Numbers in italics indicate total number of articles, corresponding to the bar graph.

This forum contains eight review articles by experts in the field; these address some of the unresolved issues. The first article in this volume, by Williams and Griendling (39), discusses how ROS influence vascular function and structure and how free radicals contribute to vascular injury and remodeling in hypertension. This review focuses on the signaling pathways whereby ROS control vascular cell function, why different radicals induce opposing effects, and what the implications of aberrant vascular redox signaling are in hypertension. It also highlights the complexity of redox signaling and the importance of distinct spatial and temporal profiles in determining cellular functional responses in an oxidative milieu.

To complement the review of Williams and Griendling (39), Gupte and Wolin (12) dissect how changes in oxygen partial pressure in the vascular wall contribute to oxidant and redox signaling in hypertension. In particular, they introduce the concept that changes in pO_2 influence intracellular redox state, which in turn alters intracellular $[Ca^{2+}]_i$ by influencing ion channel activity, intracellular Ca^{2+} mobilization, and Ca^{2+} sensitivity to myofilaments. Such vascular pO_2 sensing could significantly affect cardiovascular function in hypertension.

It is now well accepted that a major source of vascular and renal $^{\bullet}O_2^-$ is NAD(P)H oxidase (Nox enzymes) (16). The growing field of Noxes and their implication in cardiovascular homeostasis and disease was recently reviewed in a previous forum issue of the journal (13). Mechanisms regulating NAD(P)H oxidase are complex and multifactorial. Here Laurindo *et al*. (17) provide new concepts about some mechanisms that fine-tune oxidase-mediated ROS generation. They focus on protein disulfide isomerase (PDI), a ubiquitous dithiol disulfide oxidoreductase chaperone from the endoplasmic reticulum. They have demonstrated that PDI exerts a functionally relevant regulation of NADPH oxidase activity in vascular smooth muscle and endothelial cells, in a thiol redox-dependent manner. Hence PDI may be a novel target in the regulation of NAD(P)H oxidase.

A second theme that emerges in this forum is the (patho)physiologic role of ROS in the (dys)regulation of endothelial function. Endothelial dysfunction is a common feature in hypertension, occurring in >60% of patients with mild-to-moderate (stage 1) uncomplicated hypertension (23), and probably in most if not all hypertensive subjects with additional risk factors, a not uncommon occurrence. Fundamental to abnormal endothelial function in hypertension is reduced bioavailability of nitric oxide. The article by Watson *et al*. (24) provides a comprehensive overview of how nitric oxide synthase (NOS), oxidative stress, and inflammation affect endothelial function in hypertension and what the putative role of endothelial progenitor cells (EPCs) is in this process. They also introduce the concept that EPCs may act as important markers of vascular health. The number and function of EPCs reflect the balance between endothelial integrity and repair and can be used as a surrogate marker of endothelial function. EPCs have been shown to correlate inversely with various cardiovascular risk factors. However, the data are conflicting with respect to hypertension, as discussed (24).

To understand how ROS regulate endothelial function, Alom-Ruiz and colleagues (2) focus on signaling pathways whereby ROS modulate endothelial function and on the enzyme systems responsible for endothelial cell production of $^{\bullet}O_2^-$. Although NAD(P)H oxidase, possibly Nox4 based (1), seems to be a key in endothelial generation of free radicals, other enzymes including mitochondrial electron-transport chain, xanthine oxidase, cytochrome P450, and uncoupled endothelial NO synthase (eNOS) are important.

Schulz *et al*. (31) expand upon the significance of eNOS uncoupling in the context of oxidative stress and endothelial dysfunction in hypertension and focus particularly on the role of tetrahydrobiopterin (BH_4) in this process. One of the key mechanisms causing eNOS uncoupling is attributed to a decrease in intracellular BH_4 levels. Recognition of this phenomenon has led to clinical trials evaluating therapeutic effects of BH_4 supplementation in the management of hypertension (19). Although results from these trials will be made available only in the coming year, preliminary data are encouraging (36). Moreover. Schultz *et al*. (31) provide practical suggestions as to how eNOS uncoupling could be assessed in the vasculature, a strategy that may become useful in clinical medicine, especially if BH_4 is found to have blood pressure–reducing and cardiovascular protective actions.

The third theme in this forum relates to systems that counterregulate oxidative stress. In particular, Ebrahimian (9) dis-

cusses the role of the thioredoxin system in vascular biology, describing its redox activities and biologic properties in the vascular wall and the implications of thioredoxin dysfunction in the pathogenesis of hypertension. Thioredoxin is emerging as an interesting target in cardiovascular disease, with some evidence indicating beneficial effects of thioredoxin in atherosclerosis, ischemic heart disease, cardiomyopathy, and hypertension (15, 40).

Finally, if oxidative stress is truly implicated in the pathophysiology of hypertension, then strategies to reduce bioavailability of ROS, either by decreasing the production or by scavenging free radicals once formed or both, should have important therapeutic potential in the management of hypertension.

Delles *et al*. (4) provide an up-to-date overview of strategies to target oxidative stress in both experimental models and humans. In addition, they discuss which patients could benefit from antioxidant treatment and underscore the importance of diagnostic testing for oxidative stress before commencing antioxidant therapy. However, currently, no standard procedures evaluate oxidative status in the clinic. Until this matter is resolved, determining whether a patient has increased levels of ROS and oxidative injury will remain a challenge.

Taken together, it is apparent that the association between ROS and hypertension is highly complex. Much research is still needed to understand whether oxidative stress is indeed a primary factor in hypertension, why superoxide-generating systems are upregulated and antioxidant systems are downregulated in hypertension, how free radicals induce cardiovascular and renal injury, what factors predispose to redox-sensitive *versus* redox-insensitive hypertension, and why large antioxidant clinical trial results have been negative, whereas data from experimental studies and small clinical studies are mostly positive. Additionally, sensitive and specific biomarkers and indices that can be used clinically to assess the oxidant/redox status of patients must be developed. Finally, clinical trials designed to address specifically the role of oxidative stress in the development of hypertension must be undertaken. The need to pursue further research in the field of ROS, oxidative stress, redox signaling, and hypertension is paramount. With a greater understanding of processes regulating free radical metabolism and clarification of events that promote oxidative excess, it should be possible to target therapies more efficiently so that the detrimental actions of ROS can be reduced and protective actions of NO can be enhanced. Such approaches would be invaluable in the management of numerous diseases associated with oxidative damage, including hypertension.

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