Editorial Comment

Myeloperoxidase – a link between inflammation and cardiovascular disease

Matthew J. Sorrentino

Department of Medicine, University of Chicago Pritzker School of Medicine, 5842 S. Maryland Ave, MC 6080, Chicago, Illinois 60637, USA

The majority of acute myocardial infarctions occur because of the sudden development of a thrombus in a coronary artery. The thrombus is frequently associated with a ruptured plaque releasing tissue factor into the circulation which is highly thrombogenic. Plaques that are prone to rupture tend to have large lipid pools, a large number of inflammatory cells, and a thin fibrous cap. The inflammatory cells are thought to contribute to the vulnerability of the plaque by inhibiting cells that synthesize collagen and by releasing proteinases that degrade collagen in the fibrous cap. The measurement of inflammatory makers such as C-reactive protein has been proposed as a potential way to identify patients that have inflamed and vulnerable plaques. Therapies, such as high doses of statins, can be initiated to reduce cardiovascular events in part by reducing inflammation and stabilizing vulnerable plaques.

Myeloperoxidase (MPO) is a heme-containing enzyme released from neutrophils and monocytes in response to an inflammatory stimulus. The enzyme generates a variety of reactive oxygen and nitrogen species as a part of the normal host defense system against invading pathogens. MPO has been found to be elevated in patients with coronary artery disease and, therefore, may be involved in the development of atherosclerosis.

MPO can bind to endothelial cells. It may contribute to the progression of atherosclerosis by depleting the endothelial cells of nitric oxide, stimulate the production of leukocyte chemotactic factors and activate tissue factor and proteinases. MPO can bind to lipoproteins associated with low density lipoprotein (LDL) and high density lipoprotein (HDL) particles. MPO may modify apolipoprotein B100; the lipoprotein associated with LDL particles. This allows the LDL to bind via the scavenger receptor to tissue bound macrophages leading to the formation of foam cells. The MPO interaction with HDL particles may impair cholesterol efflux from atherosclerotic plaques and make HDL particles more susceptible to degradation. Studies have shown the presence of MPO-modified lipoproteins within atherosclerotic lesions. Finally, MPO may activate matrix metalloproteinases (MMP) and deactivate tissue inhibitors of MMPs promoting weakening and thinning of the fibrous cap. The presence of elevated levels of MPO, therefore, may identify individuals at higher risk for plaque rupture.

Clinical studies have shown that MPO levels are elevated in patients with coronary artery disease. The CAPTURE trial measured serum levels of MPO in 1090 patients with an acute coronary syndrome and determined the rate of death or myocardial infarction during a six month follow-up. An elevated MPO level indicated a marked increase in cardiac risk. This elevated risk was particularly striking in patients with normal troponin levels suggesting that MPO release can occur prior to myocardial injury. High MPO levels may identify patients with unstable plaques and signify localized recruitment and activation of neutrophils in the coronary circulation.

MPO levels may be useful in helping to categorize the risk of patients presenting to the emergency department with chest pain. In a study of 604 patients presenting to the emergency department with chest pain, initial MPO levels were an independent predictor for myocardial infarction even in patients with negative troponin levels. MPO levels remained predictive of a myocardial infarction at 30 days and six months after the chest pain presentation.

MPO levels can be predictive of future risk in patients presenting with an acute ST-segment myocardial infarction (STEMI). A recent study of 384 STEMI patients showed that MPO is independently predictive of death and recurrent MI in these patients. A Veteran Affairs study of 193 patients with an acute coronary syndrome indicated that MPO is a strong and independent predictor of myocardial infarction out to at least two years of follow-up.

Xing and colleagues in this issue of The Journal of Geriatric Cardiology have added important clinical data to the utility of MPO in patients with coronary artery disease. The study evaluated 274 consecutive patients with an acute coronary syndrome that underwent angiography. MPO lev-
els were measured and the coronary artery disease was classified by a severity score. As in previous studies, there were more events (death, myocardial infarction and revascularization) in patients with high MPO levels at six months. The high MPO cohort was more likely to be diabetic, have a previous history of having a cardiac event, and have a higher coronary artery disease score.

MPO is emerging as a new marker for high risk coronary artery disease patients. It is an independent predictor of a cardiac event in patients presenting with chest pain or with an acute coronary syndrome. Since MPO is generated by activated neutrophils and macrophages, it may be a powerful marker for an inflamed and vulnerable plaque. High MPO levels may allow identification of patients that have plaques that are likely to rupture. MPO itself may promote plaque instability by modifying lipoproteins, cause endothelial dysfunction, and enhance protease degradation of the fibrous cap. MPO may then prove to be a treatment target as we develop strategies to heal inflamed plaques. Therapies that lower MPO levels may be a surrogate marker for plaque stabilization. Before we can determine the best methods to stabilize plaques, we need to be able to identify vulnerable patients. MPO in conjunction with other inflammatory markers may allow us to identify patients before they present with their myocardial event.

References