Role of Oxidative Stress in the Pathogenesis of Abdominal Aortic Aneurysms

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Abstract—The role of inflammation in the pathogenesis of abdominal aortic aneurysms (AAA) is well established. The inflammatory process leads to protease-mediated degradation of the extracellular matrix and apoptosis of smooth muscle cells (SMC), which are the predominant matrix synthesizing cells of the vascular wall. These processes act in concert to progressively weaken the aortic wall, resulting in dilatation and aneurysm formation. Oxidative stress is invariably increased in, and contributes importantly to, the pathophysiology of inflammation. Moreover, reactive oxygen species (ROS) play a key role in regulation of matrix metalloproteinases and induction of SMC apoptosis. ROS may also contribute to the pathogenesis of hypertension, a risk factor for AAA. Emerging evidence suggests that ROS and reactive nitrogen species (RNS) are associated with AAA formation in animal models and in humans. Although experimental data are limited, several studies suggest that modulation of ROS production or activity may suppress AAA formation and improve experimental outcome in rodent models. Although a number of enzymes can produce injurious ROS in the vasculature, increasing evidence points toward a role for NADPH oxidase as a source of oxidative stress in the pathogenesis of AAA. (Arterioscler Thromb Vasc Biol. 2007;27:000-000.)

Key Words: aneurysm ■ reactive oxygen species ■ oxidative stress ■ NADPH oxidase ■ inflammation

Abdominal aortic aneurysms (AAA) occur in up to 9% of humans >65 years of age and are characterized by localized structural deterioration of the aortic wall, leading to progressive aortic dilatation. The most dreaded complication of AAA is rupture, the likelihood of which is directly related to aneurysm diameter. Over the last decade it has become obvious that AAA are not passively enlarging vascular structures, but exhibit features of inflammation and tissue degeneration common to many forms of chronic disease. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) have been shown to play causal roles in many chronic disease states, including cardiovascular diseases such as atherosclerosis and hypertension. The continued formation of ROS during normal metabolism, or the enhanced production of ROS associated with localized inflammatory responses, can cause progressive cell and tissue damage (e.g., oxidative stress), and increasing evidence points to these factors in the pathogenesis of AAA. The purpose of this review is to critically analyze the evidence linking oxidative stress with the pathogenesis of AAA. We will also briefly discuss the potential role of nitrosative stress in AAA formation.

Inflammation, AAA, and Oxidative Stress

Many studies published over the past decade support the view that inflammation is not only associated with the clinical presence of AAA, but that it actually plays a key role in the pathogenesis of the disease. Examples of associations between AAA and inflammation include an increase in systemic CRP levels and a local influx of inflammatory cells, particularly lymphocytes and macrophages, into the aorta. These inflammatory responses could promote aneurysm formation through several mechanisms. For example, infiltrating leukocytes are major sources of matrix metalloproteinases (MMPs) and serine proteases that degrade structural proteins such as elastin, collagen, and laminin, thereby weakening the aortic wall.

Also, infiltrating immune cells can exacerbate tissue injury through release of cytokines (e.g., interleukin (IL)-6, MCP-1, osteopontin), leading to further recruitment of immune cells and induction of apoptotic cell death pathways such as Fas and perforin. These pathways can lead to death of smooth muscle cells (SMC), which are largely responsible for production of the aortic extracellular matrix.

Additional proteases may be released from dying SMC, further contributing to matrix degradation. This enhanced degradation of structural proteins, together with a reduced capacity to synthesize new matrix proteins, most likely act in concert to progressively weaken the aortic wall, resulting in dilatation.

Oxidative stress is invariably increased in, and contributes importantly to, the pathophysiology of inflammation. Oxidative stress can be defined as tissue damage occurring secondary to...
increased production and/or decreased destruction of ROS. Thus, the balance between production and destruction of ROS depends not only on the activity of ROS-generating systems, such as NADPH oxidase, but also on levels of endogenous cellular antioxidants and antioxidant enzymes. A comprehensive review of the factors that regulate oxidative stress in the vasculature is beyond the scope of this article. The reader is referred to several recent review articles devoted to this purpose.12–14 Here, we intend to focus on the evidence that oxidative stress is increased in AAA, the potential enzymatic sources of the ROS, and the mechanisms whereby oxidative stress may contribute to the pathogenesis of AAA.

### Evidence of Increased Oxidative Stress in Human AAA

The notion that ROS and RNS may be involved in the pathogenesis of human AAA has been considered by investigators for many years. In 1987, Dubick et al reported that levels of ascorbic acid and Cu, Zn superoxide dismutase (SOD) activity were reduced in tissue samples from patients with AAA and atherosclerotic occlusive disease (AOD) as compared with nondiseased aorta from a different group of patients.15 Subsequently, the same investigators showed that MnSOD, glutathione peroxidase, and glutathione reductase activities were reduced, while levels of lipid peroxidation products were increased, in AAA and AOD tissues as compared with nondiseased aorta.16 In addition, Zhang et al showed evidence of increased expression of inducible nitric oxide synthase (iNOS) in the media and adventitia of human AAA tissues as compared with normal aorta.17 The iNOS expression was primarily localized to lymphocytes, macrophages, and SMC and was associated with positive immunostaining for nitrotyrosine, a marker for amino acid oxidation induced by several oxidant species, including peroxynitrite. Nitrite levels (a marker of nitric oxide formation) were found to be markedly increased in human aneurysms (at a level that can potentially degrade elastin).18 In contrast, neither nitrotyrosine nor iNOS were detected in normal aorta.17 Collectively, these data suggest that ROS and RNS are increased in human AAA tissues. Because the AAA tissues were compared with nondiseased aorta obtained from different groups of patients, however, it is not possible to conclude from these studies whether oxidative and/or nitrosative stress is specifically localized to AAA segments, or whether it is diffusely increased throughout the aorta of these patients.

Plasma levels of vitamin E have been reported to be reduced in patients with atherosclerosis as compared with age- and sex-matched controls, which presumably reflects an increased state of oxidative stress in these patients.19 Very little is known about levels of vitamin E in patients with AAA. In a small study, Sakalihasan et al reported that plasma levels of vitamin E were reduced in patients with AAA as compared with patients with coronary artery disease in the absence of AAA.20 These intriguing findings raised the possibility that AAA in humans is associated with a greater degree of oxidative stress than is observed in patients with generalized atherosclerosis. Alternatively, it is possible that increased oxidative stress was related to factors other than AAA in this patient population.

### Potential Sources of Oxidative Stress in AAA

Several lines of evidence suggest that the local environment within AAA may be especially conducive to the development of oxidative stress. First, in AAA, the large numbers of infiltrating leukocytes, particularly macrophages, can generate copious amounts of O$_2^-$ and other oxidant species, such as H$_2$O$_2$, via the membrane-bound NADPH oxidase. Myeloid cells—macrophages and neutrophils—also contain myeloperoxidase, which converts H$_2$O$_2$ into HOCl. HOCl can react with the apolipoproteins in LDL, leading to formation of secondary reaction products (chloramines) that can initiate lipid peroxidation and cause tissue damage. In addition, vascular SMC, endothelial cells, and fibroblasts are capable of forming O$_2^-$ via several pathways, including a nonphagocytic NADPH oxidase. Interestingly, pulsatile and mechanical stretch have been demonstrated to increase ROS production by NADPH oxidase in SMC, which in turn activates NF-$\kappa$B and increases matrix metalloproteinase (MMP)-2 expression and activity.21,22 Thus, mechanical forces present in AAA may further exacerbate oxidative stress, inflammation, and aortic remodeling through this mechanism.

The tissue-infiltrating macrophages associated with inflammatory sites, as well as activated SMC, also release proinflammatory cytokines that not only lead to recruitment of additional inflammatory cells, but also induce production of ROS by upregulation of NADPH oxidase activity in resident vascular cells.23,24 In addition, some studies suggest that tumor necrosis factor (TNF) expression is redox regulated and/or that ROS are involved in TNF signaling.25–27 These processes represent only a few examples of the complex interplay between inflammation and oxidant stress that may be relevant to AAA.

Lipoxygenases catalyze the oxidation of polyunsaturated fatty acids, yielding a variety of bioactive mediators that are involved in many disease states, including atherosclerosis.28 Lipoxygenases are also capable of directly generating ROS, or amplifying ROS production by leukocytes, through several mechanisms. Although the contribution of lipoxygenases to the pathogenesis of atherosclerosis is well established, very little is known about the role of lipoxygenases in AAA formation. Recently, 5-lipoxygenase was reported to promote AAA formation in hyperlipidemic mice.29 Although 5-lipoxygenase is not traditionally viewed to be an ROS-producing enzyme,30 it was reported to contribute to O$_2^-$ release in skeletal muscle.31 The role of 12/15-lipoxygenase in AAA formation has not been examined. However, expression of this enzyme, which plays an important role in oxidation of LDL, was reported to be upregulated in an animal model of AAA formation.32

In addition to lipoxygenase, cyclooxygenase- and cytochrome P450-mediated metabolism of fatty acids may produce ROS in the vasculature (for review, see reference 33). A number of studies suggest that cyclooxygenase (COX) may be involved in the pathogenesis of AAA. Both the expression of COX-2, and the formation of its metabolite prostaglandin (PG) E$_2$, are upregulated in human AAA.34,35 Also, inhibition of COX attenuates AAA progression in animals and perhaps in humans.36–38 Because COX and its metabolites could modulate AAA formation through numerous mechanisms other than ROS production, the beneficial effects of COX inhibition do not definitively implicate oxidative stress in this process.
Endogenous vascular wall cells and infiltrating myeloid cells are also significant sources of nitric oxide (NO), formed by the enzymatic actions of NOS. Whereas myeloid cells and SMC contain an inducible form of this enzyme (iNOS), the enzyme is constitutively expressed in endothelial cells (eNOS). The neuronal isoform (nNOS) is also expressed in SMC.39 Endothelial production of NO, and its subsequent reactions with SMC, are essential components in the normal regulation of blood vessel dilation. However, the production of large quantities of NO by eNOS may lead to tissue injury through several mechanisms, eg, by reaction of NO with metals to form metal nitrosyl complexes, or with molecular O2 or O2− to form RNS.12 Moreover, when eNOS becomes uncoupled from its cofactors, it can generate large amounts of O2−. The reaction product of O2− and NO, peroxynitrite (ONOO−), is highly reactive—more reactive than either O2− or NO alone—and the subsequent protein nitration can lead to inactivation of vasculoprotective enzymes, including glutathione transferase (important in removal of products of lipid peroxidation), ceruloplasmin (prevents metal-dependent ROS formation), PG I2 synthase, and manganese superoxide dismutase (MnSOD).40–43 Thus, production of injurious ROS and RNS by NOS could contribute to the pathogenesis of AAA through several mechanisms.

Although it is clear that many different enzymes may produce ROS and RNS in the vasculature, increasing evidence points toward a critical role for NADPH oxidase as a source of ROS in pathophysiological states. Many factors present in AAA could potentially stimulate vascular production of ROS by NADPH oxidase. In addition to cytokines and mechanical stretch, which were discussed previously, growth factors (eg, angiotensin II and platelet-derived growth factor), lipid mediators (eg, leukotrienes and lysophosphatidic acid [lysoPA]), and oxidized LDL may upregulate vascular NADPH oxidase activity (for review, see reference 44). Moreover, there is increasing evidence that ROS and lipid peroxidation products themselves may upregulate NADPH oxidase activity, suggesting a "feed-forward" mechanism of amplification of ROS production.45,46 The potential mechanisms linking inflammation, mechanical forces, and oxidative stress to vascular NADPH oxidase activity in AAA are shown in Figure 1.

Potential Mechanisms Whereby Oxidant Stress Could Contribute to the Pathogenesis of AAA

Recruitment of inflammatory cells into the aortic wall is a critical part of the process of AAA formation both in humans and experimental animal models. Chemotactic cytokines and adhesion molecules are two key factors that regulate leukocyte recruitment into the vasculature, and both can be modulated by ROS (for review, see reference 47). For example, ROS increase production of monocyte chemoattractant peptide-1 (MCP-1) and stimulate invasion of monocytes into the vascular wall.23,48 Also, H2O2 was shown to play a key role in upregulation of IL-8 production and intercellular adhesion molecule-1 (ICAM-1) expression in endothelial cells.49 In addition, H2O2 rapidly upregulated P-selectin expression in endothelial cells, thereby inducing PMN adhesion.50 Although the relevance of this latter finding to the pathogenesis of AAA remains to be determined, levels of P-selectin were reported to be increased in patients with AAA, and expression of P-selectin in the aorta is markedly upregulated during experimental AAA formation.51,52 The effects of oxidative stress on inflammatory cytokine production and adhesion molecule expression are likely mediated, at least in part, through activation of NFκB, which functions as a molecular switch linking ROS to inflammation in many chronic disease states (reviewed in reference 53).

Osteopontin is an inflammatory cytokine whose expression in endothelial cells was reported to be upregulated by oxidative stress induced by angiotensin II.53 Interestingly, osteopontin was implicated in the pathogenesis of AAA induced by infusion of angiotensin II in apolipoprotein E−deficient mice.55 Also, osteopontin was shown to upregulate NADPH oxidase, ROS production, and pro-MMP9 activity in myofibroblasts and SMC.56 These properties suggest that osteopontin could play a dual role as both a transducer and amplifier of oxidant stress during AAA formation.

Leukocytes are also important producers of tissue proteases, particularly MMPs, which play a critical role in the pathogenesis of AAA. The balance between the MMPs and their tissue inhibitors is an important determinant of the structural integrity of the arterial wall. In human AAA, MMP2 and MMP9 appear to be the MMPs most prominently expressed. Furthermore, both genetic and pharmacological modulation of MMP activity has a protective impact on AAA in several animal models of the disease and in human subjects.57–61 For example, mice lacking MMP2 or MMP9 are protected against AAA formation.62,63 One of the main modulators for MMP activation is oxidative stress.64,65 Indeed, ROS have been reported to activate MMPs, thus leading to extra-cellular matrix degradation.65 Furthermore, in thoracic aneurysms, MMP activity was enhanced in cells that also overexpressed NADPH oxidase, a vascular source of ROS.64 Moreover, peroxynitrite was shown to increase MMP2 and MMP9 activity, and to facilitate vascular remodeling, in a murine model of arteriovenous fistula.65 Thus, ROS and RNS, as well as their reaction products, can potentially modulate proteases to induce vascular remodeling.

The plasminogen–plasmin system is another proteolytic mechanism involved in the pathogenesis of AAA. Urokinase-type plasminogen activator (uPA) is required for AAA formation induced by angiotensin II infusion, and plasminogen activator inhibitor type 1 (PAI-1), an endogenous inhibitor of plasminogen, is decreased in human AAA tissue.66,67 In addition, overexpression of PAI-1 inhibited AAA formation induced by xenotransplantation.68 Although little is known about how oxidative stress may regulate the plasminogen activation path-
Evidence of a Pathological Role for Oxidative Stress in AAA

Although it is clear from the preceding sections that human AAA display evidence of increased oxidative stress, and that oxidative stress can potentially contribute to the pathologic features of AAA, none of the aforementioned studies examined whether oxidative stress is localized to AAA segments in humans, or whether it is nonspecifically associated with AAA in these patients. Demonstration of enhanced oxidative stress locally within AAA segments (as compared with nonaneurysmal (NA)aortic segments from the same patients) would support the hypothesis that oxidative stress contributes to the pathogenesis of AAA. Miller et al addressed this important question by examining segments of infrarenal AAA and adjacent NA tissues from patients undergoing elective aneurysm repair. Histology showed atherosclerotic changes (eg, neointimal proliferation, foam cell formation) in both AAA and NA tissues, but extensive medial degeneration, typically associated with localized, intense inflammatory cell infiltration and \( \text{O}_2^- \) production, was observed predominately in the AAA tissues. Superoxide levels were 2.5-fold higher in the AAA segments compared with the adjacent NA segments. Formation of thiobarbituric acid-reactive substances and conjugated dienes, two indices of lipid peroxidation, were increased 3-fold in AAA compared with NA segments. In addition, immunostaining for nitrotyrosine was significantly greater in AAA tissue.

The authors also investigated the expression and activity of NADPH oxidase, an important source of ROS in the vasculature (for review, see 80), in AAA and NA tissues. Basal and NADPH-stimulated production of superoxide was increased in AAA segments as compared with NA segments and was strongly attenuated by diphenylene iodonium, a nonspecific inhibitor of NADPH oxidase. Additionally, expression of the NADPH oxidase subunits \( p47^{phox} \) and \( p22^{phox} \) was increased in AAA segments compared with NA segments. Ejiri et al likewise reported that levels of \( \text{O}_2^- \), and expression of \( p22^{phox} \), were increased in human thoracic aortic aneurysm tissues as compared with control thoracic aorta. In the latter study, the control aortic tissues were obtained from a different group of patients; however, they were well-matched with regard to age and risk factors for vascular disease. These findings demonstrated that oxidative stress is increased locally at the site of aortic aneurysm disease in humans. Moreover, upregulation of NADPH oxidase was detected in conjunction with increased oxidative stress, suggesting that this ROS-generating enzyme could be involved in the pathogenesis of aortic aneurysms.

As the next step in testing the hypotheses that oxidative stress and/or NADPH oxidase contribute to the pathogenesis of AAA, several groups have turned to animal models of AAA formation. Currently, most investigators work with one of several rodent models, which can be categorized as genetic, chemically induced (eg, elastase infusion, calcium chloride application), immunogenic (eg, aortic allotransplantation), or angiotensin II–dependent (reviewed in 81). Yajima et al performed DNA microarray analysis to examine expression of over 8000 genes during formation of AAA in the elastase perfusion model. The authors detected upregulation of expression of flavocytochrome B558, a heterodimer of gp91phox and p22phox, which forms the...
membrane-bound subunit of NADPH oxidase. In addition, expression of 5- and 12-lipoxygenase, iNOS, and heme oxygenase was upregulated, whereas SOD, NADPH-cytochrome b-5 reductase, and glutathione S-transferase were downregulated. This pattern of altered gene expression would be consistent with induction of oxidative stress, although parameters of such were not measured in this study.

The hemodynamic forces associated with AAA may influence aortic remodeling by increasing oxidative stress. Specifically, oscillatory and low laminar shear forces, which are present in infrarenal AAA, may increase production of ROS. Conversely, increasing laminar shear may reduce oxidative stress. Using the elastase perfusion model, Nakahashi et al performed microarray analysis to examine gene expression after creating a femoral arteriovenous fistula to increase laminar shear during AAA formation. Flow loading reduced AAA diameter while upregulating expression of heme oxygenase 1, an enzyme that can diminish oxidative stress removal through free heme and production of the antioxidants biliverdin and bilirubin. In addition, treatment with vitamin E reduced superoxide levels and ameliorated aneurysm enlargement in this model. These findings showed for the first time that antioxidants may have beneficial effects on AAA formation in an experimental model.

The angiotensin II infusion model may be particularly pertinent to mechanisms of oxidative stress, because this peptide potently induces NADPH oxidase activity and O$_2^-$ production in vascular cells and in monocytes. With this model, infusion of angiotensin II (500 to 1000 ng/kg/min) in hyperlipidemic mice for 28 days results in AAA formation in virtually all of the animals, whereas C57 (control) mice rarely develop AAA, suggesting that hyperlipidemia augments the incidence of the disease. To investigate the time course of ROS production and oxidative stress in this model, we infused vehicle or angiotensin II (1000 ng/kg/min) for 3 to 7 days into apoE$^{-/-}$ mice, after which we removed the aorta and assessed O$_2^-$ levels in situ using confocal microscopy with dihydroethidine. As shown in Figure 3A, increases in O$_2^-$ were detected throughout the aortic wall after 7-day infusion with angiotensin II as compared with vehicle. Moreover, increased expression of nitrotyrosine, a marker for OONO$^-$ and other oxidant species, was detected in conjunction with increased superoxide (Figure 3B). These data indicate that ROS and oxidative stress are induced early during the course of AAA formation in this experimental model.

We next examined the effects of vitamin E therapy on AAA formation using this model. Vitamin E treatment reduced the size of AAA as well as the incidence of aortic rupture, in conjunction with reducing isoprostane content, a marker of oxidative stress, in the abdominal aorta. Tissue histology showed a marked reduction in aortic macrophage infiltration and osteopontin expression, both of which are involved in AAA formation in this model, in the vitamin E–treated animals. In contrast, vitamin E treatment had no significant effect on the extent of aortic root atherosclerosis, activation of MMP2 or MMP9, serum lipid profile, or systolic blood pressure. These findings suggest that oxidative stress promotes AAA formation by locally enhancing inflammatory cell infiltration and cytokine production in the abdominal aorta.

The role of NADPH oxidase in the pathogenesis of AAA was investigated by Thomas et al using the angiotensin II infusion model. We showed that deletion of p47$^{phox}$, a cytosolic subunit of NADPH oxidase, blocked NADPH oxidase activity in aorta and leukocytes; reduced oxidative stress, macrophage infiltration, and MMP2 activity in the abdominal aorta; and markedly attenuated AAA formation in this experimental model. Although deletion of p47$^{phox}$ was also shown to blunt the pressor response to angiotensin II, the reduction in blood pressure was not responsible for the beneficial effects on AAA formation. These findings are likewise suggestive of a local role for oxidative stress in the pathogenesis of AAA.

With regard to the role of RNS in experimental AAA formation, the data are less clear. Deletion of the eNOS gene in apoE$^{-/-}$ mice led to an increase in AAA formation that was not related to the subsequent elevation in systolic blood pressure. Moreover, inhibition of NO production by either aminoguanidine or L-NAME (which inhibit both iNOS and eNOS) limited formation of AAA in the elastase infusion model in rats, despite an increase in systolic blood pressure. Together, these findings suggest that eNOS protects against, whereas iNOS facilitates,
AAA formation. However, deletion of the iNOS gene was not protective against AAA in elastase-infused mice, and actually exacerbated the disease in females. These somewhat contradictory outcomes underline the diversity of the animal models, the complex functions of NOS, and the multiple interactions between various oxidative species—both ROS and RNS—that may have opposing effects depending on their levels and the specific milieu where they are found.

**Antioxidant Therapy for AAA in Humans: Challenges and Opportunities**

Although the aforementioned studies support the hypothesis that oxidative stress may contribute to the pathogenesis of AAA, to date there have been no randomized trials specifically conducted to test this hypothesis in humans. The α-Tocopherol, β-Carotene Cancer Prevention (ATBC) Study was a randomized, double-blind placebo-controlled trial conducted in male smokers to examine the effects of vitamin supplementation on development of lung cancer and other forms of cancer. A number of cardiovascular end points were also monitored during the study; however, because evaluation for AAA was not a part of the protocol, the true incidence and rate of progression of AAA in this patient population are unknown. Nevertheless, patients who underwent elective or urgent surgery for AAA, and those with documented AAA rupture, were identified through registry data. There was no difference in the incidence of AAA rupture among any of the groups of patients. The incidence of surgical repair of nonruptured AAA was 11.7 per 10,000 person years in the control group and 9.7 per 10,000 person years in the α-tocopherol group, a 30% (nonsignificant) reduction. Thus, α-tocopherol therapy was not proven to be beneficial, although a benefit could not be ruled out because the low frequency of identified cases of AAA diminished the statistical power of the study (only 181 cases of AAA were diagnosed in >29,000 subjects).

The data from the ATBC trial in humans might, on first consideration, appear to conflict with the data in rodent models of AAA formation. However, it must be noted that the doses of vitamin E administered in the rodent studies were far greater (on a per weight basis) than was employed in the ATBC trial, in which patients took an equivalent of 50 IU/d of vitamin E. Also, lipophilic vitamin E may not adequately protect against oxidant stress in the aqueous cytosolic environment. Also, many oxidant species that are capable of causing cellular damage are not effectively scavenged by vitamin E, particularly at the dose ranges commonly used in human studies.

Whereas antioxidant therapy has not been proven effective at preventing or treating atherosclerosis in humans, the possibility of a beneficial effect with regard to AAA cannot be excluded. However, before a study is undertaken to test this hypothesis, it would be prudent to identify an antioxidant regimen that is effective at ameliorating aortic oxidative stress in these patients. This could be accomplished by performing pilot studies using various antioxidant regimens preoperatively in patients scheduled for elective AAA repair to determine which regimen most effectively reduces parameters of oxidative stress in the AAA tissues. Once an effective antioxidant regimen has been identified, a randomized clinical trial could then be designed to test the role of oxidative stress in the pathogenesis of AAA in humans.

**Conclusions**

The results of these studies demonstrate that ROS and RNS possess several properties that could ultimately lead to aneurysm development and progression. These interactions are summarized in Figure 2. The general hypothesis is that oxidant stress has the ability to change the balance between destruction and regeneration of the aortic wall by enhancing matrix proteolysis, increasing SMC apoptosis, altering mechanical forces, and further augmenting the cycle of inflammation. Recent evidence points toward a role for NADPH oxidase in the pathogenesis of AAA in experimental models and perhaps in humans, suggesting that this enzyme could be a molecular target for treatment of AAA.

**Sources of Funding**

This work was supported by NIH grants HL070860, HL076684, and HL62384 (to N.J.W.), and by an American Heart Association Postdoctoral Fellowship Award (to D.G.).

**Disclosures**

None.

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Arterioscler Thromb Vasc Biol. April 2007


