NADPH Oxidases: Functions and Pathologies in the Vasculature

Bernard Lassègue; Kathy K. Griendling

Abstract—Reactive oxygen species are ubiquitous signaling molecules in biological systems. Four members of the NADPH oxidase (Nox) enzyme family are important sources of reactive oxygen species in the vasculature: Nox1, Nox2, Nox4, and Nox5. Signaling cascades triggered by stresses, hormones, vasoactive agents, and cytokines control the expression and activity of these enzymes and of their regulatory subunits, among which p22phox, p47phox, Noxa1, and p67phox are present in blood vessels. Vascular Nox enzymes are also regulated by Rac, ClC-3, Poldip2, and protein disulfide isomerase. Multiple Nox subtypes, simultaneously present in different subcellular compartments, produce specific amounts of superoxide, some of which is rapidly converted to hydrogen peroxide. The identity and location of these reactive oxygen species, and of the enzymes that degrade them, determine their downstream signaling pathways. Nox enzymes participate in a broad array of cellular functions, including differentiation, fibrosis, growth, proliferation, apoptosis, cytoskeletal regulation, migration, and contraction. They are involved in vascular pathologies such as hypertension, restenosis, inflammation, atherosclerosis, and diabetes. As our understanding of the regulation of these oxidases progresses, so will our ability to alter their functions and associated pathologies. (Arterioscler Thromb Vasc Biol. 2010;30:00-00.)

Key Words: atherosclerosis ■ blood vessels ■ hypertension ■ NADPH oxidase ■ reactive oxygen species

Our knowledge of the signaling role of reactive oxygen species (ROS) in vascular physiology and pathophysiology has expanded tremendously in the past 15 years. NADPH oxidases (Nox) have emerged as major sources of ROS in the vasculature, multiple Nox subtypes have been cloned and analyzed structurally and functionally, and the relationship of Nox enzymes to signaling pathways, cellular function, and vascular disease has begun to be investigated.

The Nox family consists of 7 catalytic homologues, 4 of which (Nox1, Nox2, Nox4, and Nox5) are found in the vasculature. These enzymes transfer electrons from NADPH to a molecular oxygen producing superoxide (O$_2^-$). Because O$_2^-$ does not readily cross membranes and is short-lived, its effect is mostly local. Depending on Nox subcellular location, O$_2^-$ is released either inside organelles or extracellularly, with corresponding internal signaling or paracrine effects. Superoxide dismutase rapidly converts O$_2^-$ to longer-lasting and membrane-diffusible H$_2$O$_2$, thus modifying the signal and expanding its range of action. Whereas some effects of Nox enzymes, such as inactivation of nitric oxide (NO) in blood pressure regulation are mediated directly by O$_2^-$, many are instead attributable to protein modification by H$_2$O$_2$, including growth signal transduction in vascular smooth muscle cells (VSMC).

In this brief review, we discuss our current understanding of vascular NADPH oxidases, especially their roles in physiology and disease. We first describe each oxidase separately, before presenting an overview of their interactions and connections with other systems.

Materials and Methods

Nox1

Nox1 is expressed in endothelium, smooth muscle, and adventitial fibroblasts, at the plasma membrane, caveolae, and endosomes. Interestingly, in VSMC Nox1 is complexed with the novel activator Noxa1 and the phagocytic organizer p47phox (Figure 1). Unlike Nox1, p47phox requires activation by phosphorylation, allowing for regulation of enzymatic activity. The identity of Nox1 regulatory subunits in other vascular cells is not known. Nox1 also closely associates with protein disulfide isomerase, a chaperone essential to its activity.

Other proteins essential to Nox1 activity do not necessarily associate with it. Because Nox enzymes carry electrons across membranes, they require charge compensation. Agonist-induced Nox1 activity in VSMC endosomes is blocked by deletion of the chloride/proton antiporter ClC-3 and rescued by transfection of intact channels. By exchanging protons for chloride anions, the antiporter prevents oxidase-induced cytosol acidification and accumulation of endosomal negative charges (Figure 1). Targeting anion channels could be used to inhibit oxidases, but their tissue and Nox subtype specificity remain to be investigated.

Nox1 is most highly expressed in intestinal epithelium, because of transcriptional upregulation of its promoter by cytokines involved in host defense. In VSMC, Nox1 is induced by growth factors and vasoactive agents (Table), resulting from preferential activation of another promoter, located further upstream in the gene, in VSMC.
stimulated to grow by injury or angiotensin II (AngII). The resulting longer transcript produces a protein with a slightly longer N-terminus, whose activity is identical to epithelial Nox1. This promoter is responsible for Nox1 upregulation by PDGF or PFG2α via a signaling cascade including protein kinase-δ (PKCδ), EGFR transactivation, and either PI3K, ATF-1, and MEF2B or ERK1/2 and JunB. Binding sites for transcription factors MEF2B and JunB have been identified.\(^{10,14,15}\)

JunB. Binding sites for transcription factors MEF2B and JunB have been identified.\(^{10,14,15}\)

Figure 1. Spatial and molecular organization of vascular Nox enzymes. Nox1, Nox2, and Nox5 are represented here in different cellular compartments but can be located either within cells or at the plasma membrane, thus releasing O$_2^-$/inside vesicles or extracellularly after activation of receptor (R) by ligand (L). O$_2^-$ may affect cytosolic signaling after crossing membranes via anion channels, reversible protonation, or conversion to H$_2$O$_2$.\(^{9}\) In contrast, Nox4 is always intracellular and constitutively produces a higher proportion of membrane-permeable H$_2$O$_2$ than other oxidases.\(^{116}\) All oxidases, except Nox5, form a membrane complex with p22phox. Cytosolic activators vary with oxidase subtype: Rac, p47phox, and Nox1 for Nox1 in VSMC; Rac, p47phox, and p67phox for Nox2; Poldip2 for Nox4; and Ca$^{2+}$ for Nox5. Charge compensation mechanisms are unknown, except for VSMC endosomal CIC-3, which supports Nox1 activity. All vascular cells express multiple Nox subtypes simultaneously.

The role of Nox1 in cardiovascular disease has been studied mainly in hypertension. Vascular or kidney Nox1 is upregulated in experimental models, such as renal transgenic, 2 kidney 1-clip,\(^{16}\) or Dahl salt-sensitive rats.\(^{17}\) AngII-induced hypertension is blunted by in vivo administration of p22phox siRNA\(^ {18}\) or PKC inhibitor, which reduces Nox1 upregulation.\(^ {19}\) Here, p22phox and PKC likely activate Nox1, because Nox2 deletion has no effect. Similarly, p47phox ablation prevents hypertension induced by Bmp4, a Nox1-dependent endothelial cell (EC) agonist.\(^ {20}\) More directly, Nox1 overexpression in smooth muscle cell-targeted transgenics potentiates AngII-induced hypertension and hypertrophy.\(^ {21}\) Conversely, Nox1 deletion improves AngII-induced,\(^ {22}\) but not ROS-independent norepinephrine-induced, hypertension.\(^ {23}\) Unexpectedly, Nox1 deletion prevents AT1R cell surface expression.\(^ {24}\) Whatever the mechanisms, these data implicate Nox1 in AngII-induced hypertension. In contrast, Nox1 deletion does not improve hypertension in renin transgenics,\(^ {25}\) implying that other mechanisms control chronic hypertension.

Because growth factors stimulate ROS production in VSMC, the role of Nox1 in proliferative vascular disease was investigated. Nox1 is activated or upregulated in VSMC treated with AngII, low-density lipoprotein, or AGE.\(^ {1,2,26}\) Nox1 overexpression increases serum-induced proliferation and PDGF-induced migration in VSMC.\(^ {27}\) Conversely, Nox1 deletion inhibits VSMC proliferation induced by serum,\(^ {1}\) thyroid hormone,\(^ {28}\) or PDGF,\(^ {27}\) as well as PDGF or bFGF-induced migration.\(^ {27,29}\) which is rescued by Nox1 transfection.\(^ {29}\) Moreover, Nox1 is activated or upregulated in vessels from diabetic animals.\(^ {30,31}\) Remarkably, not only is injury-induced intimal hyperplasia accompanied by Nox1 upregulation\(^ {1} \) but also it is inhibited by Nox1 deletion.\(^ {27}\) Thus, Nox1 can clearly mediate abnormal vascular growth and possibly atherosclerosis.

In this context, a possible link between Nox1 and vascular inflammation was also investigated. Thrombin increases VSMC Nox1 expression, IL-6 secretion, and NFκB translocation. These latter effects may be mediated by Nox1, as they are inhibited by atorvastatin,\(^ {32}\) which downregulates Nox1.\(^ {1}\) Furthermore, tumor necrosis factor-α or IL-1β induce Nox1-dependent VSMC NfκB activation.\(^ {5}\) Likewise, increased Nox1 expression and activity by hyperhomocysteinemia in rat coronary arteries appears to be mediated by tumor necrosis factor-α.\(^ {33}\) No less important, Nox1 in macrophages is required for foam cell formation, thereby contributing to vascular lesion formation.\(^ {34}\) Therefore, Nox1 appears to mediate vascular inflammation via multiple mechanisms.

Although Nox1 is clearly implicated in vascular pathology, it also has beneficial physiological roles. For example, it is likely responsible for shear-induced outward vessel remodeling, because this response is blocked by deletion of p47phox, but not Nox2.\(^ {35}\) Nox2

Nox2 is found in all vascular wall cells, except VSMC from large arteries, and produces intracellular or extracellular superoxide (Figure 1).\(^ {1,3,6,37}\) Even in large arteries, EC and adventitial fibroblasts are important sources of Nox2-derived superoxide.\(^ {2}\) Nox2 is activated by pathways similar to vascular Nox1 or phagocytic Nox2, such as p47phox phosphorylation by PKC and Sc,\(^ {38,40}\) Similar downstream signals are also affected by Nox1 and Nox2 as described at length in other reviews.\(^ {7}\) For example, Nox2 promotes EC proliferation by p38MAPK and Akt stimulation.\(^ {41}\) On a larger scale, Nox2 also affects vascular function and pathology. Because O$_2^-$ rapidly neutralizes vasodilator NO, Nox2 is expected to induce contraction, Nox2 expression is inversely correlated with endothelium-dependent relaxation in isolated aorta.\(^ {42,43}\) Furthermore, Nox2 deletion inhibits PKC-mediated aortic contraction,\(^ {44}\) restores acetylcholine-induced cerebral artery vasodilatation,\(^ {44}\) and increases contraction in males.\(^ {45}\) These results suggest that Nox2 may affect blood pressure.

A correlation between Nox2 expression and hypertension has been observed repeatedly. Aortic Nox2 is elevated in stroke-prone SHR in rats exposed to aldosterone plus salt and in AngII-infused mice.\(^ {1,46}\) Tempol improves both small intrapulmonary artery Nox2 expression and pulmonary hypertension in renin transgenic rats.\(^ {47}\) As expected, hypertension is worsened by Nox2 overexpression in endothelial-targeted transgenics after acute or chronic AngII treatment.\(^ {48}\) In converse experiments, hypertension can be improved by Nox2 deletion, but results depend on the experimental model. Nox2 ablation in mice reduces systemic hypertension in 2-kidney 1-clip or DOCA salt animals,\(^ {49,50}\) and prevents hypoxia-induced pulmonary hypertension.\(^ {51}\) In contrast, Nox2 deletion does not prevent hypertension induced by AngII infusion but decreases medial hypertrophy,\(^ {1}\) possibly affecting blood pressure later. Likewise, hypertension is unaffected in renin transgenics.\(^ {52}\) These results suggest that
treatments targeting Nox2 could improve some forms of hypertension.

Accumulating evidence suggests that Nox2 in resident EC and adventitial fibroblasts as well as recruited macrophages promote inflammation and atherosclerosis.2,53–55 Nox2 mRNA, O2−/H2O2 production, and monocyte binding are increased by oscillatory shear stress in EC.56 Furthermore, in animal models of surgical vascular injury or high-cholesterol diet, Nox2 is significantly upregulated, at least during the chronic phase of the disease, even in the absence of inflammation.1,57 Similarly, in human vessels Nox2 expression is correlated with lesion severity,1,58 although part of the effect derives from macrophage infiltration in advanced lesions. Moreover, Nox2 deletion greatly reduces descending aortic lesion burden in hyperlipidemic mice.59 Overall, these results favor a causal role of Nox2 in atherosclerosis.

**Nox 4**

Nox4 mRNA is present in all vascular wall cells and is significantly more abundant than other Nox enzymes.1,60–63 The protein is located in perinuclear space or endoplasmic reticulum in EC,64–67 nucleus in EC, and VSMC,4,68,69 and in focal adhesions and stress fibers in VSMC.4,60 Because the only regulatory subunit Nox4 shares with Nox1 and Nox2 is p22phox,70,71 Nox4 was thought to be constitutively active72 and responsible for basal ROS production;70,71 however, a recent report shows that Poldip2 enhances its activity (Figure 1).74

Nox4 is consistently upregulated and acutely activated by TGF-β in all cell types tested.7 In fact, TGF-β is responsible for Nox4 activation in response to other stimuli, such as hypoxia.75 Investigations of downstream signaling pathways suggest that p38MAPK is a target of Nox4,67,76,77 Nox4 also activates the Ras/ERK pathway, JNK and Akt.64,76,78 In addition to tyrosine kinase signaling pathways, Nox4 has been implicated in the activation of Rho in VSMC, consistent with its effects on the cytoskeleton.7,74

Because there is no report to date of genetic models with altered Nox4 expression, current knowledge derives mostly from interventions in cell culture. Nox4 is linked to decreased vascular cell growth in many studies. For example, whereas serum withdrawal upregulates Nox4 mRNA in VSMC and EC,1,61 growth-promoting agents such as AngII, PDGF, IL-1β, thrombin, and phorbol esters downregulate Nox4 mRNA in VSMC and adventitial fibroblasts.1,62,73 However, these results may need to be re-evaluated because of a recent study showing that Nox4 mRNA and protein expressions are not always correlated.79 Nevertheless, Nox4 is required to maintain the quiescent VSMC phenotype and tumor necrosis factor-α–induced apoptosis in EC.60,66,80 In contrast, Nox4 appears to stimulate growth in other instances. Thus, proliferation induced by urotensin or hypoxia (via TGF-β) in pulmonary VSMC requires Nox4.72,74 Similarly, in EC, Nox4 promotes growth and inhibits apoptosis, and Nox4 knockdown impairs endothelial growth factor–tat-induced and

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Upstream Signals</th>
<th>Nox1 Regulation</th>
<th>Downstream Signals</th>
<th>Downstream Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td></td>
<td>Upregulation</td>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Aldosterone</td>
<td></td>
<td>Upregulation</td>
<td></td>
<td></td>
<td>111</td>
</tr>
<tr>
<td>AngII</td>
<td>Ca2+</td>
<td>Upregulation</td>
<td>P-Akt</td>
<td>Hypertrophy</td>
<td>1, 112</td>
</tr>
<tr>
<td>PKC</td>
<td></td>
<td>Activation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rac1</td>
<td></td>
<td></td>
<td>SHP-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Src</td>
<td></td>
<td></td>
<td>Inactivation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI3K</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bFGF</td>
<td>PI3K</td>
<td>Activation</td>
<td>JNK</td>
<td>Migration</td>
<td>29</td>
</tr>
<tr>
<td>PKC</td>
<td></td>
<td></td>
<td>P-paxillin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rac1</td>
<td></td>
<td></td>
<td>MMP2, MMP9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclic stretch</td>
<td></td>
<td>Upregulation</td>
<td></td>
<td></td>
<td>113</td>
</tr>
<tr>
<td>IL-1β</td>
<td></td>
<td>Activation</td>
<td>NFκB</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>LDL oxidized</td>
<td></td>
<td>Upregulation</td>
<td></td>
<td></td>
<td>1, 25</td>
</tr>
<tr>
<td>LDL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDGF</td>
<td>PKC</td>
<td>Upregulation</td>
<td>NFκB</td>
<td>Hypertrophy</td>
<td>1, 27, 114, 115</td>
</tr>
<tr>
<td>PGF2α</td>
<td>EGFR either PI3K, ATF-1, MEF2B or ERK, JunB</td>
<td>Upregulation</td>
<td>MCP-1</td>
<td>Migration</td>
<td></td>
</tr>
<tr>
<td>PMA</td>
<td></td>
<td>Upregulation</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Serum</td>
<td>Upregulation</td>
<td>Proliferation</td>
<td></td>
<td></td>
<td>1, 27</td>
</tr>
<tr>
<td>Statins</td>
<td>Downregulation</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>T3</td>
<td>Upregulation</td>
<td></td>
<td></td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Thrombin</td>
<td>Upregulation</td>
<td></td>
<td>NFκB</td>
<td>Proliferation</td>
<td>1, 32</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Activation</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

EGFR indicates endothelial growth factor receptor; LDL, low-density lipoprotein; TNF, tumor necrosis factor.
human immunodeficiency virus–tat–induced proliferation.54,78,81

Further studies are required to reconcile these conflicting results.

A similar conundrum holds for the role of Nox4 in migration. Whereas Nox4 siRNA decreases PDGF-induced VSMC migration and wound-healing–activated EC migration,74,81 Nox4 overexpression also decreases migration in PDGF-stimulated VSMC and adventitial fibroblasts exposed to AngII.62,74 It is likely that too little Nox4 prevents focal adhesion formation, whereas too much Nox4 prevents focal adhesion dissolution, both of which are required for cell motility.

In some cases Nox4 appears linked to pathways protecting vessels against disease. In EC, Nox4 is upregulated by physiological shear stress and downregulated by pathological stress.56,82 Similarly, Nox4 is increased during redifferentiation of smooth muscle after vascular injury.1 However, Nox4 expression is also correlated with deleterious responses. The proinflammatory mediators tumor necrosis factor-α and oxidized phospholipid Ox-PAPC increase Nox4 expression or activity, respectively.80,83 Basal and urostenol-induced pro-fibrotic PAI-1 gene expression in pulmonary artery VSMC is dependent on Nox4, and Nox4 downregulation blocks IL-8, MCP-1, low-density lipoprotein receptor, and ROS production in EC stimulated with Ox-PAPC.76,77,83 Furthermore, Nox4 is elevated in cerebral aneurysms and in vessels from diabetic mice.30,64,85 (except31). Of interest, treatment with the PPARγ agonist rosiglitazone mitigates Nox4 upregulation.86

Overall, our knowledge of Nox4 in the vasculature is incomplete. Current evidence suggests that it is involved in numerous essential cell pathways mediating differentiation, growth, and migration. Its role is still controversial, suggesting that a central aspect of its function remains to be discovered.

**Nox5**

Nox5 differs from other Nox enzymes by its additional N-terminal regulatory domain. Nox5, which requires no additional subunit, is activated by calcium binding to N-terminal EF-hands (Figure 1). Calcium sensitivity is increased by calmodulin and phosphorylation by PKC.7 In transfected leukemia cells, Nox5 is activated by H2O2 in a positive feedback loop involving c-Abl.87 Five splice variants with different tissue distributions are known: Nox5α, Nox5β, Nox5γ, Nox5δ, and Nox5γ, a short form without calcium-binding domain. Multiple isoforms are expressed in the vasculature.58 Within cells, Nox5 can be found in cytoskeletal fraction, endoplasmic reticulum, or plasma membrane.59–91

Because Nox5 is not present in rodents, experimental models are limited to cultured cells and isolated tissue. In VSMC, Nox5 participates in PDGF-induced proliferation via the JAK/STAT pathway.92 In EC, Nox5 overexpression slightly increases proliferation and formation of capillary-like tubes, whereas Nox5 depletion reduces thrombin-stimulated growth and tube formation.93 In intact vessels, adenosine-mediated Nox5 overexpression paradoxically increases endothelial NO synthase activity, but as expected, reduces bioavailable NO via inactivation by O2-93 leading to impaired endothelium-dependent relaxation and increased phenylephrine-induced contraction. One study shows that atherosclerosis increases Nox5 expression and calcium-sensitive oxidase activity in coronary arteries. Nox5 is detected in the endothelium of control arteries, in the neointima of diseased arteries, and in smooth muscle underlying complex lesions in arteries with advanced atherosclerosis.94

These studies are provocative, suggesting an important role for Nox5 in vascular function. Clearly, additional work is needed to further explore its physiological and pathological roles.

**Discussion**

**Interactions Between Oxidases**

Because most cells simultaneously express multiple Nox enzymes, some of their functions may be redundant. For example, both Nox2 and Nox4 in EC are required for the angiogenic response and participate in serum-induced prolif-eration.77,41,81,95 Both enzymes are similarly regulated by shear stress56 and colocalize with endoplasmic reticulum markers,37 and knockdown of one subtype upregulates the other,96 suggesting that their functions are overlapping, although not entirely identical.41

Most often, however, Nox enzymes in the same cell mediate distinct functions. For example, in VSMC from large arteries, Nox1 is required for hypertrophy and proliferation,1 whereas Nox4 mediates differentiation.60,80 These enzymes respond to different agonists,1,60 participate in migration via different mechanisms,27,74 and have distinct localizations.4 Similarly, in transfected HEK293 cells, Nox2 and Nox4 are expressed in different compartments, and each responds to different agonists and activates distinct signaling pathways.97 Therefore, subcellular localization seems to be an essential factor in determining Nox function.

With regard to vascular disease, multiple NADPH oxidases appear to contribute to the pathophysiological response. Both Nox1 and Nox2 have been implicated in hypertension,59–51,98,99 because they contribute directly to blood pressure elevation and to end-organ damage or remodeling.24,98,100 The expression of
activates Nox enzymes and increases their own production in a Nox-dependent manner.107 In hypertension, AngII stimulation of these cells enhances mitochondrial ROS production in a Nox-dependent manner.107 In hypertension, Nox activation leads to the formation of peroxynitrite, which upregulates endothelial NO synthase, leading to a dramatic enhancement of \( \text{O}_2^{-\cdot} \) production.103 Moreover, ROS can also activate Nox enzymes and increase their own production in a positive feedback loop (Figure 2).47,48,103,108–110 Such self-reinforcing loops may set new homeostatic points of ROS production and lock the organism in a sustained pathological state.

**Conclusion**

The evidence summarized in this review clearly shows that Nox enzymes are essential to normal vascular function and participate in the development of vascular disease. They modulate intracellular signaling pathways to regulate cell survival, vessel contraction, and relaxation. In pathological conditions, they contribute to VSMC proliferation and migration, angiogenesis, inflammation, hypertension, and medial hypertrophy. Because of their varied and essential functions, it is not surprising that antioxidants designed to scavenge ROS produced from these enzymes provide ineffective protection against vascular disease. The work described here strongly argues for a change in therapeutic strategies to target only deleterious sources of ROS while leaving intact those that are required for normal vascular function.

That said, more research is necessary to fully understand the roles of different Nox enzymes in the vasculature. Additional studies should focus on identifying the specific molecular pathways that are targets of each Nox. The creation of tissue-specific, genetically modified animals will permit a better analysis of their roles in physiology and disease. Moreover, subtype-specific inhibitors are needed to allow the field to advance therapeutically once pathological targets have been identified. Studies such as these will allow us to truly test the oxidative hypothesis of vascular disease.

**Sources of Funding**

This work was supported by National Institutes of Health grants HL38206, HL058863, and HL095070.

**Disclosure**

None.

**References**


Lassègue and Griendling  Vascular NADPH Oxidases


Arterioscler Thromb Vasc Biol  February 2010


NADPH Oxidases: Functions and Pathologies in the Vasculature
Bernard Lassègue and Kathy K. Griendling

Arterioscler Thromb Vasc Biol. published online November 12, 2009;
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/early/2009/11/12/ATVBAHA.108.181610.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/