Does Increased Oxidative Stress Cause Hypertension?

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Hypertension is associated with increased vascular oxidative stress; however, there is still a debate whether oxidative stress is a cause or a result of hypertension. Animal studies have generally supported the hypothesis that increased blood pressure is associated with increased oxidative stress; however, human studies have been inconsistent. Oxidative stress promotes vascular smooth muscle cell proliferation and hypertrophy and collagen deposition, leading to thickening of the vascular media and narrowing of the vascular lumen. In addition, increased oxidative stress may damage the endothelium and impair endothelium-dependent vascular relaxation and increases vascular contractile activity. All these effects on the vasculature may explain how increased oxidative stress can cause hypertension. Treatment with antioxidants has been suggested to lower oxidative stress and therefore blood pressure. However, to date, clinical studies investigating antioxidant supplements have failed to show any consistent benefit. It is noteworthy that lowering blood pressure with antihypertensive medications is associated with reduced oxidative stress. Therefore, it seems that oxygen stress is not the cause, but rather a consequence, of hypertension.

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Metabolism of oxygen by cells generates potentially deleterious reactive oxygen species, including superoxide anions radicals, hydrogen peroxide, and hydroxyl radicals. Under normal physiologic conditions, the rate and magnitude of oxidant formation is balanced by the rate of oxidant elimination. Overproduction of oxidants that overwhelm the cellular antioxidant capacity results in pathogenic oxidative stress. There is increasing evidence that oxidative stress and associated oxidative damages are mediators of vascular injury and may therefore be involved in the pathogenesis of hypertension.

Hypertension is associated with increased vascular oxidative stress; however, there is still a debate whether oxidative stress is a cause or a result of hypertension. In this article, the view that oxidative stress is not a cause but rather a result of hypertension is supported.

To identify oxidative stress as a cause of hypertension, several criteria should be fulfilled: *1*) Oxidative stress should be associated with hypertension. *2*) The mechanism by which oxidative stress causes hypertension should be known. *3*) Oxidative stress should cause hypertension in experimental animals. *4*) Antioxidation should lower blood pressure. The evidence available to fulfill these criteria will be assessed, and it will be shown that there is no evidence to support the concept that hypertension is caused by oxidative stress.

ASSOCIATION BETWEEN OXIDATIVE STRESS AND HYPERTENSION

— Vascular oxidative stress has been demonstrated in spontaneous (genetic) and experimental models of hypertension (1–11). In aortas from hypertensive rats, p22phox mRNA expression and NADH/NADPH oxidase activity are increased (9). Increased oxidative stress has been demonstrated in aortic and mesenteric vessels of stroke-prone spontaneously hypertensive rats (10). Enhanced superoxide anion formation was described in vascular tissues from spontaneously hypertensive and desoxycorticosterone acetate-salt hypertensive rats (11). Vascular oxidative stress has also been demonstrated in many forms of experimentally induced hypertension, such as angiotensin (Ang) II–mediated hypertension, Dahl salt–sensitive hypertension, lead-induced hypertension, obesity-associated hypertension, aldosterone-provoked hypertension, and nitric oxide synthase inhibitor–induced hypertension (1–8). Unlike the findings in animal models, the association between oxidative stress and hypertension in humans is less consistent, and results vary depending on the marker of oxidative damage being investigated (12). Studies using nonspecific markers of oxidative damage have observed higher superoxide and hydrogen peroxide production in hypertensive subjects, which returned to levels observed for control subjects after blood pressure reduction (13). Russo et al. (14) showed that essential hypertension is associated with greater than normal lipoperoxidation and an imbalance in antioxidant status, suggesting that oxidative stress is important in the pathogenesis of essential hypertension or in arterial damage related to essential hypertension. Reductions in superoxide dismutase and glutathione peroxidase activity have been observed in newly diagnosed untreated hypertensive subjects compared with control subjects, with superoxide dismutase activity being inversely correlated with blood pressure within the hypertensive group, but not control subjects (15). Higher production of hydrogen peroxide has also been observed in treated and untreated hypertensive subjects compared with normotensive subjects, with a significant correlation between hydrogen peroxide levels and systolic blood pressure (16). Studies examining more specific markers of oxidative damage have not been as conclusive. Concentrations of F2-isoprostane measured in spot urine were found to be the same in subjects with mild-to-moderate untreated hypertension and normotensive control subjects (17). Ward et al. (18) have recently demonstrated no difference in either plasma or

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Abbreviations: Ang, angiotensin; MAPK, mitogen-activated protein kinase; ROS, reactive oxygen species.

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24-h urinary F2-isoprostanes in treated or untreated hypertensive subjects compared with normotensive control subjects. Tse et al. (19) did not find differences in levels of some antioxidants between hypertensive patients and normal control subjects.

FOOD INTAKE, OBESITY, BLOOD PRESSURE, AND OXIDATIVE STRESS

— Obesity is associated with diabetes and elevated blood pressure (20). Obesity reflects chronic overnutrition and is associated with marked oxidative stress, as reflected by an increase in indexes of lipid peroxidation, protein carbonylation, and oxidative damage of amino acids (21). High caloric intake composed of glucose, lipid, or protein causes an increase in the generation of reactive oxygen species (ROS) by leukocytes and p47phox protein (a key protein in the enzyme NADPH oxidase), along with the activation of nuclear factor-κB and inflammation (22–25). Different macronutrients induce a distinct pattern of increase in ROS generation (26). Glucose induces a peak in ROS generation by both mononuclear cells and polymorphonuclear leukocytes at 2 h, whereas lipid produces a peak at 1 h. The peak increase in ROS generation is the greatest with glucose and the least with protein. Lipid intake causes a prolonged increase in lipid peroxidation. In obese subjects, caloric restriction and weight loss, over a short period of 4 weeks, lead to a decrease in ROS generation by leukocytes and oxidative damage to lipids, proteins, and amino acids (21). Moreover, in normal subjects, a 48-h fast reduced ROS generation, total oxidative load, and oxidative damage to amino acids (27). Ang receptor blockade with valsartan or irbesartan exerted a profound and rapid ROS and inflammation-suppressive effect that may explain the beneficial effect of these compounds (28,29). These beneficial effects were not observed with ACE inhibitors and HMG-CoA reductase inhibitors. The observed association between glucose and macronutrient intake, obesity, Ang II, and oxidative stress may also suggest that oxidative stress plays a role in the pathogenesis of obesity-hypertension.

POSSIBLE MECHANISMS BY WHICH OXIDATIVE STRESS MAY CAUSE HYPERTENSION

— Oxidative stress may contribute to the generation and/or maintenance of hypertension via a number of possible mechanisms, as outlined in Table 1. These include quenching of the vasodilator nitric oxide (NO) by ROS such as superoxide (30); generation of vasoconstrictor lipid peroxidation products, such as F2-isoprostanes (31); depletion of tetrahydrobiopterin (BH4), an important NO synthase cofactor (32); and structural and functional alterations within the vasculature (33). These vascular changes may be mediated in several ways, including direct damage to endothelial and vascular smooth muscle cells, effects on endothelial cell eicosanoid metabolism, altered redox state, increases in intracellular free calcium concentrations, and stimulation of inflammatory and growth-signaling events (33–35). Thus, oxidative stress promotes vascular smooth muscle cell proliferation and hypertrophy and collagen deposition, leading to thickening of the vascular media and narrowing of the vascular lumen. In addition, increased oxidative stress may damage the endothelium and impair endothelium-dependent vascular relaxation and increases vascular contractile activity (30). Oxygen radicals may also induce endothelial permeability, with extravasation of plasma proteins and other macromolecules and recruitment of inflammatory proteins and cells, which could further impair endothelial function and aggravate vascular damage. All these effects on the vasculature may explain how oxidative stress can cause hypertension.

Table 1—*Possible mechanisms by which oxidative stress may cause hypertension*

- Quenching of the vasodilator nitric oxide
- Generation of vasoconstrictor lipid peroxidation products
- Depletion of tetrahydrobiopterin (BH4)
- Damage to endothelial cells
- Damage to vascular smooth muscle cells
- Increase in intracellular free calcium concentration
- Increased endothelial permeability
- Stimulation of inflammation
- Stimulation of growth signaling events

CAN OXIDATIVE STRESS CAUSE HYPERTENSION IN EXPERIMENTAL ANIMALS?

— Indeed several studies showed that oxidative stress plays a role in the pathogenesis of hypertension in various animal models (36). However, others failed to show that oxidative stress induces hypertension. Zhang et al. (37) investigated the involvement of reactive oxygen species on changes in the hemodynamics of conscious normotensive rats. They studied blood pressure responses and cardiovascular mitogen-activated protein kinase (MAPK) activities induced by acutely administered Ang II, or phenylephrine, an α-adrenoceptor agonist, with or without treatment with the antioxidant tempol. They found that Ang II rapidly increased mean arterial blood pressure and phosphorylated MAPKs (ERK1/2, JNK, p38) and thiobarbital reactive substances in the aorta and cardiac left ventricle. Tempol suppressed the augmented phosphorylation of cardiovascular MAPKs and increased thiobarbital reactive substance levels induced by Ang II, but had no effect on arterial pressure elevation. Administration of phenylephrine also showed tempol-sensitive cardiovascular MAPK activation and tempol-insensitive blood pressure elevation. These data indicate that Ang II or phenylephrine provoked an increase in oxidative stress in the cardiovascular tissues and that oxidative stress might not have a major contribution to the hypertensive responses elicited by the vasoconstrictors.

Similarly, Elmarakby et al. (38) showed in Sprague-Dawley rats fed a high-salt diet that two antioxidants, tempol and apocynin, prevented an endothelin-1–mediated increase in plasma 8-isoprostane, an indicator of oxidative stress, and aortic superoxide production, but failed to attenuate blood pressure rise. These findings also suggest that oxidative stress might not have a major contribution to the hypertensive responses elicited by endothelin.

DOES ANTIOXIDATION LOWER BLOOD PRESSURE?

— Some studies in animal models of hypertension, such as Ang II–induced hypertension and salt-sensitive hypertension, and in spontaneously hypertensive rats showed that antioxidation may reduce blood pressure (39–43). However, others failed to show that antioxidation reduces blood pressure (37,38).

The data from clinical studies are less convincing. A number of trials have investigated the use of antioxidant supplements; however, most of the studies did not focus on blood pressure as a primary end point. Galley et al. (44) showed in a small group of normotensive and hypertensive subjects ($n = 38$) that short-term oral high-dose combination antioxidant

therapy reduces blood pressure, possibly via increased availability of nitric oxide. Several studies showed the efficacy of vitamin C in reducing blood pressure (45–47). Unlike these studies, many other studies failed to show blood pressure reduction with antioxidant supplementation. One of the largest studies, undertaken by the Heart Protection Collaborative Group (48), observed no improvement in blood pressure after treatment with an ascorbic acid, synthetic vitamin E, and β-carotene combination versus placebo after 5 years in subjects thought to be at high risk of cardiovascular disease. Kim et al. (49) observed no reduction in blood pressure with long-term moderate doses (500 mg/day) of vitamin C supplementation.

Ward et al. (50) recently showed a significant increase in both ambulatory systolic and diastolic blood pressure in treated hypertensive subjects after 6 weeks of combination vitamin C and grape-seed polyphenols versus placebo or either treatment alone. Palumbo et al. (51) failed to show a blood pressure–lowering effect with vitamin E. They studied the effect of vitamin E supplementation (300 mg/day) on clinic and 24-h ambulatory blood pressure in 142 treated hypertensive patients. After 12 weeks, clinic blood pressure decreased whether or not patients were randomized to vitamin E. Ambulatory blood pressure showed no change in systolic blood pressure and only a small decrease in diastolic blood pressure. In another large study, Rumbold et al. (52) failed to show blood pressure reduction with antioxidant supplementation in nulliparous women between 14 and 22 weeks of gestation. In this multicenter randomized trial, nulliparous women were assigned to daily supplementation with 1,000 mg vitamin C and 400 IU vitamin E or placebo until delivery. Of the 1,877 women enrolled in the study, 935 were randomly assigned to the vitamin group and 942 to the placebo group. There were no significant differences between the vitamin and placebo groups in the risk of preeclampsia, death, or serious outcomes in the infant or having an infant with a birth weight below the 10th percentile for gestational age. Unexpectedly, women in the vitamin group had an increased risk of being admitted antenatally for hypertension and being prescribed antihypertensive drugs. This large study showed that supplementation with vitamins C and E during pregnancy does not reduce blood pressure. In the large Heart Outcomes Prevention Evaluation (HOPE) study, 9,541 subjects ≥55 years of age who were at high risk for cardiovascular events were randomly assigned to receive either 400 IU vitamin E daily from natural sources or matching placebo for a mean of 4.5 years (53). There were no significant differences in the primary end points or in the number of deaths from cardiovascular causes, myocardial infarction, or stroke between the treatment groups. Data on blood pressure levels were not published, which suggests that vitamin E in this study did not reduce blood pressure.

Thus, the evidence to support using antioxidants as a blood pressure–lowering agent is limited. It is noteworthy that antihypertensive drug therapy, in addition to the blood pressure–lowering properties, also has beneficial effects on both oxidative stress and endothelial function. Treatment with a β-blocker or Ang receptor blockers has been shown to reduce both blood pressure and markers of oxidative damage (54). Similarly, other studies have reported beneficial effects on blood pressure, oxidative stress, and endothelial function after treatment with ACE inhibitors (55) or calcium antagonists (56). Because many blood pressures–lowering agents reduce oxidative stress, it seems logical that lowering blood pressure per se rather than the agents used reduces oxidative stress.

CONCLUSIONS — Oxygen stress is associated with hypertension; however, it is unclear whether ROS initiate the development of hypertension, or if they are a consequence of the vascular damage observed in hypertension.

The potential value of antioxidant supplements to reduce blood pressure via reductions in oxidative stress is limited. In some cases, their use may even be detrimental. On the other hand, lowering blood pressure is associated with reduced oxidative stress. Therefore, it seems that oxygen stress is not the cause, but rather a consequence, of hypertension.

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