Cells within the vessel wall have the capacity to produce a variety of reactive oxygen species (ROS: superoxide anion, hydrogen peroxide [H$_2$O$_2$], hydroxyl radical, etc). In diverse experimental models and in patients with disease, levels of ROS in blood vessels increase and contribute to vascular pathophysiology. Although not widely appreciated initially, it has become increasing apparent that relatively low concentrations of ROS can function as signaling molecules, and thus may be involved with normal regulation of vascular structure and function.

Superoxide can be produced by multiple enzymatic and non-enzymatic sources and is the precursor for many ROS including the highly reactive hydroxyl radical (Figure). In addition to the rate of production, steady state levels of ROS are also determined by the activity of an array of antioxidant enzymes including superoxide dismutases (SOD) which convert superoxide to H$_2$O$_2$ (Figure). H$_2$O$_2$ levels are regulated by catalase and a group of glutathione peroxidases which metabolize H$_2$O$_2$ to water (Figure).

Discovered in 1818 by the French chemist Louis-Jacques Thenard, H$_2$O$_2$ has a wide array of uses including as an antiseptic, a bleaching agent, in food processing, and as a fuel for rockets. Much more recently, the role of H$_2$O$_2$ in vascular biology has begun to be appreciated and better defined. In both disease models and in normal aging, local concentrations of H$_2$O$_2$ increase in blood vessels and in vascular cells in culture. Although SOD activity is a major source of H$_2$O$_2$ (Figure), there may be other sources as well. For example, ROS in vascular cells can be produced by NAD(P)H oxidases (Figure) and the NAD(P)H oxidase containing Nox4 [NAD(P)H oxidase 4] may predominantly produce H$_2$O$_2$, rather than superoxide (Figure).

Increasing evidence suggests that H$_2$O$_2$ may play diverse and important roles in vascular biology. Water and H$_2$O$_2$ share many physical features. The addition of a second oxygen atom to water (described as “oxygenated water” by Thenard), however, results in a molecule with many distinct chemical and biological properties. Similar to nitric oxide (NO), H$_2$O$_2$ is chemically more stable than superoxide and other ROS. H$_2$O$_2$ is also relatively cell permeable, although some movement through cell membranes may occur via aquaporins. Both short- and long-term effects of H$_2$O$_2$ on vascular cells continue to be explored. For example, H$_2$O$_2$ produces relaxation of many blood vessels, but can produce vasoconstriction depending on the species, the segment of the vasculature, and the concentration of H$_2$O$_2$ (Figure). Vasodilation in response to H$_2$O$_2$ can occur indirectly through endothelium-dependent relaxation or via direct effects on vascular muscle, possibly including formation of calcium sparks. H$_2$O$_2$ can mediate vascular responses to varied stimuli including endothelium-dependent agonists, increases in blood flow, and arachidonic acid. H$_2$O$_2$ may contribute to increases in myogenic tone with increases in blood pressure. In addition to promoting the formation of other vasoconstrictors, H$_2$O$_2$ may function as one of a family of endothelium-derived hyperpolarizing factors. Along with effects on vascular tone, H$_2$O$_2$ can increase permeability of endothelium.

Regarding more long-term effects, H$_2$O$_2$ has the potential to alter expression of many genes, including some thought to play a major role in vascular biology (Figure). For example, H$_2$O$_2$ activates transcription factors including NF-$\kappa$B, which stimulates expression of endothelial and inducible isoforms of NO synthase (eNOS and iNOS, respectively) and components of NAD(P)H oxidase. Substantial evidence suggests that H$_2$O$_2$ functions as a mediator of vascular growth contributing to vascular hypertrophy during hypertension (Figure). Whether H$_2$O$_2$ plays a role in other structural changes such as inward vascular remodeling is unclear. H$_2$O$_2$ may play a larger role in the development and progression of atherosclerosis than does superoxide and may contribute to vascular injury and cell death, particularly after conversion to hydroxyl radical (Figure). Interestingly, the rate of cardiovascular events in patients with atherosclerosis is inversely related to activity of glutathione peroxidase in erythrocytes, which is consistent with a role for H$_2$O$_2$ in vascular disease.

Although ROS can themselves alter vascular tone, these molecules can also impair vasomotor responses to other stimuli. The impact of superoxide on endothelial function continues to be a major area of research focus. Wei and Kontos provided the first evidence that ROS can impair endothelium-dependent relaxation. Superoxide reacts highly efficiently with NO (Figure), reducing its bioavailability for further signaling. Studies using exogenous application of H$_2$O$_2$ or mice deficient in expression of glutathione peroxidase suggest that H$_2$O$_2$ can also impair NO-mediated signaling in blood vessels. Nevertheless, the mechanism(s) by which H$_2$O$_2$ impairs endothelial function are likely to be more complex. For example, H$_2$O$_2$ may impair endothelium-dependent relaxation after conversion to hydroxyl radical. H$_2$O$_2$ can stimulate NAD(P)H oxidase in vascular cells (Figure), reduce levels of tetrahydrobiopterin, and thus may promote uncoupling of eNOS, further...
Schematic summary of selected changes within the vessel wall in relation to $\text{H}_2\text{O}_2$. Superoxide ($O_2^\cdot$) is produced from molecular oxygen by a variety of sources including NAD(P)H oxidase (Nox). Superoxide can react with nitric oxide (NO) to form peroxynitrite (ONOO$^-$). $\text{H}_2\text{O}_2$ is formed from the activity of superoxide dismutases (SOD) or possibly directly by NAD(P)H oxidase containing Nox4. $\text{H}_2\text{O}_2$ can be degraded to water by glutathione peroxidases (GPx) or catalase (Cat). $\text{H}_2\text{O}_2$ can exert multiple effects in blood vessels including: (1) amplify oxidative stress by further increasing expression and activity of NAD(P)H oxidase, (2) form hydroxyl radical (via an iron dependent process), a highly reactive free radical species, (3) increase expression of arginase, thus reducing levels of L-arginine available to NO synthesis, (4) increase or decrease vascular tone, (5) alter expression of clusters of genes, and (6) increase vascular growth (hypertrophy). See text for details.

There are two isoforms of arginase, and RT-PCR data suggested that only arginase I is expressed in coronary arterioles. Other studies indicate, however, that both arginase I and II are expressed in vascular cells, and this expression can change in disease. $^{57-59}$ Thus, the question of the relative importance of different arginase isoforms under physiological and pathophysiological conditions remains unanswered. Most studies, including the study by Thengchaisi, $^{54}$ used pharmacological inhibitors that do not discriminate between arginase isoforms.

In summary, oxidative stress in the vasculature is common in diverse experimental models and occurs in diseased blood vessels in humans. Because of their complex interrelationships, it has been difficult to fully define the role of specific ROS in blood vessels. There is increasing interest into the role of $\text{H}_2\text{O}_2$ in vascular biology, both as a signaling molecule and a mediator of vascular disease and altered growth. The wide variety of effects that $\text{H}_2\text{O}_2$ has in vascular cells is already impressive in scope but continues to grow.

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Frank M. Faraci

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