Abstract—Myeloperoxidase (MPO) is a leukocyte-derived enzyme that catalyzes the formation of a number of reactive oxidant species. In addition to being an integral component of the innate immune response, evidence has emerged that MPO-derived oxidants contribute to tissue damage during inflammation. MPO-catalyzed reactions have been attributed to potentially proatherogenic biological activities throughout the evolution of cardiovascular disease, including during initiation, propagation, and acute complication phases of the atherosclerotic process. As a result, MPO and its downstream inflammatory pathways represent attractive targets for both prognostication and therapeutic intervention in the prophylaxis of atherosclerotic cardiovascular disease. (Arterioscler Thromb Vasc Biol. 2005;25:1102-1111.)

Key Words: atherosclerosis ■ free radical ■ heart failure ■ high-density lipoprotein ■ low-density lipoprotein ■ myeloperoxidase ■ nitric oxide ■ scavenger receptor ■ vulnerable plaque

Inflammatory events have been implicated at all stages in the evolution of atherosclerotic plaque, from the early development of endothelial dysfunction, through to formation of the mature atheroma and its subsequent rupture. Elucidation of the factors that coordinate this complex cascade has assumed increasing importance in the search to identify accurate predictors of cardiovascular risk and targets for therapeutic intervention.

Myeloperoxidase (MPO) has emerged as a potential participant in the promotion and/or propagation of atherosclerosis. A member of the heme peroxidase superfamily, MPO generates numerous reactive oxidants and diffusible radical species that are capable of both initiating lipid peroxidation and promoting an array of post-translational modifications to target proteins, including halogenation, nitration, and oxidative cross-linking. MPO, the most abundant component of azurophilic granules of leukocytes, is secreted on leukocyte activation, contributing to innate host defenses. Found predominantly in neutrophils, monocytes, and some subtypes of tissue macrophages, MPO amplifies the oxidative potential of its cosubstrate hydrogen peroxide, forming potent oxidants capable of chlorinating and nitrating phenolic compounds. The hydrogen peroxide substrate may be derived from a number of sources in vivo, including leukocyte NADPH oxidases, xanthine oxidase, uncoupled nitric oxide synthase (NOS), and various Nox isoenzymes. MPO is unique in its ability to generate reactive chlorinating species such as hypochlorous acid (HOCl), the active component of bleach, which possesses potent bactericidal and viricidal activities. In addition, HOCl reacts with electron-rich moieties of a large range of biomolecules.

The essential role of MPO as a component of the innate immune response to foreign invasion was first recognized nearly 4 decades ago. The past decade has witnessed a resurgence in research efforts focusing on this unique heme protein. Spurred initially by the recognition that MPO is enriched within human atheroma, both MPO and its reactive oxidants have been implicated as participants in tissue injury...
during a large number of inflammatory conditions. In this review, evidence linking MPO and its oxidative pathways with the initiation, propagation, and both acute and chronic complications of atherosclerotic cardiovascular disease (CVD) are highlighted.

**Myeloperoxidase and Cardiovascular Disease**

**The Human Experience**

Multiple lines of evidence suggest that MPO may play a role in atherogenesis in humans. Immunohistochemical and biochemical analyses localize the enzyme and its oxidation products within human atherosclerotic lesions. Individuals with total or subtotal MPO deficiency, a defect with a frequency of 1 in every 2000 to 4000 whites, appear less likely to have CVD develop. Further, individuals harboring a promoter polymorphism associated with a reported 2-fold reduction in MPO expression appear cardioprotected, with markedly reduced angiographic evidence of coronary artery disease, nonfatal myocardial infarction, and cardiac death. Increasing systemic levels of MPO have also been demonstrated to predict the presence of angiographic coronary artery disease. Individuals who possess MPO levels in the fourth quartile among sequential subjects undergoing diagnostic cardiac catheterization at a tertiary referral center were 15- to 20-fold more likely to demonstrate abnormal coronary angiograms (defined as >50% stenosis in one or more major coronary arteries) compared with subjects in the lowest quartile. This relationship remained significant after statistical adjustments for Framingham risk score and C-reactive protein. In addition, plasma and serum levels of MPO have been shown to predict risks of subsequent major adverse cardiac events (nonfatal myocardial infarction, death, and need for revascularization) in patients presenting with either chest pain or acute coronary syndromes. Thus, numerous biochemical and genetic studies in humans demonstrate strong and independent relationships between MPO and CVD risks.

**The Mouse Experience**

In contrast, data from animal studies of atherosclerosis have failed to demonstrate such relationships. When low-density lipoprotein (LDL) receptor knockout mice underwent irradiation and subsequent infusion of bone marrow from MPO knockout mice, the extent of atherosclerotic lesions actually modestly increased. Similarly, no significant impact of the MPO-null genotype on atherosclerosis development was observed in the atherosclerosis prone apolipoprotein E–null background mouse model. At first glance, these results suggested that MPO has little role, or may even be atheroprotective, in the murine atherosclerosis model. However, on further inspection, it was highlighted that atherosclerotic lesions in both LDL receptor–null and apolipoprotein E–null mouse models are virtually devoid of any trace of either MPO or its specific oxidation product, chlorotyrosine. Moreover, murine leukocytes were found to carry 10- to 20-fold less MPO per cell compared with corresponding human leukocyte types.

These findings highlight a clear species difference between human and murine atherosclerosis. This has led to the conclusion that common mouse models of atherosclerosis may not permit investigation of the potential involvement of MPO in human atherogenesis. Although murine atherosclerosis models to date have yet to demonstrate the presence of MPO or its catalytic activity within the target organ/tissue (ie, arterial tissues), it is notable that more acute inflammation models in mice (ie, those with clear neutrophil involvement) demonstrate both the presence of MPO and its oxidation products. Murine models in which both MPO and its oxidative products are observed have been used to support a key role for the enzyme in promotion of lipid peroxidation, protein nitration and other oxidative modifications, endothelial dysfunction, and adverse ventricular remodeling in the setting of acute myocardial infarction, as discussed.

**Potential Mechanisms for Myeloperoxidase**

**Contributing to the Promotion of Vascular Disease**

A role for MPO throughout the evolution of the atherosclerotic process has been supported by numerous investigations (Figure 1). As described herein, mechanistic links exist between MPO and the generation of atherogenic lipoproteins, consumption of nitric oxide (NO) and development of endothelial dysfunction, initiation and propagation of the mature atheroma and its subsequent complications of plaque rupture, thrombosis, and ventricular remodeling.

**Myeloperoxidase Converts LDL Into an Atherogenic Form**

Population studies have consistently demonstrated that the incidence of CVD correlates directly with circulating concentrations of LDL. Similarly, therapeutic interventions that reduce systemic levels of LDL are associated with a marked atheroprotective benefit. Despite these relationships, a role for native LDL in cholesterol accumulation within cells of the artery wall has proven difficult to demonstrate, because replete intracellular stores of cholesterol trigger downregulation of the LDL receptor and inhibition in the rate limiting step in de novo cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase. Rather, LDL that has undergone modification, predominantly by oxidation, appears to play a central role in promoting the atherogenic processes, such as cholesterol accumulation through recognition by scavenger receptors. LDL that accumulates in the subendothelial space may become modified, such as through oxidation and glycation and subsequently taken up by macrophages to become foam cells, the first cellular hallmark of the atherosclerotic plaque. Immunohistochemical studies have demonstrated the presence of oxidized LDL in atherosclerotic lesions. Oxidized LDL is cytotoxic and circulating levels of antibodies directed against oxidized LDL correlate with the presence of CVD. In addition, immunization against oxidized LDL is atheroprotective in animal models. Despite the overwhelming evidence supporting a pathogenic role for oxidative processes in atherogenesis, elucidation of the precise pathways that modify LDL in vivo proved difficult to demonstrate given the fact that most oxidation products may be generated by multiple distinct pathways and are thus noninformative with respect to the mechanisms of their formation.

Use of quantitative analytic methods to identify structurally defined molecular markers for distinct oxidative processes has provided valuable mechanistic insights into the role of MPO and
its derived oxidants in the conversion of LDL into an atherosclerotic form within human atheroma. Mass spectrometry and immunohistochemical studies demonstrate that MPO is catalytically active within human atheroma because chlorotyrosine, a specific product of protein modification by MPO-generated halogenating oxidants, is enriched within human atherosclerotic lesions compared to normal arterial intima. More recent studies demonstrate marked enrichment of bioactive chlorinated lipid oxidation products within human atheroma as well. Additionally, alternative oxidation products which may be generated by MPO, as well as other pathways, such as nitrotyrosine (a post-translational modification generated by reactive nitrogen species) and dityrosine (an oxidative crosslink formed by tyrosyl radical–mediated pathways), are similarly enriched within human atheroma. In addition, LDL isolated from human atheroma contains greater amounts of these products than circulating LDL from healthy controls. Thus, multiple lines of evidence confirm a role for MPO as a catalyst for oxidant generation within the artery wall in CVD subjects.

Multiple lines of evidence suggest that proatherogenic biological consequences may be triggered by oxidative modification of targets in the artery wall by MPO-generated reactive species. Lipid oxidation products of plasmalogens generated by the MPO-derived oxidant HOCl are both enriched within human atheroma and possess potent leukocyte chemotactic activity. Incubation of HOCl and LDL results in oxidation of lysine residues in apolipoprotein B-100, the predominant protein of LDL. Increasing anionic surface charge, as well as HOCl-induced lipoprotein aggregation, both convert LDL into a high-uptake form, and appear to occur within human atheroma. Under physiological conditions, activated human monocytes also use MPO-generated reactive nitrogen species to render LDL atherogenic, converting it into a high-uptake form for macrophages, while simultaneously promoting both apolipoprotein B-100 protein nitration and initiation of LDL lipid peroxidation (Figure 2). The oxidized form of LDL generated, termed “NO2LDL,” has since been demonstrated to be selectively recognized by the scavenger receptor CD36, a major participant in fatty streak and atherosclerotic lesion development. Detailed subsequent studies using biochemical, mass spectrometry, and chemical synthesis have identified a novel family of oxidized phospholipids that serve as high affinity ligands for the macrophage scavenger receptor CD36 on both NO2-LDL and other forms of oxidized LDL, as well as documented their enrichment within atherosclerotic lesions (Figure 2).

A central role for MPO as a physiological catalyst for initiation of lipid peroxidation in vivo has been established using neutrophils isolated from humans with MPO deficiency versus normal subjects and subsequently activated within plasma. Studies with MPO knockout mice also confirm a dominant role for MPO in the initiation of lipid peroxidation at sites of acute

Figure 1. Scheme illustrating multiple processes throughout the evolution of atherosclerosis in which MPO is implicated. MPO has been linked to events that participate in the initiation and progression of plaque formation including lipid peroxidation, generation of atherogenic lipoproteins and dysfunctional HDL, and catalytic consumption of nitric oxide (NO). MPO may thus contribute to endothelial dysfunction, leukocyte transmigration, and accumulation of foam cells. MPO may participate in ischemic complications of atherosclerosis via activation of protease cascades and promotion of endothelial cell (EC) apoptosis, leading to breakdown of the fibrous cap. Mechanistic links with activation of tissue factor (TF) and the coagulation cascade are also reported. Studies with MPO knockout mice and models of myocardial infarction have supported a role for the heme protein in progression of myocardial necrosis to adverse ventricular remodeling and heart failure via its ability to activate proteases and promote degradation of the extracellular matrix.
inflammation, because >75% of the F3-isoprostanes and other bioactive eicosanoids formed are attributable to MPO as the source. Similarly, a role of MPO as a catalyst of extracellular protein nitration, such as at some sites of inflammation, is supported by studies using MPO knockout mice. It is thus significant that recent clinical studies demonstrate protein-bound nitrotyrosine predicts atherosclerotic risk and burden and is modulated by atorvastatin therapy.

**Myeloperoxidase Selectively Modifies Apolipoprotein A-I, Generating Dysfunctional High-Density Lipoprotein**

High-density lipoprotein (HDL) particles are the major carriers of lipid hydroperoxides in circulating plasma. The enzymatic source of these lipid hydroperoxides, however, is unknown. In vitro studies of HDL oxidation have been reported to have either a beneficial, neutral, or detrimental impact on the degree of site-specific modification of apolipoprotein A-I and the precise oxidative pathways that modify HDL within the diseased artery wall. Recent evidence has emerged to identify HDL as a target for site-specific modification by MPO-derived oxidants in the artery wall with concomitant functional impairment.

A role for MPO in the oxidative modification of HDL in vitro, with consequent functional inactivation, has been supported by results from several groups. HDL isolated from atherosclerotic lesions contain numerous MPO-derived peptides, including site-specific oxidative modifications by reactive chlorinating and nitrating species. Moreover, HDL isolated from human atheroma contains MPO, consistent with the recent finding that MPO selectively binds to apolipoprotein A-I within plasma via a specific region on helix 8 of the lipoprotein. Analysis of apolipoprotein A-I isolated from plasma of subjects with CVD versus that from healthy controls reveals that a greater content of nitrotyrosine (NO2Tyr) and chlorotyrosine (ClTyr) per apolipoprotein A-I particle are observed within subjects with CVD. The degree of this modification was found to correlate with the frequency of coronary artery disease and CVD findings that have now been independently confirmed. Examination of nearly 100 sequential subjects to an outpatient preventive cardiology clinic revealed that patients harboring the highest tertile of apolipoprotein A-I NO2Tyr and ClTyr content were 6- and 16-fold more likely to have CVD than those in the respective lowest tertile. Moreover, apolipoprotein A-I isolated from atherosclerotic plaque demonstrates a much greater degree of modification (by several orders of magnitude) than a typical protein within plasma or atherosclerotic plaque, with up to 1 of every 2 HDL particles recovered from human atherosclerotic lesions bearing a ClTyr or NO2Tyr modification in some subjects. These results suggest that MPO-catalyzed oxidation of apolipoprotein A-I preferentially occurs in the arterial wall. Consistent with this finding, immunohistochemical analysis of human atheroma specimens reveals MPO- and HOCl-modified proteins colocalize with apolipoprotein A-I in the region of macrophages.

Using tandem mass spectrometric techniques, specific sites on apolipoprotein A-I have been identified as the preferred targets for modification by MPO-derived oxidants, with associated functional impairment of the lipoprotein. Residues on helix 8 (eg, Tyr 192) appear to be the predominant site of MPO-catalyzed oxidation in vitro and within human atheroma and colocalize with the MPO-binding site identified on apolipoprotein A-I within HDL. Remarkably, the degree of site-specific modification of apolipoprotein A-I and enrichment of apolipoprotein A-I with NO2Tyr and ClTyr are each associated with a reduction in the ability of apolipoprotein A-I to promote ABCA-1–dependent cholesterol efflux in vitro and in vivo (Figure 3). Findings which have been independently confirmed. In vitro studies also demonstrate...
that HDL exposed to the MPO-generated oxidant HOCl competes with unmodified HDL as a ligand for the scavenger receptor BI, suggesting that MPO-generated oxidants may interfere with the normal interaction of apolipoprotein A-I with scavenger receptor BI, a key step in the promotion of cholesterol efflux.82

A major determinant of plaque progression or regression rate is the balance between cholesterol uptake versus efflux pathways. These results suggest that MPO may adversely impact on both processes, fostering the net deposition and accumulation of cholesterol within cells of the artery wall. The correlation between MPO levels and angiographic evidence of atherosclerotic plaque,83 as well as the apparent atheroprotective effects of genetic deficiencies of MPO,26–30 are consistent with the hypothesis that MPO participates in the initiation and/or propagation of CVD (Figure 1). Studies directly assessing systemic levels of MPO in parallel to quantitative indices of human atherosclerotic plaque volume will be both informative and of potential prognostic relevance.

Myeloperoxidase Promotes Endothelial Dysfunction
Dysfunction of the endothelial cell layer is one of the earliest changes of atherogenesis.1 This state is characterized by the development of abnormal vascular reactivity and expression of various proinflammatory and prothrombotic factors. A key factor promoting endothelial dysfunction involves a reduced bioavailability of NO.78,79 Abnormal vascular reactivity has been demonstrated in patients with both cardiovascular risk factors80 and with established coronary heart disease.81 Further, numerous therapeutic interventions with a proven atheroprotective benefit have been demonstrated to improve vascular reactivity.82

Recent studies strongly suggest a direct role for MPO as a participant in the development of endothelial dysfunction through limitation in NO bioavailability. Although a potential role of NO as a cosubstrate for prostaglandin H synthase had been suggested,83 it had yet be investigated as a potential substrate for leukocyte heme peroxidases like MPO until the first report by Abu-Soud and Hazen.84 Given the colocalization of MPO within atherosclerotic plaque, a direct role for the enzyme in promoting endothelial dysfunction via consumption of NO has subsequently been explored by several groups. MPO-generated oxidants have been reported capable of inhibiting the activity of NOS. Chlorination of arginine groups. MPO-generated oxidants have been reported capable of inhibiting the activity of NOS. Chlorination of arginine groups.85,86 Reactive nitrogen species such as those generated by MPO have also been shown to uncouple NOS.87 NO synthesis is further inhibited by HDL modified by a MPO-generated chlorinating system, which results in delocalization of endothelial NOS from its normal plasma membrane location.88 Further, MPO and HOCl both reduce the availability of NADPH, an essential NOS cofactor.89 A combination of both direct catalytic consumption, radical–radical scavenging effects, and modulation of NOS activity through oxidation of its substrates and cofactors all likely contribute to the observations that MPO inhibits NO-dependent dilatation of preconstricted arterial37,86 and tracheal segments.90

Direct in vivo support for MPO as a catalytic sink for NO is supported by studies in murine models. Arterial segment NO-dependent relaxation was shown to be reduced after endotoxin administration in wild-type relative to MPO knockout mice.37 The demonstrations that MPO avidly binds to endothelial cells and is subsequently transcytosed to the subendothelial space,38 the compartment where immunohistochemical studies localize both MPO and nitrotyrosine,91 further suggests that MPO is anatomically positioned between endothelial cells and their target smooth muscle cells to intercept NO and limit its bioavailability.

Experimental data implicating a role for MPO in the development of endothelial dysfunction have recently been extended to humans. Vita et al demonstrated that serum MPO levels independently predict the prevalence of endothelial dysfunction in a cohort of 298 subjects.92 A strong inverse correlation was observed between MPO levels and flow-mediated dilatation of the brachial artery. After adjusting for the presence of traditional cardiovascular risk factors, medications, and prevalent CVD, MPO remained a robust predictor of endothelial dysfunction, with individuals possessing fourth-quartile MPO levels remaining 6.4-fold more likely to demonstrate endothelial dysfunction compared with subjects with MPO levels in the lowest quartile. Similarly, MPO has recently been shown to enhance NO catabolism during myocardial ischemia and reperfusion.93 Myocardial tissues from patients presenting with acute myocardial infarction were shown to demonstrate intense recruitment of MPO-positive neutrophils localized along infarct-related vessels, as well as diffuse endothelial distribution of free MPO immunoreactivity. Parallel endothelium-dependent microvascular function studies demonstrated that forearm blood flow in patients with symptomatic coronary artery disease was strongly and inversely correlated with MPO plasma levels ($r = -0.75$, $P < 0.005$). Thus, kinetic, cellular, animal model, and human clinical studies all point toward a role for MPO as a major enzymatic sink for NO within diseased coronary vessels.

Myeloperoxidase and Development of Vulnerable Plaque
The majority of clinical ischemic events result from the breakdown of the fibrous cap overlying the atherosclerotic plaque.94 Pathological studies have established that culprit lesions are typically macrophage rich atheroma containing large amounts of matrix metalloproteinases and prothrombotic material.95,96 These plaques are more likely to undergo thinning and subsequent breakdown of the overlying fibrous cap. This exposes circulating blood to the plaque’s thrombogenic core, resulting in thrombus formation, luminal compromise, and ischemia (Figure 1). Factors that promote the inflammatory cascade in atherosclerotic plaque are likely to be associated with the development of clinical ischemia.

The ability of systemic MPO levels to predict the likelihood of clinical events suggests that MPO plays a role in the
transition of a mature atherosclerotic plaque to the vulnerable state. Brennan et al demonstrated the prognostic value of plasma MPO levels in a cohort of 604 sequential patients presenting to the emergency department with chest pain.32 Subjects in the highest MPO quartile had a 3.9-fold higher likelihood of having a myocardial infarction on presentation and were 4.7-fold more likely to have a major adverse cardiac event in the ensuing 30 days and 6 months. Remarkably, this relationship was observed both in the presence and absence of biochemical evidence of myocardial necrosis. The predictive value of MPO over the ensuing 6-month period exceeded that of other established biomarkers including troponin T, CK-MB, and C-reactive protein. In a similar fashion, Baldus et al found that serum MPO was an independent predictor of adverse cardiac outcomes at 30 days and 6 months in patients with acute coronary syndromes participating in the CAPTURE study.33 Patients with MPO levels in the top tertile were ~3 times more likely to experience death or nonfatal myocardial infarction within 72 hours of enrollment compared with patients in the lowest MPO tertile. The ability of serum MPO levels obtained at the time of subject randomization to predict adverse outcomes over the past 6 months was independent of other prognostic markers, including troponin, C-reactive protein, and soluble CD40 ligand.33

Acute coronary syndromes are characterized by evidence of leukocyte activation. Pathological studies have localized both a marked infiltration of neutrophils97 and colocalization of MPO- and HOCl-modified proteins with macrophages in culprit lesions associated with intracoronary thrombi.12 In addition, unstable angina is characterized by an increase in the expression of leukocyte activation markers,98 as well as the presence of a transcoronary reduction in intracellular leukocyte MPO staining, consistent with systemic leukocyte activation.99 Further studies have demonstrated potential mechanisms by which MPO may promote plaque instability. MPO-derived oxidants colocalize with macrophages and the latent form of matrix metalloproteinase-7 in atherosclerotic lesions.100 In vitro studies demonstrate that HOCl promotes the activation of latent matrix metalloproteinase-7 via oxygenation of a thiol residue in the enzyme’s cysteine switch.100 This molecular switch provides a mechanistic rationale for the demonstration 2 decades ago by Weiss et al that neutrophils release and activate gelatinase by a HOCl-dependent process.101 This process appears to be under dynamic control because oxidative modification of tryptophan and glycine residues in the catalytic domain of matrix metalloproteinase-7 serve as a potential mechanism for restraining proteolytic activity during inflammation.102

Libby et al recently reported that MPO-generated HOCl may contribute to intracoronary endothelial cell desquamation and the engenderment of a prothrombotic phenotype. Physiologically relevant levels of HOCl were shown to promote endothelial cell apoptosis and detachment of endothelial cells in vitro.103 MPO-triggered endothelial cell apoptosis has been suggested as a mechanism for development of superficial erosions, the apparent inciting event in intracoronary thrombus formation in more than one-quarter of acute coronary syndromes, with particular prevalence in women and smokers.104 Interestingly, MPO levels in women appear to exhibit a trend toward being a stronger predictor of clinical events,105 and estradiol has recently been identified as a potential endogenous substrate for MPO-catalyzed lipid peroxidation.4 Whether these observations provide a mechanistic link for the observation that superficial plaque erosions are more commonly observed in females, and are enriched with MPO, remains to be established.106

Several lines of evidence suggest that MPO may also increase the propensity to thrombus formation in the setting of plaque instability. The appearance of detached apoptotic cells in the systemic circulation is a potential stimulus for platelet activation and aggregation.107 The ability of MPO to reduce NO bioavailability renders the normally antithrombotic endothelial surface thrombogenic via the expression of various prothrombotic and antifibrinolytic factors.108 In addition, MPO-derived lipid oxidation products enriched in atheroma activate endothelial cells, promoting the surface expression of P-selectin, favoring platelet adhesion.23 Incubation of endothelial cells with low doses of MPO, or MPO-expressing macrophages, results in increased expression and activity of tissue factor.103 Latent tissue factor pathway activity is also activated by lipid hydroperoxides,109,110 which are generated by the activity of MPO in vivo.3,4

MPO Promotes Myocardial Dysfunction and Abnormal Ventricular Remodeling After Myocardial Infarction

Inflammation continues to play a central role in the pathological events that occur after rupture of the fibrous cap and luminal occlusion. Leukocyte migration to peri-necrotic zones and reperfusion of an occluded artery exposes the ischemic territory to further inflammatory and oxidative stresses. It remains to be determined whether the increase in MPO activity that accompanies models of ischemia reperfusion injury contributes to the resulting tissue damage and infarct extension.111 However, recent studies have demonstrated that MPO contributes to adverse ventricular remodeling after myocardial infarction. Using a chronic coronary artery ligation model, MPO knockout mice demonstrated a marked reduction in leukocyte infiltration and left ventricular dilatation, associated with delayed myocardial rupture and preservation of systolic function (Figure 4).38 This benefit was associated with reductions in the oxidative inactivation of plasminogen activator inhibitor-1 and subsequent tissue plasmin activity. By promoting the development of abnormal ventricular geometry, MPO may thus play a role in the susceptibility to and progression of heart failure after myocardial infarction.

Development of MPO-Targeted Therapeutic Interventions

The many links between MPO and proatherogenic activities that might participate in many stages of cardiovascular disease has stimulated considerable interest in the development of therapeutic strategies to inhibit MPO catalysis. One potential difficulty with development of an MPO inhibitor is the concern that such a drug might have adverse effects related to impairment in the role of enzymes in innate host defenses. It should be noted, however, that only subjects with profound (near total or complete) deficiencies in MPO appear...
21 Days after LAD Ligation

Figure 4. Echocardiographic analysis of ventricle size in wild-type and MPO knockout mice after acute myocardial infarction. Representative m-mode echocardiographic recordings from wild-type (WT) and MPO knockout (MPO−/−) animals 21 days after chronic ligation of the left anterior descending (LAD) artery. Note that WT animals experience marked left ventricle (LV) chamber dilatation and wall thinning after myocardial infarction compared with the MPO−/− mice. Functional studies demonstrate marked preservation in myocardial contractile capacity (fractional shortening) as well in the MPO−/− mice. LVEDD indicates left ventricular end-diastolic diameter. Reprinted with permission from Askan et al.38

to have a significant increase in risk for infections, and only in the setting of concomitant factors that predispose to immunosuppression, such as diabetes.112 Moreover, whereas levels of MPO per leukocyte appear relatively stable in a given subject over time, there appears to be a wide range of MPO levels per leukocyte within populations of normal subjects, and thus a large potential therapeutic range may exist while maintaining MPO levels still within a functional range for host defenses.31 Finally, MPO stores within leukocytes may be relatively protected from inhibition because the enzyme is stored in a crystalline form within granules and only released into the phagolysosome compartment and extracellular space upon leukocyte activation.113 As a result, through use of more polar inhibitors, it may be possible to target extracellular MPO, such as enzyme trapped within the subendothelial space, and not to significantly impede leukocyte killing of phagocytosed pathogens. The development of MPO inhibitors awaits further investigation.

Summary

Generation of reactive oxidant species via MPO-catalyzed pathways may have a substantial impact on the promotion of inflammatory events that contribute not only to immune defenses but also to the tissue damage that results from a range of inflammatory conditions, including atherosclerosis. MPO appears to participate in a range of events involved in the initiation, propagation and subsequent complications of atherosclerotic plaque. As a result, the components of the MPO pathway represent attractive targets for the development of prognostic biomarkers and therapeutic interventions to prevent atherosclerotic cardiovascular disease.

Acknowledgments

Research cited in this review was supported by National Institutes of Health grants P01 HL076491, U01 HL077107, HL70621, HL077692, and HL61878, and the General Clinical Research Center of the Cleveland Clinic Foundation (RR018390). S.J.N. is supported by a Ralph Reader Overseas Research Fellowship from the National Heart Foundation of Australia.

References

24. Beckman JS, Ye YZ, Anderson PG, Chen J, Accavitti MA, Tarpey MM, White R. Extensive nitration of protein tyrosines in human atheroscle-


64. Bowry VW, Stanley KK. High density lipoprotein is the major carrier of lipid hydroperoxides in human blood plasma from fasting donors. Proc Natl Acad Sci U S A. 1992;90:10316–10320.


96. Davies MJ. Going from immutable to mutable atherosclerotic plaques. Am J Cardiol. 2001;88:2F–9F.


Myeloperoxidase and Cardiovascular Disease
Stephen J. Nicholls and Stanley L. Hazen

Arterioscler Thromb Vasc Biol. 2005;25:1102-1111; originally published online March 24, 2005;
doi: 10.1161/01.ATV.0000163262.83456.6d
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231
Copyright © 2005 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/25/6/1102

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/