**Brief Review**

**Endothelial Function in Hypertension**

The Role of Superoxide Anion

Martin McIntyre, David F. Bohr, Anna F. Dominiczak

**Abstract**—Much attention has been focused on the role of nitric oxide in hypertension and cardiovascular disease. More recently, the role of superoxide anion and its interaction with nitric oxide has been investigated in this context. This review will concentrate on the role of superoxide in human and experimental hypertension, paying particular attention to the potential sources of superoxide within the vasculature and discussing some of the molecular mechanisms surrounding its production and dismutation. We discuss what is known about the human superoxide dismutase enzymes. We conclude that the balance between nitric oxide and superoxide is more important than the absolute levels of either alone. (*Hypertension. 1999;34:539-545.*)

**Key Words:** free radicals ■ nitric oxide ■ endothelium ■ hypertension, experimental

For many years, nitric oxide (NO) was regarded as a noxious pollutant in car exhaust fumes, fossil fuel smoke, and cigarette smoke, responsible for acid rain and depletion of the ozone layer. However, interest in the physiological role of this simple diatomic molecule has risen exponentially in the 12 years since the endothelium-derived relaxing factor (EDRF), first proposed by Furchgott and Zawadski in 1980, was identified in 1987 by Palmer et al as NO. In 1992, interest was such that NO was voted “molecule of the year” by *Science* and earned Robert F. Furchgott, Louis J. Ignarro, and Ferid Murad the Nobel Prize in Physiology or Medicine in 1998 for their discoveries concerning “nitric oxide as a signaling molecule in the cardiovascular system.”

Human essential hypertension and several animal models of hypertension are associated with increased peripheral vascular resistance. Because NO is an endogenous vasodilator, there are theoretical reasons why reduced NO production or bioavailability would lead to vasoconstriction and hence, increased peripheral vascular resistance. NO has been found to regulate the tone of normal vessels, including resistance vessels. In addition, NO causes renal vasodilatation with consequent diuresis and natriuresis. These actions would tend to lower blood pressure; therefore, a reduction in this mechanism is another way in which NO deficiency may theoretically contribute to hypertension. However, there are many conflicting reports about the role of NO deficiency in experimental models of hypertension and human essential hypertension. These have been extensively reviewed elsewhere and will not be discussed in this review.

More recently, the role of the superoxide anion (O$_2^-$) has been examined in relation to endothelial dysfunction. NO can be scavenged by O$_2^-$ to form peroxynitrite (ONOO$^-$), effectively reducing the bioavailability of endothelium-derived NO. Therefore, circumstances that result in increased O$_2^-$ can be harmful in several ways: first, by removing the beneficial effects of NO, and second, by the damaging effects of ONOO$^-$, which can be protonated to peroxynitrous acid, the cleavage products of which are among the most reactive oxygen species in the biological system. In addition, several studies have demonstrated that O$_2^-$ can act as a vasoconstrictor.

**Superoxide Anion**

Despite being essential for most forms of life, the high content of O$_2$ in the atmosphere means that oxidation reactions are commonplace in our environment. Although our body uses O$_2$ and oxidation reactions to good effect for generating energy and killing invaders, unwanted side reactions are unavoidable. Therefore, to support aerobic metabolism, mechanisms had to evolve for the biological control of O$_2$. One such mechanism involves its complete reduction to water (Figure 1), which produces the free radical O$_2^-$ by the 1-electron reduction of molecular O$_2$ as the first intermediate in this pathway. The majority of O$_2$ is reduced by the cytochrome oxidase complex, which prevents release of the reactive intermediates. However, the evolution of a variety of superoxide dismutase (SOD) enzymes, catalase, and peroxidase to remove the reactive intermediates suggests that a significant proportion of O$_2$ is reduced by this route. It has been estimated that a typical human cell metabolizes $\approx 10^{12}$ molecules of O$_2$ per day and generates some $3 \times 10^9$ molecules of H$_2$O$_2$ per hour.

Unlike NO, O$_2^-$ is not membrane permeable and is therefore restricted to reacting in the compartment in which it is
**Figure 1. Steps in the 4-electron (e\textsuperscript{−}) reduction of molecular oxygen (O\textsubscript{2}) to water (H\textsubscript{2}O) via superoxide radical (O\textsubscript{2}\textsuperscript{−}), hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}), and hydroxyl radical (OH) intermediates.**

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**O\textsubscript{2}− Production**

The main intracellular source of O\textsubscript{2}− is the respiratory chain of enzymes in the mitochondria,\textsuperscript{14} including the reduced nicotinamide adenine dinucleotide (NADH) dehydrogenase and ubiquinone Q–cytochrome b complex. Mitochondrial O\textsubscript{2}− generation is greatest when the respiratory chain carriers are highly reduced, which is regulated by the availability of NAD-linked substrates, succinate, ADP, and O\textsubscript{2}.\textsuperscript{15} Mitochondrially generated O\textsubscript{2}− spontaneously dismutates to H\textsubscript{2}O\textsubscript{2}, or the reaction is efficiently catalyzed by mitochondrial manganese (Mn) SOD.\textsuperscript{16} This enzyme will be further discussed later. Mitochondrial production of O\textsubscript{2}− can be increased by physiological concentrations of NO, which inhibits cytochrome oxidase and succinate– and NADH–cytochrome c reductase in rat heart mitochondrial membranes.\textsuperscript{17}

Other minor sources of O\textsubscript{2}− include aldehyde oxidase, dihydro-orotic dehydrogenases, flavin dehydrogenases, peroxidases, and autoxidation of a large group of compounds including catecholamines, flavins, and ferredoxin.\textsuperscript{18} In the cerebral circulation at least, another source of O\textsubscript{2}− is cyclooxygenase.\textsuperscript{19} Curiously, autoxidation of tetrahydrobiopterin (BH\textsubscript{4}), 1 of the cofactors essential for NO synthase (NOS) activity, has also been shown to generate O\textsubscript{2}−, which causes contraction in the canine basilar artery.\textsuperscript{20} However, most studies that use electron spin resonance to detect O\textsubscript{2}− suggest that BH\textsubscript{4} is an antioxidant.\textsuperscript{21} Paradoxically, NOS, the enzyme responsible for NO synthesis, can also be a source of O\textsubscript{2}−. This will be discussed in detail later.

**Superoxide Dismutases**

As described above, organisms that depend on oxidative metabolism have evolved a number of enzymes to reduce O\textsubscript{2}−, which is formed as an intermediate. One such family of enzymes are the SODs, which catalyze the reaction of O\textsubscript{2}− with an electron and 2 protons to form H\textsubscript{2}O\textsubscript{2} (Figure 1). Three mammalian SODs have so far been identified: copper/zinc SOD (Cu/Zn SOD; SOD1), Mn SOD (SOD2), and extracellular SOD (EC-SOD; SOD3). The 3 human SOD genes have been cloned and characterized\textsuperscript{22–24} and are shown schematically in Figure 2. Not surprisingly, SOD1 and SOD3 show \textasciitilde50% amino acid homology,\textsuperscript{25} particularly at the catalytic site,\textsuperscript{26} but neither shows any homology to SOD2.

**Cytosolic Cu/Zn SOD**

This enzyme was the first member of the family to be discovered in mammals in 1969.\textsuperscript{27} It is composed of 2 identical 16-kDa subunits, each containing 1 copper and 1 zinc atom. It is located in the cytosol and nucleus of all cell types. The enzyme is very sensitive to cyanide,\textsuperscript{28} which helps distinguish it from Mn SOD, which is relatively resistant.

The human gene for Cu/Zn SOD (Sod1) has been localized to the 21q22.1 region of chromosome 21.\textsuperscript{29} Therefore, patients with Down syndrome (trisomy 21) have an extra copy of the gene and have been shown to have Cu/Zn SOD activity 50% greater than the normal diploid population, in keeping with the gene-dosage effect.\textsuperscript{29} Transgenic rats containing an extra copy of the human Sod1 gene display some of the neurological defects characteristic of Down syndrome, including premature aging, suggesting that this gene is involved in the pathogenesis of Down syndrome.\textsuperscript{30} Whereas the SOD isoenzymes are normally thought to be protective, it is postulated that increased Cu/Zn SOD activity produces increased amounts of H\textsubscript{2}O\textsubscript{2}, which become toxic in the presence of normal catalase activity.\textsuperscript{30} Therefore, increased Cu/Zn SOD activity may only be beneficial when balanced with...
increased catalase activity, and induction of 1 does not necessarily lead to induction of the other.31

The increased Cu/Zn SOD activity in Down syndrome may further indicate a role for O$_2^-$ in hypertension. With a higher Cu/Zn SOD activity, Down syndrome patients will have reduced O$_2^-$ levels. If O$_2^-$ excess is involved in the pathogenesis of hypertension, then one would expect Down syndrome patients to have lower blood pressure. This was recently found to be the case in a well-controlled study by Morrison et al.32

The beneficial effect of increased fluid shear stress on endothelial function has been attributed to increased NO production. However, some of the beneficial effect may also be due to reduced NO scavenging by O$_2^-$, as Sod1 has been shown to be upregulated by laminar shear stress in human aortic endothelial cells in culture.33

**Mitochondrial Mn SOD**

This was the second mammalian enzyme to be discovered in 1973.34 Mn SOD is a homotetramer, each 16-kDa subunit containing 1 manganese atom. It is synthesized in the cytoplasm and directed to the mitochondria by a signal peptide, where it is involved in dismutating the O$_2^-$ generated by the respiratory chain of enzymes described above. The essential role of Mn SOD in maintaining mitochondrial function is demonstrated by the neonatal lethality of mice with targeted disruption of the gene for Mn SOD (Sod2).35 Such Sod2- “knockout” mice die within the first 10 days of life with dilated cardiomyopathy, which is in keeping with the fact that Mn SOD activity is greatest in the heart.

As shown in Figure 2, the human Sod2 gene has several regulatory sequences, which suggest that it is subject to a degree of transcriptional regulation. The nuclear factor (NF)-κB sequence in the 3′-untranslated region is likely to be responsible for the upregulation of Sod2 in response to reactive oxygen species, tumor necrosis factor-α, and shear stress.

**Extracellular Cu/Zn SOD (EC-SOD)**

This is the third and currently the last mammalian SOD to be characterized. It was purified from human lung by Marklund in 1982.36 Most mammalian EC-SOD exists as a homotetramer of molecular weight 130 000, and like Cu/Zn SOD, each 30-kDa subunit contains 1 copper and 1 zinc atom. Again like Cu/Zn SOD, EC-SOD activity is extremely sensitive to cyanide. EC-SOD is produced in fibroblasts and glial cells37 and secreted into the extracellular fluid, where it is the principal SOD.38 The enzyme is a glycoprotein, which binds sulfated polysaccharides, such as heparin and heparan sulfate, via a cluster of 6 basic amino acids.39 Therefore, EC-SOD will exist in the vasculature mainly bound to the surface of the endothelial cells and the extracellular matrix, both of which have an abundance of heparan sulfate, although some enzyme activity can be detected in the plasma.40 A polymorphism in the Sod3 gene has been shown to reduce binding to endothelial cells and to increase serum EC-SOD levels.41 It has not been reported whether the carriers of this polymorphism have altered blood pressure or cardiovascular risk. Because of its location, EC-SOD has been hailed as the principal regulator of endothelium-derived NO bioavailability,42 although cytosolic Cu/Zn SOD is also thought to be important.43

The important antioxidant role of EC-SOD is shown by mice lacking the Sod3 gene. Such Sod3-knockout mice have been generated and characterized.44 When kept under normal laboratory conditions, null mutant mice develop normally and remain healthy until at least 14 months of age, despite no compensatory induction of Cu/Zn SOD or Mn SOD activity. However, when exposed to the oxidative stress of >99% oxygen, the survival time of the homozygous −/− mice was significantly reduced compared with wild-type mice. The cause of death was fulminant pulmonary edema, which is in keeping with the fact that the lung is the tissue containing the highest amount of EC-SOD in mice.

**O$_2^-$ in Hypertension**

Since the landmark study on renovascular hypertension by Goldblatt et al45 in 1934, it has become clear that the renin-angiotensin system plays a major role in hypertension. The mechanism of renin-angiotensin system–induced hypertension has generally been attributed to the vasoconstrictor effects of angiotensin II and the mineralocorticoid effects of aldosterone. However, recent work has revealed an additional potential mechanism. Angiotensin II has been shown to stimulate O$_2^-$ generation by increasing the activity of the enzyme NAD(P)H cytochrome P-450 oxidoreductase, more commonly termed NAD(P)H oxidase, in cultured rat vascular smooth muscle cells46 and in intact aortas of rats made hypertensive by angiotensin II infusion.47 This seems to be a fairly specific effect, as rats made hypertensive to a similar degree by infusion of noradrenalin showed no increase in NAD(P)H oxidase activity.47 Blood pressure and vascular reactivity could be restored by exogenous liposome-encapsulated SOD in the angiotensin II hypertensive rats, but not the noradrenalin hypertensive rats, which further implicates O$_2^-$ in hypertension associated with high angiotensin II states.48

This same group went on to demonstrate increased mRNA expression of the gene p22phox, which encodes NAD(P)H oxidase, in the aortas of rats made hypertensive by infusion of angiotensin II.49 They concluded that this was further evidence that angiotensin II–induced hypertension activates the NAD(P)H oxidase system and that this system is associated with the pathology of hypertension in vivo. They took these studies further by demonstrating that vascular smooth muscle cell hypertrophy induced by angiotensin II is exerted via the angiotensin type 1 receptor, which upregulates p22phox as above. Endogenous SOD enzymes dismutate the resultant O$_2^-$ excess to H$_2$O$_2$, which overwhelms the endogenous catalase system, thereby altering the redox state of the vascular smooth muscle cells, which they speculate causes hypertrophy.50

The only described polymorphism in any O$_2^-$-related gene with regard to cardiovascular disease relates to the p22phox gene. Inoue et al51 described a C242T polymorphism in the potential heme-binding domain of the gene. They found the frequency of the T allele to be significantly reduced in
coronary artery disease patients compared with controls, independent of other known risk factors. Mutations and polymorphisms in the Sod2 gene have been reported in various neurodegenerative diseases, but no Sod gene polymorphisms have been thus far linked to hypertension or cardiovascular disease.

O$_2^-$ has been implicated in other models of experimental hypertension. Grunfeld et al.$^{52}$ used lucigenin chemiluminescence to demonstrate that in aortas of the stroke-prone spontaneously hypertensive rat (SHRSP) model of genetic hypertension, excess O$_2^-$ could exactly account for the reduced bioavailability of NO detected by their porphyrinic microsensor. The following year, Tschudi et al.$^{53}$ used an adapted porphyrinic microsensor to confirm normal NO production but increased decomposition by O$_2^-$ in the mesenteric resistance vessels of SHRSP.

We have recently confirmed that NO production is greater in SHRSP compared with the normotensive Wistar-Kyoto (WKY) strain (Figure 3a).$^{54}$ Despite this greater production, we found that NO bioavailability is reduced in the hypertensive strain (Figure 3b). This suggests that NO may be scavenged by O$_2^-$ in the hypertensive strain. In keeping with this theory, we subsequently demonstrated that O$_2^-$ generation is greater in the aortas of SHRSP and that the source of the O$_2^-$ is the endothelium.$^{55}$ O$_2^-$ generation in the aortas from SHRSP, but not from WKY, could be inhibited by N$^\bullet$-nitro-L-arginine methyl ester, suggesting that endothelial NOS (NOS III) is the enzyme responsible.$^{55}$

O$_2^-$ generation by NOS has been reported before. Purified rat brain NOS (NOS I) has been shown to produce O$_2^-$ in a reaction that is inhibited by N$^\bullet$-nitro-L-arginine methyl ester (L-NAME) but not N$^\bullet$-monomethyl L-arginine.$^{56}$ Heinzel et al.$^{57}$ showed that purified porcine NOS I can produce H$_2$O$_2$ under conditions of low L-arginine concentrations, and Xia et al.$^{58}$ confirmed this finding in intact human kidney cells stably transfected with the rat Nos1 gene, which encodes NOS I. NOS III has also been suggested as the source of O$_2^-$ in human umbilical vein endothelial cells stimulated with native low density lipoprotein, as it can be inhibited by L-NAME.$^{59}$

The reason why NOS changes from generating beneficial NO to generating harmful O$_2^-$ remains unclear. Recent studies have implicated BH$_4$, which is 1 of the essential cofactors for NOS activity.$^{60}$ Wever et al.$^{61}$ used purified NOS III obtained from a baculovirus/Sf9 expression system to confirm that NOS III can indeed generate O$_2^-$.

Figure 3. a. Nitric oxide synthase (NOS) III activity in aortic endothelial cells from Wistar-Kyoto (WKY) and stroke-prone spontaneously hypertensive (SHRSP) female (F) and male (M) rats. Cells were scraped from fresh aortas into homogenizing buffer, and NOS III activity was measured by the l-citrulline assay. Enzyme activity is significantly greater in SHRSP compared with WKY. b. Basal NO bioavailability in the same 4 groups of rats as measured by the change in isometric tension of aortic rings after addition of the NOS inhibitor N$^\bullet$-nitro-L-arginine methyl ester (100 µmol/L) to the organ bath. In contrast to NOS III activity, basal NO bioavailability is significantly greater in WKY compared with SHRSP and in females compared with males in both strains.

O$_2^-$ generation was not inhibited by L-arginine but was dose-dependently inhibited by BH$_4$. Stroes et al.$^{62}$ demonstrated restoration of endothelial function in the forearm of hypercholesterolemic humans by BH$_4$. We have shown that the excess O$_2^-$ in the aortas of SHRSP can be reduced by exogenous BH$_4$. These effects of BH$_4$ may be merely the expected increase in NO production with consequent reduction in O$_2^-$ by scavenging. Cosentino et al.$^{63}$ have tried to address this issue. They showed that in the absence of exogenous BH$_4$, aortas from prehypertensive, 4-week-old SHR treated with A23187 displayed increased O$_2^-$ generation (detected by lucigenin chemiluminescence) and reduced NO release (detected by a porphyrinic microsensor) compared with WKY. In the presence of exogenous BH$_4$, this imbalance was reversed.

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NOS need not be totally dysfunctional to produce O$_2^-$. The C-terminal domain of each isoform shows significant homology with NAD(P)H cytochrome P-450 reductase.$^{64}$ For this reason and also because of its rare spectral characteristics, NOS was thought to belong to the P-450 superfamily of enzymes.$^{65}$ Indeed, NOS I has been shown to reduce certain cytochromes and will reduce O$_2$ to H$_2$O$_2$ in a calmodulin- and NAD(P)H-dependent manner, although this effect is more marked when l-arginine or BH$_4$ is deficient.$^{66}$

It appears, therefore, that NOS is capable of generating both NO and O$_2^-$ and that the relative proportion of each seems to be determined by the local concentration of BH$_4$. How then does BH$_4$ achieve this control? One theory suggests that BH$_4$ stabilizes NOS in the active dimeric form.$^{67}$ Although Raman et al.$^{68}$ have demonstrated crystallographically that NOS III can dimerize in BH$_4$-free solution. Instead, Klatt et al.$^{69}$ proposed that the heme moiety is responsible for dimerization of the enzyme, thus allowing BH$_4$ and l-arginine to bind. Another theory suggests that O$_2^-$ is generated by the oxygenase domain of NOS by dissociation of the ferrous dioxygen complex, which can be prevented by BH$_4$.$^{70}$ Contrary to all of this evidence that BH$_4$ deficiency is so important in O$_2^-$ generation, Brandes et al.$^{71}$ showed that in porcine coronary artery rings, O$_2^-$ generation could be reduced by inhibition of BH$_4$ synthesis. This may reflect reduced autoxidation of BH$_4$ as a source of O$_2^-$ rather than generation by NOS. Interestingly, as long ago as 1987, it was found that BH$_4$ synthesis is impaired in prehypertensive SHR.
albeit in the adrenal cortex.\(^7^1\) If this abnormality were to exist in the endothelium, then it may contribute to the endothelial dysfunction demonstrated in genetically hypertensive rats.

Also in the SHR, Nakazono et al\(^7^2\) were able to lower blood pressure by intravenous injection of a fusion protein of SOD linked to a C-terminal basic domain, which has high affinity for heparin-like proteoglycans on vascular endothelial cells. Using immunohistochemistry, they demonstrated that the fusion protein was localized to the endothelium and to the tunica interna and elastica interna of the aorta and resistance vessels. They also found arterial xanthine oxidase activity and aortic SOD activity to be similar in SHR and WKY. Ito et al\(^7^3\) also found increased $O_2^-$, detected by formazan staining, in the hypertrophied heart of SHR compared with WKY, and in this study, reduced SOD activity rather than increased $O_2^-$ generation was found to be the underlying mechanism.

Endogenous $O_2^-$ has been shown to affect tone in human vessels.\(^7^4\) Increased $O_2^-$ generation, albeit by neutrophils, has also been demonstrated in human essential hypertension.\(^7^5\) Although the mechanism remains unclear, the effect can be reversed by $\beta$-adrenoceptor blockade with celiprolol.\(^7^5\) This is in contrast to an earlier study by Seifert et al,\(^7^6\) who found no difference in neutrophil superoxide-forming NAD(P)H oxidase in human essential hypertension. Red blood cell SOD activity was also found to be reduced in patients with essential hypertension compared with normotensive controls, but the groups were very poorly matched for age.\(^7^7\) Although not directly measured in this study, the implication is that $O_2^-$ would consequently be increased in the hypertensive group, perhaps contributing to the hypertension.

**Conclusion**

There remains little doubt that NO is an important molecule in cardiovascular physiology. Through its interaction with NO, $O_2^-$ is now emerging as a molecule of equal if not greater importance in cardiovascular pathology and perhaps even physiology. It is now becoming clear that the balance between these 2 radicals is more important than the absolute levels of either alone.

The precise source of $O_2^-$ in different pathophysiological circumstances is still a subject of much debate. NAD(P)H oxidase seems to be important in certain circumstances, but through the enzyme NOS, BH$_4$ and/or other cofactors may be important in controlling the balance and determining which of the 2 species predominates. Some of the complex interactions that determine the balance between NO and $O_2^-$ within the vasculature are illustrated in Figure 4. Pharmacological intervention to tip this balance in favor of NO may be useful in the prevention and treatment of a host of diseases common to the Western world, including hypertension, atherosclerosis, diabetes, etc.

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