Editorial

Myeloperoxidase and Plaque Vulnerability
Stanley L. Hazen

Inflammation and the Vulnerable Plaque
Sudden cardiac death remains the leading cause of mortality in industrialized societies, outpacing all cancer-related deaths combined. The majority of sudden cardiac deaths arise from acute myocardial infarction secondary to intracoronary artery thromboses. Remarkably, the culprit lesions involved are typically not flow-limiting stenoses, but rather inflamed lipid-laden lesions. Whereas plaque fissuring or rupture, which exposes the intensely prothrombogenic lipid core, occurs in a majority of cases, fully 40% of intracoronary artery thromboses arise at sites of superficial erosions, where endothelial cell (EC) loss and denudation occurs. The mechanisms responsible for plaque vulnerability leading to acute coronary artery thrombosis remain poorly understood. Mounting evidence, however, points toward a critical role for inflammatory processes. Macrophages serve as the dominant cell type in the immediate site of both plaque ruptures and superficial erosions in subjects who experience acute coronary thrombosis, and recent clinical investigations reveal important associations between leukocytes, their enzymes, and their activation in subjects with unstable angina and acute coronary syndromes. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Sugiyama and colleagues significantly extend our knowledge of potential pathophysiologic inflammatory processes within vulnerable atheroma. Using a combination of biochemical, cellular, and immunohistologic studies, they describe unifying mechanistic links between the activity of the leukocyte enzyme myeloperoxidase (MPO) and two cardinal features of vulnerable plaque: EC loss/denudation and development of a prothrombotic phenotype.

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Myeloperoxidase: an Inflammatory Mediator of Atherosclerosis
First identified within human atherosclerotic plaque nearly a decade ago, MPO has emerged as an important potential participant in the atherosclerotic process. MPO, a member of the heme peroxidase superfamily, generates reactive oxidants and diffusible radical species as part of its normal function in innate host defenses. A unique activity of MPO is its ability to use the halide chloride as cosubstrate with hydrogen peroxide to generate chlorinating oxidants such as hypochlorous acid (HOCl), a potent antimicrobial agent and specific chlorinated protein and lipid oxidation products, are all markedly enriched within human atheroma. Leukocytes use MPO to generate oxidants capable of initiating lipid peroxidation both in model systems and in vivo, including conversion of low density lipoprotein into an atherogenic form recognized by macrophage scavenger receptors. MPO may also contribute to the atherosclerotic process by promoting endothelial dysfunction, by virtue of its capacity to catalytically consume nitric oxide as a substrate in vitro and in vivo, resulting in formation of nitric oxide–derived oxidants. Indeed, recent clinical studies demonstrate that systemic levels of MPO serve as a strong and independent predictor of endothelial dysfunction in subjects, as well as angiographic evidence of CAD. Finally, recent human genetic studies support a potential role for MPO in CAD because MPO deficiency in subjects is reportedly cardioprotective, and individuals possessing a functional polymorphism associated with approximately two-fold decrease in MPO expression have reduced cardiac risks.

Myeloperoxidase and Plaque Vulnerability
Despite the many links between MPO and CAD development and progression, only recently has there been a potential role for MPO and its oxidants in development of vulnerable plaque been addressed. Libby and colleagues first described the strong colocalization between macrophage MPO expression and HOCl-modified proteins within culprit lesions of subjects with sudden cardiac death, suggesting a potential mechanistic role for MPO. Subsequent clinical studies by Brennan et al and Baldus and colleagues both revealed the potential utility of circulating MPO levels as a predictor of plaque vulnerability in subjects at risk for incident major adverse cardiac events, even in the absence of detectable levels of myocardial necrosis. Although the ability of MPO to activate latent matrix metalloproteinases into active forms may play a role in the association of MPO immunostaining at sites of plaque fissuring, potential mechanisms linking MPO to development of superficial coronary erosions and a prothrombotic endothelium remained essentially unexplored.

In this issue, Sugiyama and colleagues extend these prior observations by demonstrating that MPO-generated HOCl, at doses likely formed at sites of inflamed vascular lesions, provokes a biphasic response in human ECs. Low doses of HOCl (<10 μmol/L) led to EC activation and elaboration of tissue factor messenger RNA, protein, and tissue factor pathway activity (Figure). Higher yet physi-
ologically relevant doses (30 to 50 μmol/L) promoted EC death and detachment by apparent apoptotic mechanisms, based on demonstrations of rapid caspase-3 activation, decreased EC Bcl-2, cytochrome-C release, poly (ADP-ribose) polymerase degradation, and DNA laddering. Similar phenomena were observed using MPO-positive, but not MPO-negative, human macrophages, suggesting that MPO-generated HOCl within the subendothelium may contribute to plaque vulnerability by evoking EC death, plaque erosion, and induction of a prothrombogenic surface (Figure). A critical role for depletion of intracellular reduced glutathione (GSH), a kinetically favored target of HOCl oxidation, was suggested in their studies by demonstrating reversal of HOCl-, MPO-, and MPO-positive macrophage-mediated effects by either preloading EC with GSH esters or pretreatment with the cell-permeable statin cerivastatin.

An attractive feature of Sugiyama et al’s study is that it provides a unifying mechanistic framework accounting for numerous clinical, histological, biochemical, and cellular results linking MPO and oxidant stress with EC apoptosis, tissue factor pathway activity, and development of vulnerable plaque. Loss of endothelial functional integrity with accompanying endothelial dysfunction appears to be a common molecular disorder of unstable atherosclerotic vascular disease. There is a growing appreciation of the prevalence of EC apoptosis in atheroma, and increased levels of apoptotic ECs are reported within the systemic circulation of subjects with symptomatic atherosclerotic disease. The demonstration that MPO-containing macrophages provoke EC apoptosis may serve as a mechanism contributing to the previously observed colocalization of both MPO and HOCl-modified proteins within culprit lesions of subjects with sudden cardiac death. Similarly, demonstration of EC tissue factor expression and activation in response to physiological levels of HOCl provides a mechanistic rationale for the previously reported association between MPO and HOCl-modified proteins at sites of intracoronary artery thromboses in autopsy specimens. An additional potential mechanism for the association may include the demonstration that lipid hydroperoxides, species generated by MPO in vivo, promote the activation of latent tissue factor pathway activity. Additionally, MPO-generated oxidation products of plasmalogens were recently shown to be both markedly enriched within human atheroma and capable of promoting EC activation and P-selectin surface expression.

Vermani and colleagues reported the observation that superficial coronary artery erosions with accompanying occlusive intraarterial thrombi occur in more than a quarter of cases of sudden cardiac death. Remarkably, superficial erosions, as opposed to a fissure or crack within the fibrous plaque, are observed three times as often in females compared with males. The mechanism(s) responsible for this female gender-preference is unknown. Alterations in matrix via protease activation likely contribute to plaque destabilization and rupture, whereas a primary role for EC injury and desquamation seems probable in superficial erosions. Given the reported findings of Sugiyama et al in this issue of the Journal, and their prior report that sites of superficial coronary erosions possess subendothelium enriched in MPO and HOCl-modified proteins, one might speculate that MPO-generated HOCl-mediated EC apoptosis may partly underlie the female sex-specific difference. To further explore the possibility that MPO differentially
estradiol has recently been identified as a potential endog-
males (P < 0.08) (Table). Although plasma levels of MPO tended to
lar risks (Table). Although plasma levels of MPO tended to
be lower in females (P = 0.05), they showed a tendency
toward being a stronger predictor of risk in females than in
males (P = 0.08) (Table). It is of interest to note that estradiol has recently been identified as a potential endoge-
substrate for MPO in plasma that is capable of
initiating lipid peroxidation.24 Whether these findings are
linked and explain the female predilection for coronary
erosions with underlying MPO-laden plaque remains un-
known. Further evaluation into this area is warranted.

In summary, a growing body of evidence suggests
important mechanistic links between inflammation and
development of the vulnerable plaque phenotype. MPO is
emerging as a potential prognostic indicator of near term cardiovascular risks, as well as a participant in the under-
lying pathophysiologic processes. Development of an
MPO inhibitor may represent a novel therapeutic strategy
for preventing or interrupting development of vulnerable
plaque.

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pathways for monocyte-mediated protein nitration and lipid peroxidation
in the initiation of lipid peroxidation in plasma as studied in neutrophils

Gender Associated Effects on Myeloperoxidase Levels and Odds Ratio for Major Adverse
Cardiac Events (30 days)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>MPO (pM)</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Q2</td>
</tr>
<tr>
<td>Male</td>
<td>63.9 (51.2–72.7)</td>
<td>192.1 (112.5–378.4)</td>
</tr>
<tr>
<td>Female</td>
<td>64.8 (51.5–75.1)</td>
<td>166.2 (97.3–334.6)</td>
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