Clinica Chimica Acta 493 (2019) 36–51

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Review

Myeloperoxidase – A bridge linking inflammation and oxidative stress with cardiovascular disease

Gjin Ndrepepa

Department of Adult Cardiology, Deutsches Herzzentrum München, Technische Universität, Lazarettstrasse 36, 80636 Munich, Germany

ARTICLE INFO

Keywords:
Cardiovascular disease
inflammation
mortality
myeloperoxidase
oxidative stress

ABSTRACT

Myeloperoxidase (MPO) is a member of the superfamily of heme peroxidases that is mainly expressed in neutrophils and monocytes. MPO-derived reactive species play a key role in neutrophil antimicrobial activity and human defense against various pathogens primarily by participating in phagocytosis. Elevated MPO levels in circulation are associated with inflammation and increased oxidative stress. Multiple lines of evidence suggest an association between MPO and cardiovascular disease (CVD) including coronary artery disease, congestive heart failure, arterial hypertension, pulmonary arterial hypertension, peripheral arterial disease, myocardial ischemia/reperfusion-related injury, stroke, cardiac arrhythmia and venous thrombosis. Elevated MPO levels are associated with a poor prognosis including increased risk for overall and CVD-related mortality. Elevated MPO may signify an increased risk for CVD for at least 2 reasons. First, low-grade inflammation and increased oxidative stress coexist with many metabolic abnormalities and comorbidities and consequently an elevated MPO level may represent an increased cardiometabolic risk in general. Second, MPO produces a large number of highly reactive species which can attack, destroy or modify the function of every known cellular component. The most common MPO actions relevant to CVD are generation of dysfunctional lipoproteins with an increased atherogenicity potential, reduced NO availability, endothelial dysfunction, impaired vasoreactivity and atherosclerotic plaque instability. These actions strongly suggest that MPO is directly involved in the pathophysiology of CVD. In this regard MPO may be seen as a mediator or an instrument through which inflammation promotes CVD at molecular and cellular level. Clinical value of MPO therapeutic inhibition remains to be tested.

1. Historical perspective

Myeloperoxidase (MPO; EC 1.11.1.7) is a member of the superfamily of heme peroxidases. Peroxidase activity (oxidation of guaiac) in plant and animal tissues was first reported in 1855 by Schönbein [1]. In 1868, Klebs detected guaiac oxidation by pus suggesting the origin of peroxidase activity from the white blood cells [2]. In 1898, Linossier made a key observation that hydrogen peroxide (H_2O_2) was required for peroxidase reactions by white blood cells [3]. In 1920, Graham [4] reported the release of peroxidase from neutrophil cytoplasmic granules during phagocytosis. In 1941, Agner [5] purified MPO from the purulent fluids of patients with tuberculosis empyema and named the enzyme verdoperoxidase due to its intensive green color. Two years later, Theorell and Åkeson [6] purified a brown-green peroxidase from cow's milk and showed that the enzyme was different from verdoperoxidase and proposed the name myeloperoxidase to reflect its myeloid origin. In 1960 Hirsch and Cohn [7] described a degranulation process in phagocytes in which the content of the granules was discharged into the phagosome. Schultz et al. [8] and Zgliczynski et al. [9] defined many structural and enzymatic features of MPO and hypothesized that MPO may participate in human host defense. Klebanoff [10,11] established links between neutrophil MPO and MPO-related oxidant destruction of ingested bacteria in the phagosomes (MPO-H_2O_2-Cl^- system). MPO has been implicated in a wide range of human diseases [12]. This review focused on the association (or involvement) of MPO with cardiovascular disease (CVD).

2. MPO structure, reactions and functions

Human MPO is a homodimeric protein with a mass of 146 kDa, consisting of two 73 kDa identical and functionally independent monomers joined by a single disulfide bond at cysteine residue 153 [13]. Each monomer has 2 polypeptide chains: a glycosylated heavy chain consisting of 467 amino acid residues and a mass of 58.5 kDa and a light chain with 106 amino acid residues and a mass of 14.5 kDa. There are 5 intra-chain disulfide bonds within the heavy chain and one disulfide bond within the light chain [14]. Each heavy chain monomer contains a heme (protoporphyrin IX derivative) and a calcium binding

E-mail address: ndrepepa@dhm.mhn.de.

https://doi.org/10.1016/j.cca.2019.02.022
Received 8 January 2019; Received in revised form 20 February 2019; Accepted 20 February 2019
Available online 21 February 2019
0009-8981/ © 2019 Elsevier B.V. All rights reserved.

site which is crucial for chain interaction and stability of the structure. A detailed description of MPO structure and spatial organization of its catalytic site is provided in a review by Fortmüller et al. [14] Of note, the surface of MPO molecule contains numerous lysine and arginine residues which make the MPO a highly cationic molecule (PI~10). This enables electrostatic interaction of MPO with a multitude of compounds or cells that have a negatively charged surface (or domain) including bacterial cells [15], endothelial cells [16], extracellular matrix components, particularly polyanionic glycosaminoglycans [17,18], apolipoprotein B-100 [19] and apolipoprotein A-I [20], albumin [21], cytokeratin I [22], α_1-antitrypsin [23] and ceruloplasmin [24]. The binding of MPO to endothelial cells and glucosaminoglycans is inhibited by heparin which may explain anti-inflammatory actions of this drug [25,26].

The gene coding for human MPO is located on the long arm of chromosome 17 (segment q23.1) and consists of 11 introns and 12 exons, approximately 11 kb in size [27–29]. MPO gene mRNA expression is detected at myeloblast and promyelocyte myeloid maturation stages in the bone marrow and the expression ceases in fully differentiated myeloid cells. A number of polymorphisms, mostly single nucleotide polymorphisms within or near the promoter region have been identified. The most intensively studied polymorphisms lie in the Alu-receptor response element in the upstream promoter region [12]. The -463G/A polymorphism is the most important and G allele is associated with increased promoter activity whereas the A allele is associated with lower MPO expression in monocytes and macrophages [30,31]. Furthermore, the Alu-receptor response element interacts with multiple transcription factors and it may be responsible for MPO aberrant expression in cells including macrophages, astrocytes and hepatocytes [32,33]. Under normal circumstances, these cells do not show MPO activity. Although -463G/A polymorphism seems not to affect MPO circulating levels, this polymorphism has been implicated in various human diseases including atherosclerosis [12]. The -129G/A polymorphism is another polymorphism located within the promoter region of the MPO gene. Neutrophils of the individuals carrying the -129A allele show reduced MPO activity [34]. Polymorphisms located within the coding regions have also been identified and at least 2 of these, 638C/A located in the 5' flanking region and V53F polymorphism located in the exon 2 are reported to modulate MPO gene expression with individuals having -638A and 53F alleles showing a higher MPO activity in the neutrophils [35]. Details of MPO synthesis and post-translational changes have been recently reviewed by Nauseef [36]. The mature enzyme is stored primarily in neutrophil azurophilic granules and monocyte lysosomes. It has been estimated that MPO represents more than 5% of the total protein content in neutrophils [8] and 1% in monocytes [37]. Monocytes loose MPO in the course of their transformation into macrophages [12]. It has been suggested that small amounts of MPO escape from the neutrophils (as proMPO monomers) and are released into the extracellular space [38]. Although MPO is predominantly found in neutrophils and monocytes, other cells including $CD4^+$ and $CD8^+$ lymphocytes [39], resident tissue macrophages such as Kupffer cells [40], peritoneal macrophages [41], and microglia [42], infiltrating macrophages in inflammatory diseases including atherosclerotic lesions [43] and vasculitis [44] show MPO activity. MPO activity has been detected in prostate tissue [45], neurons [46] and astrocytes [32]. MPO is detected in endothelial cells and platelets and its origin may be from internal or external sources. In the case of endothelial cells, endogenous expression of MPO has been confirmed [47,48]. Although monocytes loose MPO upon transformation into macrophages, the latter cells show MPO activity [49] potentially related to endocytosis of neutrophils or MPO internalization via various pathways [50].

The catalytic cycle of MPO is shown in Fig. 1. In quiescent neutrophils MPO is in inactive state as long as these cells are not activated and H_2O_2 is absent. The first step in the MPO catalytic cycle involves a 2-electron oxidation of Fe^{3+}-MPO (native compound) to form compound I ($^{\cdot+}$Por-Fe[IV] = O or oxoiron[IV] porphyryl radical) and H_2O. This step occurs in the presence of H_2O_2 which serves as an electron acceptor. The most important supplier of H_2O_2 is NADPH oxidase. Upon neutrophil activation, typically occurring in the setting of phagocytosis, NADPH oxidase complex is recruited to the internal surface of the phagosome membranes and the activated enzyme produces superoxide radicals ($O_2^{\cdot}$) which are transformed spontaneously or by superoxide dismutase to H_2O_2 [14,50,51]. Compound I may be converted to the native enzyme via 2-electron reduction by halides (Cl^-, Br^-, I^- but not F^-) or pseudohalides (SCN^-) to produce the respective (pseudo) hypohalous acids (HOCl, HOBr, HOI or HOSCN) and restore the native enzyme in the ferric state. This series of reactions is called halogenation cycle. Hypochlorous acid (HOCl) is the most abundant and important product of MPO reaction due to the overwhelmingly higher concentrations of Cl^- in human plasma compared with other halides [52]. HOSCN is produced in larger amounts in smokers, known to have higher levels of SCN^- compared with non-smokers [53]. Alternatively compound I may enter the so-called peroxidase cycle and use other electron donors including radicals (nitric oxide, $^{\cdot}$NO, or $NO2^{\cdot}$), organic compounds (tyrosine, tryptophan, serotonin, tryptamine, ascorbate, steroid hormones, phenol and indole derivatives, sulfhydryl derivatives, urate, drugs or various xenobiotics) or inorganic molecules (nitrite or hydrogen peroxide) [54]. The peroxidase cycle involves 1-electron transfer oxidation of above-listed compounds resulting in the formation of compound II (Por-Fe(IV)-OH, or oxoiron [IV]). Compound II may undergo 1-electron reduction to restore native enzyme, a process known to be the rate-limiting step in the peroxidase cycle which is facilitated by reductants such as superoxide anion and ascorbate, the latter known to be abundant in neutrophils [54]. Radical species produced by peroxidase cycle may form dimer or higher polymer derivatives or react with various cellular components including proteins and lipids [55]. Another redox form of MPO is the so-called compound III (Por-Fe^{2+}-O_2 or Por-Fe^{3+}-$O_2^{\cdot}$) which is formed either from the reaction of native MPO with superoxide or 1-electron reduction of compound I followed by reaction with molecular oxygen or by reaction of compound II with H_2O_2. Compound III is unstable and converts within minutes to native MPO form in a process accelerated by ascorbate, $O2^{\cdot}$ and paracetamol [56,57].

HOCl is the most reactive 2-electron oxidant derived from MPO that reacts avidly with nucleophile groups (sulfur and nitrogen atoms) including thiols, thioethers (cysteine and methionine residues in enzymes and proteins and glutathione), amines and amides. HOCl even at low concentrations leads to thiol group consumption (including glutathione) and perturbations in the redox balance impairing cellular protection against oxidative stress [58]. Moreover, HOCl rapidly inactivates enzymes that have cysteine residues in their active sites including major enzymes such as creatine kinase [59], glyceraldehyde-3-phosphate dehydrogenase [59] and nitric oxide synthase (NOS) [60]. On the other hand HOCl activates matrix metalloproteinases (e.g, MMP-7) by oxidation of a key cysteine residue to sulfonic acid [61]. Cardiovascular consequences of this action are discussed later in this review. The oxidation of methionine inhibits enzymes (e.g. lysozyme), protease inhibitors (alpha-1 antitrypsin), growth factors or signaling pathways (i.e. NF-kB pathway) [58]. The reaction of HOCl with amines or amides leads to formation of chloramines and chloramides. Thus HOCl reacts with nearly all classes of organic molecules including free amino acids or amino acid residues in the structure of proteins, taurine, nucleobases, nucleosides, nucleotides, amino sugars in nucleic acids, glucosaminoglycans, amine-containing phospholipids, cholesterol and unsaturated lipids with far reaching cellular consequences. The reaction of HOCl with tyrosine leads to formation of 3-chlorotyrosine which is widely used as a specific marker of HOCl generation by MPO. Of note, chlorinated compounds are secondary products that are diffusible and have a longer life compared with primary MPO species. These properties are important because they may explain why MPO-related damage may occur over longer time intervals (beyond damage related to short-

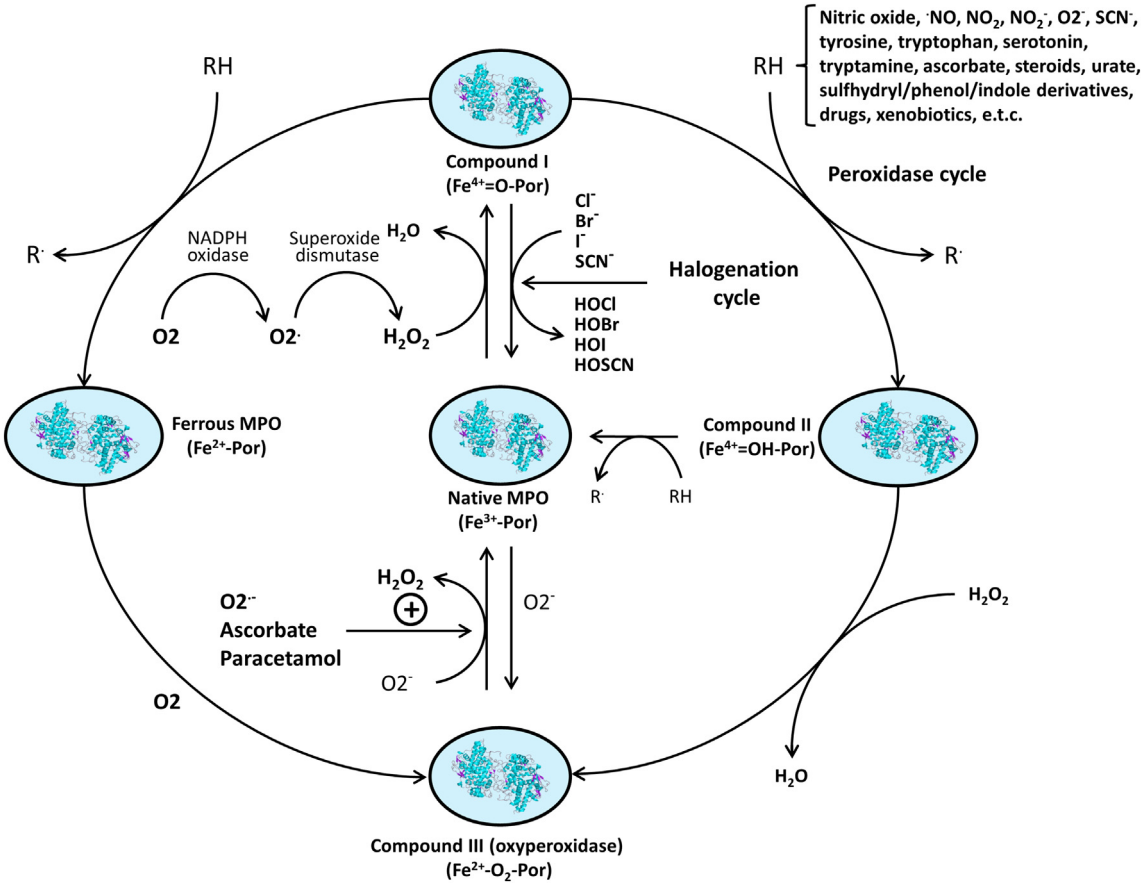

Fig. 1. The myeloperoxidase (MPO) catalytic cycle. The interconversion between enzyme states, halogenation and peroxidation cycles as well as enzyme substrates and products are shown. NADPH oxidase = nicotinamide adenine dinucleotide phosphate oxidase; por = protoporphyrin IX derivative; $R^{\cdot}$ = radical. The plus sign means a stimulatory effect.
Modified from Teng et al. 51.

lived primary products) and at locations remote from the activation site. HOCl acts with antioxidants such as ascorbate and urate [51] potentially impairing antioxidant defense. Hypobromous acid (HOBr) participates in similar reactions (as HOCl) and generates bromamines and bromamides although with differences in kinetic properties particularly in regard to a much more rapid reaction of this agent with aromatic rings and double bond compounds. Chloramines and bromamines may decompose gradually to form reactive aldehydes and the resulting carbonyl groups can react with amine groups in the structure of proteins or lipids to generate Schiff base imines which after an internal restructuration are transformed in advanced glycation end products (AGEs), known for their role in vascular disease and atherosclerosis. A detailed list of cellular targets of HOCl is provided in a review by Davies [58].

Hypothiocyanous acid (HOSCN) is another MPO product generated by oxidation of thiocyanate (SCN^-) – a pseudohalide present at elevated concentrations in smokers. Although HOSCN is less reactive than HOCl or HOBr it is highly selective for thiol groups. Oxidation of cysteine residues which are key for enzymatic functions leads to inhibition of enzymes such as glyceraldehyde-3-phosphate dehydrogenase and tyrosine phosphatases and an increase in the cellular concentration of phosphorylated proteins which may alter mitogen-activated protein kinase (MAPK) signalling pathway and promote apoptosis by this MPO product [62,63]. Although cellular targets of HOSCN remain largely unknown, this agent may act on low-density lipoproteins (LDL) and modify them by causing conjugated dienes and hydroperoxides [64]. In the peroxidase cycle, the MPO/H_2O_2 system oxidizes SCN^- to form cyanate (OCN^-). Cyanate participates in carbamylation reactions by attacking the nucleophilic groups such as lysine residues in the structure of LDL transforming them into homocitrulline residues and increasing atherogenicity of these lipoproteins. Carbamylated LDL is avidly ingested by macrophages (after interaction with scavenger receptor SRA-1) which are transformed into foam cells [65].

The MPO/H_2O_2 system oxidizes nitrite ($NO2^-$) to nitryl chloride (NO_2Cl) and nitrogen dioxide radical ($^{\cdot}NO_2$).$^{\cdot}NO_2$ radical is highly unstable but very potent in protein nitration and lipid peroxidation. Nitrotyrosine formed as a result of oxidation of tyrosine by $^{\cdot}NO_2$ is often used as a marker of MPO-related oxidative stress. Initiation of LDL lipid peroxidation is inhibited by alpha-tocopherol (vitamin E derivative) [51]. The protein and lipid modified LDL bind avidly with macrophages promoting foam cell formation [66]. Implications of these reactions with respect to atherosclerosis or CVD are discussed later in this review.

MPO circulates in plasma bound to albumin, plasma lipoproteins, erythrocytes, or within the circulating neutrophil microparticles (lipid vesicles or membranous blebs that bud off from the neutrophil plasma membrane upon neutrophil activation) [50]. Circulating MPO levels depend on multiple factors that are poorly understood. Although, MPO gene polymorphisms are reported to affect MPO circulating levels, in general heredity is believed to play a modest role in the variability of circulating MPO in healthy population. It has been suggested that other factors such as age, gender, smoking and oral contraceptives (in women) affect MPO levels. Thus neutrophil MPO activity is higher in women than men and MPO activity increases in both genders with advancing age [34]. Extracellular MPO predominantly originates from activated neutrophils which undergo degranulation either at the site of inflammation following recruitment or in circulation. MPO is released

also during neutrophil extracellular trap (NETs) formation which represent fiber-like structures composed of double-stranded DNA, histones and granule proteins (MPO and neutrophil elastase) generated by activated neutrophils to disarm and kill bacteria [67]. With respect to CVD, NETs mediate endothelial dysfunction and leukocyte recruitment and activation and promote atherosclerotic plaque vulnerability [68,69]. They also predict a poor prognosis in patients with stable coronary artery disease (CAD) [70].

It is well established that MPO plays a key role in neutrophil antimicrobial activity and human defense against various pathogens primarily by participating in phagocytosis. In hereditary partial or complete MPO deficiency neutrophil antimicrobial capacity is preserved due to compensatory increase in the cellular MPO-independent antimicrobial mechanisms. Although MPO-deficient humans and animals are susceptible to a number of fungal and yeast infections [54], an extremely increased susceptibility to severe infections is not observed. Complete hereditary MPO deficiency is rare (1:1000 to 1:4000) in the United States and Europe. Interestingly a much lower prevalence of MPO deficiency (1:57 135) is observed in Japan [71]. Emerging evidence suggests that MPO may be involved in regulation of vascular tone, angiogenesis, synthesis of collagen and extracellular matrix, protease activity, gene expression, posttranslational protein modifications, signal transduction, intracellular protein transport, neurotransmitter modulation and modulation of innate and adaptive immunity [50]).

MPO is not routinely measured and indications for MPO measurement for diagnostic or prognostic aims remain undefined. Methods used for MPO measurement in tissues or biological fluids are based on various principles such as detection of the MPO protein, surrogate biomarkers (HOCl, 3-chlortyrosine or other) or enzyme activity [51]. In general, the methods differ markedly in their accuracy and reliability and standardization of both sample collection and detection method are urgently needed. Methods used for MPO detection and measurement in experimental and clinical setting are recently reviewed [51,54].

3. MPO with CVD

Multiple studies have investigated the association between MPO and presence of CVD.

3.1. MPO and CAD

A 2001 case-control study by Zhang et al. [72] showed that leukocyte and blood MPO level was significantly higher in patients with CAD than controls. After adjustment MPO remained significantly associated with the presence of CAD with an odds ratio [OR] of 11.9 (95% confidence interval [CI] between 5.5 and 25.5 for the highest vs. lowest quartiles of leukocyte MPO and an OR = 20.4 [8.9-47.2] for the highest vs. lowest quartiles of blood MPO. Similarly, another case-control study of 680 patients with stable CAD or acute coronary syndromes (ACS) and 194 controls without angiographic CAD showed that MPO level (median with interquartile range) was significantly higher in cases than controls (74.5 [52.5-135.3] μg/L vs. 61.2 [44.6-80.9] μg/L; P < 0.001). Moreover in cases there was a progressive increase in MPO level from stable CAD to non-ST-segment elevation ACS and ST-segment elevation ACS. MPO predicted the ACS presence with an area under the receiver operating characteristic (ROC) curve of 0.731 (P < 0.001) [73]. In 38 patients with acute myocardial infarction (MI) presenting within 2 hours from the symptom onset and 50 patients with stable CAD, Goldmann et al. [74] showed that patients with acute MI had significantly higher levels of MPO compared with patients with stable CAD. Moreover in patients with MI MPO plasma levels remained elevated until 4 hours after symptom onset and declined thereafter. The study postulated that elevated MPO and a rapid peak of MPO after symptom onset suggest neutrophil activation occurring early after ischemia onset and preceding myocardial injury in patients with acute MI. Heslop et al. [75] assessed the association of MPO with the presence and severity of CAD. MPO predicted the presence of angiographic CAD (≥20% vessel narrowing) with an adjusted OR = 1.97 [1.08-3.60], P = 0.03 and severe CAD (≥50% vessel narrowing) with an OR = 1.85 [1.09-3.18], P = 0.021, both calculated per standard deviation (SD) of MPO level. In patients presenting with chest pain but without ST-segment changes and cardiac troponin T within reference range, Rebeiz et al. [76] showed that coronary stenosis ≥70% of lumen narrowing, plaque ulceration, thrombus burden and need for percutaneous coronary intervention (PCI) were more frequent with the increase in MPO level. In another case-control study plasma MPO correlated with the Gensini score – an index of atherosclerosis burden - and coronary calcium [77].

A nested case-control study in the setting of the prospective EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk population study that included 1138 case subjects (apparently healthy men and women who developed CAD over an 8-year follow-up) and 2237 control subjects (matched with cases for age, gender, and enrollment time who remained free of CAD over the same follow-up period) showed that MPO levels were significantly higher in cases than controls and they correlated with C-reactive protein (CRP) and leukocyte count. MPO predicted the risk for CAD with an OR = 1.49 [1.20-1.84], P < 0.001 for the top vs. the bottom MPO quartile; the association remained significant after adjustment for cardiovascular risk factors (adjusted OR = 1.36 [1.07-1.73] for the top vs. the bottom MPO quartile). The study showed that elevated MPO levels predict future risk of CAD in apparently healthy individuals and suggested that inflammatory activation precedes the onset of overt CAD by many years [78].

A 2008 study [79] that included 557 patients undergoing elective PCI showed that plasma MPO levels did not differ in patients with or without CAD. MPO levels were similar across ethnicity and gender, and correlated positively but weakly with CRP and fibrinogen. In the Dallas Heart Study, a probability-based population sample of 3294 subjects, MPO levels were associated with aorta plaques and aorta wall thickness but not with coronary calcium. MPO levels were higher in African Americans than non-African American participants (median: 17.5 [13.9-22.3] ng/mL vs. 16.8 [12.9-21.0] ng/mL; P < 0.0001). MPO levels did not differ by age or sex but correlated with cardiovascular risk factors such as, current smoking, diabetes, low high-density lipoprotein (HDL) level, higher body mass index, but not with hypertension or hypercholesterolemia. MPO correlated with CRP, monocyte chemoattractant protein-1, interleukin-18, pulmonary surfactant protein-B, osteoprotegerin, matrix metalloproteinase-9, tumor necrosis factor-alpha receptor-1 and soluble receptor for advanced glycation end products. The interaction testing showed that MPO was associated with prevalent aorta plaques in African Americans but not in non-African Americans (P_{int} = 0.038) [80]. Wainstein et al. [81] assessed the association between MPO genotypes and CAD severity in 118 patients. Mean MPO plasma levels were 8.6 ± 4.7 ng/mL in AA, 8.6 ± 7.0 ng/mL in AG and 9.4 ± 5.6 ng/mL in GG genotypes. The CAD severity was not associated with MPO genotypes (P = 0.43) but patients with higher CAD score had higher MPO levels (P = 0.02). The Ludwigshafen Risk and Cardiovascular Health (LURIC) study showed no difference in the MPO level in patients with or without CAD [82]. The prospective population-based Atherosclerosis Risk in Communities (ARIC) cohort study (n = 1465) assessed the association between monocyte MPO and incident CVD - a composite of CAD, congestive heart failure (CHF), stroke, peripheral artery disease (PAD) and cardiovascular mortality. There were 290 CVD events over a median follow-up of 9.6 years. There was no statistically significant association between monocyte MPO and incident CVD after adjustment for age, sex, race and other CVD risk factors [83]. A recent publication from the Dallas Heart Study that included 2924 adults free of CVD showed that the MPO/HDL(particle) ratio was associated with a 74% increase in the adjusted risk for incident CVD (first nonfatal MI, non-fatal stroke, coronary revascularization or CVD death) and a 91%

increase in the adjusted risk for total CVD (incident CVD events plus peripheral revascularization and hospitalization for CHF or atrial fibrillation [AF]) over a median of 9.4 years, calculated for highest vs. lowest MPO/HDL(particle) ratio quartiles [84].

In aggregate, the preponderance of evidence supports an association between elevated MPO level and CAD and a dose-response relationship between MPO level and CAD severity. The majority of studies had a case-control or cross-sectional design and included patients with confirmed CAD or those presenting with symptoms suggestive of CAD. These studies suggested an association but not a causal relationship between MPO and CAD. Of note, population-based studies produced conflicting results with respect to the association between MPO and the risk of CAD.

3.2. MPO and cardiovascular outcomes

Several studies have investigated the association of MPO with cardiovascular outcomes. Baldus et al. [85] assessed 6-month rates of death or MI in 547 patients with ACS. Patients with a MPO level > 350 μg/L showed an increased risk of 6-month death or nonfatal MI (18.1% vs. 8.8%, P = 0.002). However, the difference was significant within the first 72 hours (14.0% vs. 5.1%, P = 0.001) and event rate curves of patients with high and low MPO serum levels did not diverge after this time point. Moreover, the 6 month difference was mainly driven by increased rates of nonfatal MI in patients with high MPO level. After adjustment, MPO remained independently associated with the increased risk of 6-month death or MI. The study suggested that MPO is a marker and mediator of vascular inflammation and emphasized the role of neutrophil activation in the ACS pathophysiology. Brennan et al. [86] assessed the association between MPO and cardiovascular events in 604 patients presenting with chest pain. Baseline plasma MPO level predicted the risk of MI even in troponin-negative patients. Elevated MPO level predicted the risk of major adverse cardiovascular events (MACE) – a composite of MI, death or revascularization - at 30 days and 6 months after presentation in all patients and those without myocardial necrosis (troponin-negative). Cavusoglu et al. [87] showed an increased risk of MI at 2 years in ACS patients with a MPO level > 20.34 ng/ml (median value) versus those with a MPO level ≤20.34 ng/ml (MI free survival: 74% vs. 88%, log-rank test P = 0.0249). In 1524 patients with ACS treated with tirofiban who survived to 180 days, Morrow et al. [88] showed that elevated baseline MPO (> 884 pM) was associated with higher risk for non-fatal MI or rehospitalization for ACS at 30 days (9.3% vs. 4.6%, P < 0.001). MPO remained associated with the risk for recurrent ischemic events after adjustment for age, ST-segment deviation, diabetes, prior CAD, CHF, cardiac troponin I, high-sensitivity CRP and soluble CD40 ligand. In 356 patients on dialysis for each 1000 pmol/L higher MPO level the risk of 3-year mortality increased by 14% after adjusting for age, race, diabetes, dialysis vintage, Charlson comorbidity score, history of previous CVD, hemoglobin level, and serum concentrations of albumin, CRP, interleukin-6, and tumor necrosis factor-alpha [89]. Another study that included patients with stable CAD and ACS showed an independent association between baseline MPO level and the risk for inhospital MACE defined as death, recurrent angina, CHF or cardiac arrhythmia [90]. Wong et al. [91] assessed the association between MPO and incident cardiovascular events (MI, coronary revascularization, stroke, or CVD death) in 1302 asymptomatic adults without known CVD over a follow-up of 3.8 years. Subjects with a MPO level > median (257 pM) were more likely to be women, and to have higher body mass index, greater LDL cholesterol level, higher systolic and diastolic blood pressure and lower HDL cholesterol level. MPO correlated also with coronary calcium measured by computed tomography. Incident CVD events were more frequent in subjects with a MPO level above the median (4.6% vs. 2.3%, P = 0.02). The association remained significant after adjustment for age, sex, coronary calcium and risk factors. In the study by Mocatta et al. [92] that included 512 patients with acute MI and 156 healthy controls, MPO levels > median were associated with the risk of 5-year mortality (21% vs. 10%, P = 0.001). After adjustment, MPO remained independently associated with the risk of 5-year mortality. Tang et al. [93] assessed the association between MPO and incident MACE (death, MI or stroke) over a 3-year follow-up in patients with established CAD. The study showed that patients with a MPO level > 322 pmol/L had increased risk of incident MACE even after adjusting for traditional cardiac risk factors, creatinine clearance, B-type natriuretic peptide, and high-sensitivity CRP. With respect to individual end points elevated MPO was associated with increased risk of 3-year death and MI but not stroke. A more recent study [94] that included 3635 patients undergoing coronary angiography showed that a MPO level of 322 pmol/L was associated with 43% and 32% increase in the unadjusted and adjusted risk for MACE defined as death, nonfatal MI or stroke. Nicholls et al. [95] investigated the relationship between serial MPO concentrations in 490 patients presenting with acute chest pain and incident MACE (nonfatal MI, coronary revascularization or death) during 6 months of follow-up. A higher baseline MPO level was associated with a 2.4-fold higher risk of MACE at 6 months calculated for 4th vs. 1st quartile. Among all subsequent MPO measurements (performed at 4, 8 and 16 hours), the strongest association was found for 16-hour measurements (OR = 9.9 [4.7-20.9], P < 0.001 for 4th vs. 1st quartile). MPO was predictive of events even in patients in whom cardiac troponin levels remained within the reference range. Serial MPO monitoring predicted MACE risk better than baseline MPO measurements alone (*c* statistic 0.813 vs. 0.602, P = 0.002). The study suggested that combined serial MPO and cardiac troponin I measurements improved prediction of 6-month MACE, reduced the number of missed MACE events from cardiac troponin testing alone and improved risk classification in 26.1% of patients.

The LURIC study followed 3036 subjects (2391 with angiographic CAD) for a median of 7.75 years. After adjustment for cardiovascular risk factors MPO level was associated with a significant 34% higher risk for total mortality and a 42% higher risk for cardiac mortality calculated for highest versus lowest MPO quartiles. MPO concentration was positively associated with age, diabetes, smoking, markers of inflammation (interleukin-6, fibrinogen, CRP, serum amyloid A) and markers of vascular damage (vascular cellular adhesion molecule [VCAM]-1 and intercellular adhesion molecule [ICAM]-1) and negatively with HDL-cholesterol and apolipoprotein A-I. The authors assessed 5 MPO polymorphisms and found that they were associated with MPO level but not with mortality. Moreover, the Mendelian randomization analysis did not show evidence for a causal relationship between MPO and total or cardiovascular mortality [82]. In the study by Heslop et al. [75] that included 885 patients undergoing coronary angiography for CAD (651 with CAD), MPO was associated with the risk of cardiovascular mortality up to 13 years of follow-up. In patients with MPO level in the 1st to 3rd tertiles, cardiovascular deaths occurred in 8.1%, 13.6% and 18.0%, respectively. After adjustment for cardiovascular risk factors, CAD severity and CRP, MPO remained independently associated with 75% higher adjusted risk for cardiovascular mortality (calculated for 3rd vs. 1st tertile). In a study of 1019 asymptomatic patients with respect to carotid artery disease, paired carotid ultrasound examinations performed at baseline and after a median of 7.5 months showed that a MPO level of ≥310 ng/ml, was associated with progression of carotid atherosclerosis only in subjects with HDL-cholesterol level < 49 mg/dL but not in those with HDL-cholesterol level ≥49 mg/dL [96].

Few studies failed to show an association between MPO and cardiovascular outcomes. In 457 patients with ACS, Apple et al. [97] assessed the association between 7 biomarkers including MPO and adverse events (MI, need for revascularization or death) over a 4-month period. MPO (> 125.6 μg/L vs. ≤125.6) was not associated with the risk of mortality or composite adverse events. Stefanescu et al. [98] failed to show an independent association between MPO and mortality in 382 patients with angiographic CAD over a median follow-up of 3.5

years. Although the association was significant in unadjusted analysis, it was attenuated after adjustment for cardiovascular risk factors. Eggers et al. [99] did not show clinical utility of MPO measurements in patients presenting with chest pain in terms of MI diagnosis or prediction of future mortality. Scirica et al. [100] assessed the association of cardiac troponin I, N-terminal probrain natriuretic peptide, CRP and MPO with adverse cardiac events in 4352 patients with non-ST-segment elevation over a mean follow-up of 343 days. In fully adjusted models, MPO was associated with the risk for CHF but not with the risk of cardiovascular death or MI. Notably, adding MPO in multivariable models alongside clinical characteristics and other biomarkers did not provide substantial incremental prognostic information when assessed together with cardiac troponin I and N-terminal probrain natriuretic peptide. Rudolph et al. [101] assessed the diagnostic and prognostic value of serial MPO measurements in 1818 patients presenting with acute chest pain. The sensitivity and specificity of MPO to diagnose acute MI were 73.5% and 45.5%, respectively which were inferior to sensitive troponin I (sensitivity 90.7%, specificity 90.2%). Although MPO was associated with increased risk of adverse cardiac events at 30 days and 6 months, the association was attenuated after covariate adjustment. MPO did not provide incremental diagnostic information in patients with chest pain when added to sensitive troponin I. Association studies of MPO with cardiovascular outcomes are shown in Table 1.

3.3. MPO and congestive heart failure

Evidence available suggests that MPO plays an important role in the development of CHF. In an acute MI model, MPO knockout mice ($MPO^{-/-}$) showed decreased leukocyte infiltration, reduction of left ventricular dilation and preservation of left ventricular function, potentially involving decreased oxidative inactivation of plasminogen activator inhibitor 1 leading to decreased tissue plasmin activity [102]. Mass spectrometry studies of myocardial tissue from mice and murine models of acute MI demonstrated that MPO is a major source of cytotoxic aldehydes. Compared to wild type, $MPO^{-/-}$ mice showed 35.1% less left ventricular dilation and 52.2% improvement in left ventricular function 24 days after ischemia/reperfusion injury with no difference in infarct size [103]. This study offered evidence that MPO-generated oxidants have a profound adverse effect on left ventricular remodeling and function after acute MI. Epidemiological and clinical studies showed higher MPO levels in patients with CHF, a higher risk of developing CHF in subjects with elevated MPO levels and a poorer outcome in patients with CHF and elevated MPO level. Tang et al. [104] showed that plasma MPO levels were significantly higher in patients with systolic CHF compared with controls (1158 ± 2965 vs. 204 ± 139 pM, $P < 0.0001$) and they correlated with New York Heart Association class and plasma B-type natriuretic peptide levels. MPO remained associated with the prevalence of CHF even after adjustment for age and B-type natriuretic peptide. In the Cardiovascular Health Study that included 3733 subjects without CHF, MI or stroke, 569 subjects developed CHF over a mean follow-up of 7.2 years. Patients in the highest MPO quartile (> 432 pmol/L) showed higher risk of developing incident CHF after adjusting for MI, age, gender, systolic blood pressure, smoking, LDL-cholesterol, diabetes, and any subclinical cardiovascular disease (hazard ratio [HR] = 1.34 [1.06-1.72], P = 0.013). Of note, the association between MPO and CHF was stronger in subjects without traditional cardiovascular risk factors [105]. A prospective community-based study of 1360 subjects showed that subjects with left ventricular systolic dysfunction (n = 28) had significantly higher levels of brain-type natriuretic peptide, CRP and MPO. MPO predicted left ventricular dysfunction with an area under the ROC curve of 0.909. The study showed that MPO and CRP optimize detection of left ventricular systolic dysfunction when used in combination with natriuretic peptides [106]. Rudolph et al. [107] showed that patients with left ventricular systolic dysfunction had significantly higher levels of MPO, elastase and N-terminal probrain natriuretic peptide than controls. Moreover, MPO mRNA expression in circulating leukocytes was significantly increased in patients with left ventricular dysfunction suggesting that systemic leukocyte activation and increased transcription of MPO mRNA seem to be a characteristic of left ventricular systolic dysfunction implicating MPO in the pathophysiology of CHF.

Elevated MPO levels are associated with the outcome of patients with CHF. Tang et al. [108] assessed the association between MPO and echocardiographic markers of severity and long-term clinical outcome (death, heart transplantation or hospitalization for CHF) in 140 patients with established CHF over a mean follow-up of 33 months. Increasing plasma MPO levels were associated with increased likelihood of more advanced CHF. Patients who died, had heart transplantation or were hospitalized for CHF had significantly higher levels of MPO compared with patients without these outcomes. Plasma MPO levels were associated with adverse long-term clinical outcome (RR = 3.35 [1.52-8.86], P = 0.002) even after adjustment for age, left ventricular ejection fraction, plasma B-type natriuretic peptide, creatinine clearance and diastolic stage. In 667 patients presenting to the emergency department with dyspnea and observed for 1 year, MPO did not differ significantly between patients with acute CHF versus those with dyspnea due to noncardiac causes. However, in acute CHF cases, MPO was significantly associated with increased risk for 1-year mortality (HR = 1.58 [1.08-2.31], P = 0.02 for tertiles 2 and 3 vs. tertile 1). The association between MPO and 1-year mortality remained significant after adjustment (HR = 1.52 [1.03-2.24], P = 0.035] for tertiles 2 and 3 vs. tertile 1). The combination of MPO with B-type natriuretic peptide improved prediction of mortality compared with individual markers [109]. Michowitz et al. [110] showed that MPO levels were higher in patients with CHF compared to healthy volunteers (205.7 ± 272.6 vs. 123.0 ± 170.5 ng/ml, P = 0.01). MPO correlated weakly but significantly with New York Heart Association class (R = 0.12: P = 0.04), high-sensitivity CRP (R = 0.18; P = 0.004) but not with age, left ventricular ejection fraction or N-terminal probrain natriuretic peptide. MPO showed a trend (P = 0.07) for an association with mortality (106 deaths) over 40.9 months of follow-up. One study assessed the association between MPO −463 G/A polymorphism and outcome of 116 patients with impaired left ventricular function. Over a median follow-up of 1050 days, patients with GG genotype showed a significant decrease in survival (HR = 2.99 [1.19−7.50], $P < 0.05$). After adjustment, GG genotype remained significantly associated with all-cause and cardiovascular mortality. There was no association between MPO gene polymorphism and MPO protein level or between MPO concentration and outcome [111]. A recent experimental study showed that PF-1355 -an oral MPO inhibitor - decreased MPO activity in a model of MI in mice. A 7-day duration of PF-1355 treatment decreased the number of inflammatory cells and attenuated left ventricular dilation whereas a 21-day duration improved left ventricular ejection fraction (by 44%), decreased end-diastolic volume (by 53%) and left ventricular mass (by 33%) compared with controls. An early (1 hour) initiation was associated with better therapeutic effect than late (24 hours) initiation of the agent [112].

Contrary to these studies, Shah et al. [113] failed to show diagnostic or prognostic value of MPO in patients with CHF. In this prospective observational study, the diagnostic accuracy of MPO for acute decompensated CHF and the prognostic value for patients with acute dyspnea was assessed in 412 patients presenting with dyspnea over 1 year of follow-up. The diagnostic accuracy of MPO for acute decompensated CHF was low (area under the ROC curve = 0.46; P = 0.18) and the biomarker did not correlate with echocardiographic measures of cardiac structure or function. MPO levels were not associated with 1-year mortality (HR = 1.25 [0.71-2.18]; P = NS for MPO above versus below the median value).

3.4. MPO and arterial hypertension

Evidence available suggests that MPO may be involved in regulation of vascular tone [114]. MPO injection in the left atrium of open-chest

Table 1
Association of myeloperoxidase with cardiovascular outcomes.

Author (year) [reference]	Type of study	Number	Length of follow-up	Myeloperoxidase cutoff	Outcome/risk estimate	P value
Baldus et al. (2003) [85]	Subgroup from a RCT	1090 patients with ACS	6 months	> 350 μg/L	Death or nonfatal MI: Adjusted HR = 2.25 [1.32-3.82]	0.003
Brennan et al. (2003) [86]	Observational	604 patients with chest pain	30 days 6 months	Q4 (394 pM) vs. Q1 (119.4 pM)	MACE: Adjusted OR = 4.7 [2.8-7.7] MACE: Adjusted OR = 4.7 [2.9-7.7]	< 0.001 < 0.001
Kalantar-Zadeh et al. (2006) [89]	Observational	356 patients on dialysis	26 months (median)	1000 pmol/L	All-cause mortality: Adjusted HR = 1.14 [1.03-1.26]	0.01
Exner et al. (2006) [96]	Prospective	1019 patients with carotid artery disease	7.5 months (median)	≥310 ng/mL	Progesssion of carotid disease: Adjusted OR = 2.57 [1.39-4.75][a]	0.003
Cavusoglu et al. (2007) [87]	Observational	193 men with ACS	2 years	Median (20.34 ng/ml)	MI: adjusted OR = 1.60 [1.09–2.36]	0.0172
Mocatta et al. (2007) [92]	Case-control	512 with acute MI 156 healthy controls	5 years	Median (55 ng/mL)	All-cause mortality: Adjusted HR = 1.81 [1.07–3.05]	0.026
Morrow et al. (2008) [88]	Subgroup from a RCT	1524 patients with ACS	30 days 6 months	Median (884 pM)	Ischemic events (MI recurrent ACS): Adjusted OR = 2.10 [1.36–3.23] Adjusted OR = 1.26 [0.95–1.68]	0.001 0.14
Wong et al. (2009) [91]	Observational	1302 asymptomatic adults	3.8 years	Median (257 pM)	Incident CVD: Adjusted HR = 1.9 [1.0–3.6]	0.04
Roman et al. (2010) [90]	Observational	130 patients with ACS	13 months (mean)	> 93 pmol/L	MACE: Adjusted OR = 3.8 [1.2-12.0]	Not given
Heslop et al. (2010) [75]	Prospective	885 patients undergoing selective angiography	> 13 years	T 3 (> 118.7 ng/mL) vs. T 1 (< 70.2 ng/mL)	CVD mortality: Adjusted HR = 1.75 [1.16-3.10]	0.01
Nicholls et al. (2011) [95]	Observational	490 patients with chest pain	6 months	Baseline Q4 vs.Q1 (values not given)	MACE: OR = 2.4 [1.4-4.1]	0.001
Tang et al. (2011) [93]	Observational prospective	1895 patients undergoing elective angiography	3 years	> 322 pmol/L	MACE: Adjusted HR = 1.71 [1.27–2.30]	< 0.001
Tang et al. (2013) [94]	Observational prospective	3635 patients undergoing elective angiography	3 years	> 322 pmol/L	MACE: Adjusted HR = 1.32 [1.02-1.71]	< 0.036
Scharnagl et al. (2014) [82]	Population-based prospective	3036 subjects	7.75 years (median)	Q4 (> 45 ng/mL) vs. Q1 (< 21 ng/mL)	Mortality: Adjusted HR = 1.34 [1.09–1.67] Cardiac mortality: Adjusted HR = 1.42 [1.07-1.88]	0.009 0.01
Apple et al. (2007) [97]	Observational	457 patients with ACS	4 months	> 125.6 μg/L	All-cause mortality: Adjusted RR = 0.9 [0.4–2.1] MACE: Adjusted RR = 1.7 [0.8–3.7]	Not given
Stefanescu et al. (2008) [98]	Observational retrospective	382 patients with stable angina pectoris	3.5 years (median)	1standard deviation higher log MPO scale	All-cause mortality: Adjusted HR = 1.06 [0.71-1.59]	0.77
Eggers et al. (2010) [99]	Case-control	303 patients with chest pain 120 healthy controls	4.9 years (median)	> 208.1 pmol/L	All-cause mortality: adjusted HR = 1.3 [0.8–2.0] Death or acute MI: adjusted HR = 1.1 [0.8-1.5]	0.28 0.62
Scirica et al. (2011) [100]	Subgroup from a RCT	4352 patients with non-ST segment elevation ACS	343 days (mean)	> 670 pmol/L	CVD death: Adjusted HR = 1.28 [0.96–1.71] MI: Adjusted HR = 0.94 [0.75–1.17] CHF: Adjusted HR = 1.55 [1.14–2.11]	0.088 0.57 0.005
Rudolph et al. (2012) [101]	Observational	1818 patients with acute chest pain	30 days 6 months	> 517.2 pmol/L(?)	Death or MI: Adjusted HR = 1.325 [0.922-1.905] Death or MI: Adjusted HR = 1.009 [0.707–1.439]	0.13 0.96

ACS = acute coronary syndrome; CHF = congestive heart failure; CVD = cardiovascular disease; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction; MPO = myeloperoxidase; OR = odds ratio; Q = quartile; RCT-randomized controlled trial; RR = relative risk; T = tertile

[a] In patients with HDL < 49 mg/dL

pigs was associated with reduced blood flow in the left anterior descending coronary artery and internal mammary artery and reduced myocardial perfusion. Isolated internal mammary arteries treated with MPO showed diminished relaxation in response to acetylcholine and nitroglycerine compared with controls [114]. In the same study, 15 patients with low MPO expression were compared with 30 subjects with normal MPO content and activity. Nicotine-dependent activation of leukocytes caused attenuation of endothelial NO bioavailability in the control group but not in low MPO subjects. The study demonstrated that MPO content and activity in leukocytes correlated with the degree of vascular dysfunction. Limited evidence suggests that MPO may be associated with arterial hypertension. Van der Zwan et al. [115] investigated the association between MPO and arterial hypertension in a population-based cohort of elderly subjects. In age- and sex-adjusted linear regression, plasma MPO was positively associated with systolic blood pressure (2.1 mmHg per SD higher MPO level). The association was stronger in subjects with higher fasting glucose level and plasma oxidized LDL. The association between MPO and blood pressure was strongest in conditions associated with oxidative stress, such as obesity, low HDL, metabolic syndrome and diabetes. The association was marginally attenuated by adjustment for cardiovascular risk factors. A study by Cameron et al. [116] suggested an association between angiotensin signaling pathway and MPO. In this study of patients with CHF, the angiotensin type-1 receptor (AT1R) gene A1166C polymorphism was associated with higher circulating levels of plasma protein carbonyls (a marker of oxidative protein modification) compared with controls without CHF. In patients with CHF, the CC genotype was associated with higher levels of plasma protein carbonyls and MPO compared with AT1R gene AC or AA genotypes. Moreover, the regression analysis showed that AT1R genotype was an independent predictor of MPO activity in CHF patients ($P = 0.005$). This study suggested that MPO is at least partially under the control of angiotensin-signaling pathway. Although mechanisms for the association between MPO and elevated blood pressure remain not fully elucidated, MPO-related reduction of NO availability may lead to an imbalance between vasodilator and vasoconstrictor internal stimuli favoring increased vascular tone, vasoconstriction and elevated blood pressure.

3.5. MPO and pulmonary arterial hypertension

Patients with chronic thromboembolic pulmonary hypertension or idiopathic pulmonary hypertension have elevated plasma levels of DNA, neutrophil elastase and MPO [117]. Due to its cationic nature, MPO binds to anionic glycocalyx components such as glycosaminoglycans and thus it accumulates in the endothelial surface (and subendothelial space) in various vascular beds including pulmonary artery tree. Neutrophil extracellular traps (NETs) were found in the occlusive lesions and vascularized intrapulmonary thrombi. NETs promote nuclear factor κB–dependent endothelial angiogenesis and neovascularization. The NETs-induced angiogenic response depends on MPO/H_2O_2 system-dependent activation of Toll-like receptor 4/nuclear factor κB signaling pathway [117]. NETS induce the release of endothelin-1 from the human pulmonary artery endothelial cells stimulating pulmonary smooth muscle cell proliferation in vitro [117]. Klinke et al. [118] showed that MPO is elevated in patients with pulmonary arterial hypertension and it correlates with subsequent adverse outcomes. Immunohistochemical imaging of lung specimens from patients with pulmonary arterial hypertension showed enhanced immunoreactivity for MPO compared with controls. Moreover, patients with high MPO level (> 583 pmol/L) showed decreased survival ($P = 0.023$) over a median of 65 weeks compared with patients with low MPO level. In the experimental part of the study, deficient MPO mice ($MPO^{-/-}$) showed less increased right ventricular pressure upon hypoxia compared with wild type mice. Hypoxia-induced activation of the Rho-kinase pathway - a critical subcellular signaling pathway involved in vasoconstriction and structural vascular remodeling - was blunted in $MPO^{-/-}$ mice. The infusion of human recombinant MPO for 7 days increased significantly the systolic right ventricular pressure which was normalized upon co-infusion with the Rho-kinase inhibitor Y-27632. Finally, the use of the MPO inhibitor AZM198 attenuated pulmonary hypertension and pulmonary vascular remodeling in Sugen5416/hypoxia-induced pulmonary hypertension in rats. This study showed a mechanistic link between MPO and impaired pulmonary vascular function and suggested that pulmonary arterial hypertension may be ameliorated by MPO inhibition.

3.6. MPO, ischemia/reperfusion injury and microvascular obstruction after acute MI

Neutrophils play an important role in the pathogenesis of lethal myocardial ischemia/reperfusion injury [119,120] and MPO is often used as a surrogate marker of neutrophil activation in these conditions. MPO products target a wide range of cellular components contributing to cellular damage in the setting of ischemia/reperfusion cycle. Elevated MPO levels have been detected as early as 2 hours after chest pain onset in patients presenting with acute MI suggesting that neutrophil activation is an early event in these patients [74]. MPO generated reactive species attack and modify various groups that are key to functioning of ionic channels and transporters in cardiomyocytes impairing their contractility following ischemic episodes [121,122]. A recent study showed a correlation between MPO and infarct size and microvascular obstruction (assessed by cardiac magnetic resonance imaging) in 40 patients with acute MI. Compared with patients with a low MPO level, patients with a high MPO level (> 640 ng/mL) showed larger infract size and microvascular obstruction in acute phase and at 6 months after the acute event. MPO in the culprit artery correlated positively with MPO in non-culprit arteries and serum, and with cardiac troponin and peak creatine kinase levels. At 6 months, reverse systolic remodeling was twice more present in the low-MPO group. Intra-coronary plasma L-arginine level was lower in the high-MPO group in culprit and non-culprit arteries implicating MPO-related consumption of L-arginine, the substrate for NO production [123]. Baldus et al. [121] showed higher plasma MPO levels 9 ± 4 hours after reperfusion in patients with acute MI than in healthy controls. The addition of H_2O_2 to plasma of the patients was associated with higher rates of NO consumption compared with controls. An intense recruitment of MPO-positive neutrophils in the infarct-related arteries and a diffuse endothelial distribution of non-neutrophil-associated MPO immunoreactivity in myocardial specimens from patients with acute MI was observed. Moreover there was an inverse correlation between endothelium-dependent microvascular function (acetylcholine-dependent increase in forearm blood flow in patients with CAD) and MPO plasma levels. This study showed that NO consumption is an important mechanism via which MPO participates in the ischemia and reperfusion-related myocardial damage.

3.7. MPO and peripheral arterial disease

Several studies have reported higher MPO levels in patients with PAD. Berger et al. [124] showed that patients with PAD had higher levels of MPO and several other inflammatory markers (matrix metalloproteinase-9, interleukin-6, adiponectin, ICAM-1, osteoprotegrin, CD40 ligand and CRP) even after adjustment for age, sex, smoking, body mass index and diabetes. In the ARIC Carotid Magnetic Resonance Imaging Study that included 1791 participants (209 cases with PAD), monocyte MPO content was found to be significantly lower in subjects with PAD even after adjustment. The inverse relationship between monocyte MPO content and prevalence of PAD was explained by release and depletion of MPO during monocyte activation in these subjects [125]. Moreover, increased expression of MPO from intermediate monocyte subsets was reported to occur in advances stages of PAD [126]. In 69 patients with PAD undergoing endovascular therapy in

iliac or femoral arteries, inflammatory cells and MPO-positive CD68 cells were observed in nearly half of debris particles obtained from distal protection filters [127]. In concomitant CAD and PAD, a higher level of MPO in femoral circulation than in coronary circulation was reported. Moreover, the transfemoral gradient of MPO correlated with coronary artery endothelial dysfunction and the correlation was stronger after exercise. Serum from affected limbs of patients with both CAD and PAD induced a greater release of monocyte chemotactic protein 1 from human coronary artery endothelial cells than serum from aorta [128]. In 3169 participants with chronic kidney disease included in the Chronic Renal Insufficiency Cohort study, 589 (18.6%) developed PAD (defined as ankle-brachial index < 0.9) during a 6.3-year follow-up. After adjustment, MPO was independently associated with the risk of incident PAD (HR = 1.12 [1.03-1.23]; P = 0.01 for 1 log MPO) [129]. Other studies have reported an association between higher MPO levels and lower ankle-brachial index [130,131] which is considered as a surrogate marker of PAD.

Elevated MPO levels are also associated with adverse events in PAD patients. In 156 patients with symptomatic PAD, 17 patients had MI or stroke during a median follow-up of 17.5 months. Patients with a MPO level ≥183.7 pM were at higher risk of MI or stroke (HR = 6.80 [1.20-38.69]; P = 0.031) [132]. Another study investigated the association between MPO, MPO 463G > A gene polymorphism and the risk for MACE (coronary events, stroke, coronary or carotid artery revascularization and mortality) up to 3 years in 406 patients with PAD. Patients with higher MPO levels (> 115 ng/mL) showed a significant 20% higher risk of MACE and shorter time-to-first event than patients with low MPO level. Smokers with high MPO level showed a > 3-fold higher risk for MACE. After adjustment, the association between MPO-463G > A gene polymorphism and MACE was attenuated [133].

3.8. MPO and stroke

An experimental model of stroke in rats showed that MPO activity was significantly increased in the cerebral cortex perfused by anterior cerebral artery 24 hours after reperfusion and brain MPO activity correlated with the appearance of neutrophils. Neutrophil depletion by administration of an antineutrophil monoclonal antibody prevented the increase in the MPO activity 24 hours after reperfusion, attenuated postischemic increase in brain water content at 24 hours and reduced the infarct size [134]. In another experimental model of stroke in mice elevated MPO activity was observed 3 to 21 days after ischemia and MPO inhibition by 4-aminobenzoic acid hydrazide - an irreversible MPO inhibitor - reduced enzyme activity by 30% to 40% and final lesion volume by 60%. The MPO-knockout mice also showed a similar reduction in the final lesion volume [135]. In an experimental model of ischemic stroke in mice, MPO inhibition with 4-aminobenzoic acid hydrazide or congenitally absent MPO ($MPO^{-/-}$) were associated with decreased cell loss compared to wild-type mice. MPO inhibition increased cytoprotective heat shock protein 70 by 70% and p-Akt by 60% and decreased the apoptotic marker p53 level by 62%. MPO inhibition reduced infarct size and improved neurological outcome. The study demonstrated that MPO inhibition or congenital absence of the enzyme is associated with neuroprotection after ischemic stroke and suggested that MPO may be a therapeutic target for stroke therapy [136]. A potentiation of neurogenesis after stroke by MPO inhibition has also been suggested [137].

Human studies showed MPO involvement in the brain damage following brain ischemia. Case-control studies demonstrated higher MPO levels in patients with hemorrhagic [138] and ischemic [139] stroke than in controls and a correlation between MPO level with stroke severity [139], hematoma volume and 6-month mortality [138]. A previous case-control study investigated the association between MPO G-463A or G-129A polymorphisms and brain infarction confirmed by magnetic resonance imaging. Carriers of the A allele of the G-463A polymorphism showed no significant association with brain infarction. In analyses restricted to cases, an association between A allele of the G-129A polymorphism and brain infarct size or between the A allele of the G-463A polymorphism and a poorer functional short-term outcome as evaluated by the Rankin score was observed [140]. A recent study tested the association between a genetic risk score –based on MPO levels from 15 common single nucleotide polymorphisms identified from prior genome-wide studies – and the risk of primary intracerebral hemorrhage and ischemic stroke. Genetic determinants of elevated circulating MPO level were associated with the risk of hemorrhagic stroke (OR = 1.07; P = 0.04), recurrent hemorrhagic stroke (OR = 1.45; P = 0.006) and ischemic lacunar stroke (OR = 1.05; P = 0.0012). The study suggested a causal role for MPO in the progression of cerebrovascular disease [141]. The Northern Manhattan Study assessed the association between inflammatory markers, high-sensitivity CRP, lipoprotein-associated phospholipase A2 and MPO with white matter hypersintensities on brain magnetic resonance imaging in 527 stroke-free community-based subjects. Subjects with CRP, lipoprotein-associated phospholipase A2 in the upper quartile and MPO in the 3rd and 4th quartiles had a greater white matter hyperintensity volume after adjustment for sociodemographic and vascular risk factors. Adjusting for all biomarkers simultaneously, the white matter hyperintensity volume was 1.25-fold greater for MPO levels above the median [142]. A recent case-cohort study of 2176 participants (562 had a stroke as outcome) assessed the association of 13 biomarkers with the risk of stroke over a median of 5 years. After adjustment, osteopontin, neopterin, MPO and adiponectin were independently associated with the risk of stroke. After further adjustment for Stroke Prognostic Instrument-II and treatment, MPO remained independently associated with the risk of stroke [143]. Two recent studies have identified MPO in cerebral aneurisms and have implicated the enzyme in their formation and rupture [144,145].

3.9. MPO and cardiac arrhythmia

The MPO product HOCl, activates tissue metalloproteinases, inhibits their tissue inhibitors and activates mitogen-activated protein kinase leading to extracellular matrix turnover, cell proliferation, tissue fibrosis and atrial remodeling [146]. Increased MPO activity and neutrophil infiltration in canine atrial myocardium after atriotomy are reported to cause inhomogeneity in atrial conduction and facilitate induction (by burst pacing) and perpetuation of AF. Inhomegeneity in atrial conduction correlated closely with MPO activity [147]. MPO activity was increased in patients with AF undergoing radiofrequency ablation and correlated with AF recurrence within the first week after therapy [148]. Rudolph et al. [149] offered evidence on the involvement of MPO in AF pathogenesis. In this study, a 2-week infusion of angiotensin II, an agent known to cause atrial fibrosis, was associated with accumulation of 3-chlorotyrosine in atria suggesting that profibrotic action of angiotensin II is mediated via MPO activation. In MPO-deficient mice profibrotic response was markedly attenuated. Metalloproteinase 2 and 9 activity and formation of 3-chlorotyrosine were markedly attenuated as a response to angiotensin II infusion in MPO-deficient mice indicating lower tissue availability of HOCl. Right atrial electrical stimulation showed an increased susceptibility to AF in angiotensin-treated wild type mice but not in MPO-deficient mice and susceptibility to AF was restored after initiation of MPO infusion. The human part of the study involved pacemaker-carrying individuals in whom detection of AF episodes was technically feasible. Individuals who developed AF had significantly higher levels of circulating MPO and elastase suggesting that elevated MPO reflects leukocyte activation and degranulation in these patients. In 27 patients undergoing cardiac surgery, immunohistochemical analysis of specimens obtained from right atrial appendages showed significantly higher MPO deposition in atrial tissue and enhanced tissue 3-chlortyrosine content which colocalized with MPO in individuals with concomitant AF. MPO is involved in AF-related platelet hyperaggregability linked with impaired availability of NO and MPO-related inflammatory activation [150]. However

not all studies have reported an association between MPO and the risk for AF. In the population-based Gutenberg Health Study with 5000 subjects (56 ± 11 of age, 161 with AF), MPO was not linked with AF status (OR = 1.09 [0.80-1.27], P > 0.99 for SD of MPO) [151].

Limited evidence suggests that MPO may be involved in increased susceptibility for ventricular arrhythmias after acute MI. Experiments in integrin-deficient ($CD11b^{-/-}$) mice and intravenous MPO infusion showed that neutrophil infiltration was needed for MPO accumulation. Moreover the expression of redox-sensitive gap junctional protein Cx43 (connexin 43) was reduced in the peri-infarct area in wild-type compared with MPO-deficient mice and in isolated wild-type cardiomyocytes, the Cx43 protein content decreased following MPO/H_2O_2 incubation due to MPO-dependent activation of matrix metalloproteinase 7. MPO induced fibroblast-to-myofibroblast transdifferentiation by activation of p38 mitogen-activated protein kinase resulting in upregulated collagen generation and fibrosis. In a cohort of 2622 stable patients with left ventricular ejection fraction > 35% those with an arrhythmic events (ventricular arrhythmia, sudden cardiac death or cardioverter-defibrillator implantation) had significantly higher MPO levels than those without events and MPO was independently associated with arrhythmic events (adjusted OR = 1.83 [1.23–2.73]; P < 0.01 for tertile 3 vs. tertile 1). The study showed that MPO promotes arrhythmogenic left ventricular remodeling and increases susceptibility to ventricular arrhythmias [152].

3.10. MPO and venous thrombosis

MPO may increase the risk for venous thrombosis via endothelial dysfunction, reduced NO bioavailability, increased platelet activation and aggregability and atherosclerotic plaque instability in case of arterial thrombosis. Fibrin-rich coronary thrombi contain plasma markers of platelet, neutrophil and endothelial activation including MPO [153]. In an experimental study of stasis-induced vein thrombosis in mice, MPO-positive neutrophils were detected throughout the thrombus course but the number was highest at day 1 after inferior vena cava ligation [154]. Another experimental study of vein thrombosis in rats showed that neutrophil content and MPO activity increased early (at 6 hours and day 2 after inferior vena cava ligation) in the vein wall after stasis-induced vein thrombus [155]. In 304 patients (22 with venous thromboembolism) presenting in emergency department, a combination of negative D-dimer (cut-off: 500 ng/mL) and MPO (< 22 mg/ dL) increased specificity of detection of venous thromboembolism by 14% (from 59% to 73%) compared with D-dimer alone which translated into a significant improvement of the rate of negative pulmonary vascular imaging (from 38% to 25%) [156]. The role of MPO in venous thrombotic disease needs further investigation.

3.11. MPO and cardiovascular drugs

Most cardiovascular drugs exert an anti-inflammatory action which may impact on the circulating biomarkers of inflammation including MPO. Baldus et al. [25] showed that heparin administration increased MPO levels in 109 patients undergoing diagnostic coronary angiography and the increase in MPO level was higher in patients with CAD. Heparin therapy improved NO availability as evidenced by flow-mediated dilation and by acetylcholine-induced changes in forearm blood flow and MPO release was associated with improved endothelial function. The heparin-induced MPO release from arterial wall may be explained by electrostatic interaction between polyanionic glycosaminoglycan structure of heparin and cationic MPO which liberates MPO sequestrated in the arterial wall. Apart from explaining the anti-inflammatory action of heparin, this study had implications for MPO measurements using heparin-containing kits. Our group investigated the impact of statins, beta-blockers, and angiotensin-converting enzyme inhibitors in patients with stable CAD or ACS. All 3 categories of drugs were associated with significantly lower MPO levels. However, MPO-lowering effect of these drugs was observed only in patients with ACS but not in those with stable CAD. After adjustment only beta-blocker therapy was independently associated with lower MPO levels [157]. Experimental studies showed that metoprolol reduced MPO levels in a model of spinal injury in rats [158] and carvedilol (but not bisoprolol) reduced MPO levels in an ischemia–reperfusion model in rabbits [159]. Carvedilol also inhibited MPO release from the stimulated intact human neutrophils [160]. In an ischemia– reperfusion model of skeletal muscle in rats, simvastatin reduced the neutrophil infiltration and MPO activity in the tissue undergoing ischemia–reperfusion cycle [161], whereas simvastatin, atorvastatin, pravastatin, and lovastatin suppressed MPO gene expression in human and murine monocyte-macrophages and bone marrow precursors by reducing mRNA levels by 20- to 200-fold [162]. In clinical studies statins reduced circulating MPO levels in patients with CHF [163], ACS [164] and diabetes on dialysis [165]. It was shown recently that ticagrelor and clopidogrel – commonly used antithrombotic drugs - did not impact on several circulating inflammatory markers including MPO [166].

4. Mechanisms of the association between MPO and CVD

Multiple molecular mechanisms have been proposed to explain the association between MPO and CVD (Fig. 2). The most common MPO targets relevant to CVD are plasma lipoproteins, NO system, endothelium, matrix proteinases and atherosclerotic plaque.

MPO-generated species, primarily HOCl, HOSCN and SCN^-, modify LDL into chlorinated, nitrated or carbamylated forms markedly increasing their atherogenicity. Experimental studies showed that protein and lipid components are modified by MPO products. Tyrosyl residues within the apolipoprotein B100 of LDL are prime targets. The incubation of activated human neutrophils with LDL was associated with a dramatic increase in the 3-chlorotyrosine content and detection of 3-chlorotyrosine in human atherosclerotic plaques supports the hypothesis that MPO is an important pathway for oxidative modification of lipoproteins [167]. Modified LDL are transformed in high-uptake particles which are avidly ingested by macrophages after binding to macrophage scavenger receptors CD36 and SR-B1 (scavenger receptor class B, type 1) [168]. The MPO/H_2O_2/NO_2 system nitrates the tyrosyl residues of apolipoprotein B100 producing nitrated-LDL which are also avidly ingested by macrophages, a prerequisite of foam cell formation. The amount of 3-nitrotyrosine measured in the LDL obtained from the aortic atherosclerotic intima is 90-fold higher than in plasma LDL [169]. Carbamylation of lysine residues by pseudohalide SCN^- is another modification that generates atherogenic LDL which are unable to bind to macrophage LDL receptor but they bind to macrophage scavenger class A receptors favoring accumulation of these particles in macrophages and foam cell formation. Carbamylated LDL are cytotoxic and promote apoptosis of endothelial cells and proliferation of smooth muscle cells and monocyte adhesion via ICAM-1 and VCAM-1 [170]. The modification of lipid component of LDL is also important. Leukocyte-generated HOCl attacks various lipid components found in LDL structure including plasmalogens and phospholipids resulting in formation of chlorofatty aldehydes and unsaturated derivatives of lysophosphatidylcholine which exert a chemotactic action promoting monocyte entering into atherosclerotic plaques [171]. In addition, the $^{\cdot}NO_2$ radical initiates LDL lipid peroxidation which increases atherogenicity of LDL and uptake by macrophages [66]. Modified LDL by MPO-produced species shows a high atherogenic potential. Apart from promoting foam cell formation, in vitro experiments with human coronary artery endothelial cells showed that modified LDL cause endothelial NOS (eNOS) uncoupling and decrease eNOS expression and NO production which causes endothelial dysfunction which negatively impacts on vascular arterial tone [172,173]. Besides these mechanisms oxidative stress-modified LDL induces atherosclerosis by promoting monocyte infiltration in arterial wall (atherosclerotic plaques), smooth muscle cell proliferation and migration and apoptosis of endothelial

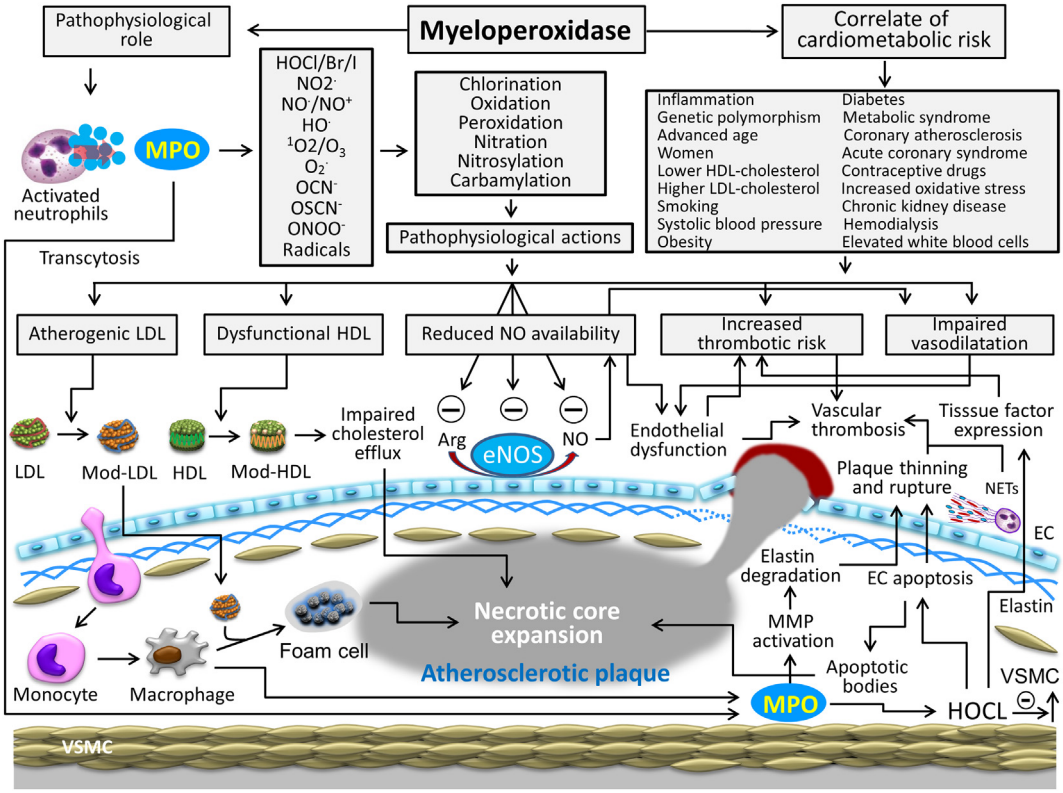

Fig. 2. Putative mechanisms of myeloperoxidase (MPO) participation in cardiovascular disease. Arg = arginine; EC = endothelial cells; eNOS = endothelial nitric oxide synthase; HDL = high-density lipoprotein; HOCl = hypochlorous acid; LDL = low-density lipoprotein; Mod = modified; NO = nitric oxide; MMP = matrix metalloproteinases; NETs = neutrophil extracellular traps; VSMC = vascular smooth muscle cells. The negative sign means an inhibitory effect.

cells. Furthermore, they promote atherothrombosis effects via various adverse actions developing within the atherosclerotic plaques and on the endothelial surface [174] which synergistically increase the thrombotic risk (Fig. 2).

The modification of HDL is another well-known action of MPO with relevance to atherosclerosis and CVD. The main HDL action is participation in reverse cholesterol transport from arterial wall via interaction of apolipoprotein A-I with ATP-binding cassette transporters ABCA1 and ABCG1. Furthermore HDL shows antioxidative (prevents LDL oxidation via enzyme paraoxonase-1 attached to HDL), anti-inflammatory, vasodilatatory, antithrombotic, antiapoptotic and cytoprotective properties and endothelium function maintenance properties and all these effects are known to reduce the risk for atherosclerosis and CVD [175,176]. Evidence available suggests that most of these vascular protective actions are lost as a result of MPO action on this lipoprotein. Immunohistochemical studies have identified the apolipoprotein A1 – the main protein component of HDL - as the main target of MPO-generated products [177]. Of 7 tyrosine residues in the structure of apolipoprotein A-1, residues 192, 166, 236, and 29 are chlorinated or nitrated as a result of MPO action [178]. The content of 3-chlorotyrosine in HDL obtained from human atherosclerotic lesions has been reported to be 8-fold higher than in circulating HDL; moreover, 3-chlorotyrosine was 13-fold higher in HDL isolated from plasma of patients with CAD than in healthy subjects [177]. It has been shown that a higher content of chlorinated and nitrated HDL is associated with diminished ABCA1-dependent cholesterol efflux capacity of the lipoprotein [20]. Oxidized apolipoprotein A1 loses ability to activate the enzyme lecithin:cholesterol acyltransferase (LCAT), which converts free cholesterol to cholesteryl ester and participates in HDL maturation [179]. Moreover, inhibition of the enzyme paraoxonase may diminish the ability of HDL to prevent LDL oxidation. Modified HDL is proinflammatory and promotes expression of VCAM-1 in endothelial cells and entering of monocytes in the arterial wall [180]. Thus MPO-mediated loss of atheroprotective properties of HDL may provide a novel mechanism linking inflammation and oxidative stress to the pathogenesis of atherosclerosis [181].

MPO plays an important role in endothelial dysfunction in humans [182]. MPO correlates directly with markers of endothelial dysfunction and the correlation is even stronger than that of CRP [183]. Moreover MPO-induced endothelial dysfunction is considered one of the most important mechanisms linking inflammation, oxidative stress and cardiovascular disease [182]. Although, there are many mechanisms that may explain why endothelial function deteriorates in the presence of MPO-generated products, reduced NO bioavailability is key to understanding the MPO-related endothelial dysfunction. MPO affects NO homeostasis by interacting with NO itself, eNOS and amino acid arginine. MPO consumes NO by its oxidation via 1-electron transfer (peroxidase cycle, Fig. 1). MPO and its products suppress eNOS activity through various mechanisms. It has been demonstrated that HOCl oxidizes eNOS causing monomerization of dimeric structure and uncoupling of synthase activity [51]. MPO-modified plasma lipoproteins may also reduce NO production by causing the dissociation of eNOS from the endothelial cell surface [51]. Finally HOCl chlorinates and consumes arginine, the physiological substrate of eNOS used for NO production [51]. Clinical studies have suggested an association between elevated MPO levels and endothelial dysfunction or impaired vasoreactivity. Vita et al. [182] measured serum MPO and brachial artery flow–mediated dilation and nitroglycerin-mediated dilation in 298 subjects. There was a strong inverse association between MPO level and brachial artery flow–mediated dilation. MPO predicted endothelial dysfunction even after adjustment for cardiovascular risk factors, CRP, CVD and concomitant cardiovascular medications.

Experimental and clinical studies have shown the presence of active MPO in atherosclerotic plaques and have implicated the enzyme in plaque progression and instability. Daugherty et al. [184] identified MPO in human atherosclerotic lesions. The eluted enzyme generated HOCl indicating that MPO is active in the atherosclerotic lesions. In

transitional plaques, a higher content of MPO was observed in the plaque shoulder regions (regions vulnerable to plaque rupture). In advanced atherosclerotic lesions intense MPO immunostaining was observed adjacent to cholesterol clefts in the necrotic core. The study strongly suggested that the enzyme participates in atherogenesis and plaque instability. Autopsic studies of patients dying with ACS have demonstrated extensive monocyte and neutrophil infiltration of the fissured thrombosed plaques and extensive staining for MPO at the sites of plaque ruptures [49,185]. Sugiyama et al. [49] showed an increased number of MPO-expressing macrophages co-localized with granulocyte macrophage colony-stimulating factor in eroded or ruptured plaques in patients with ACS. Moreover an accumulation of HOCl-modified proteins at eroded or ruptured sites of human coronary artery atheroma was observed. Interestingly, macrophages in human fatty streaks contained little or no MPO. Naruko et al. [185] analysed coronary lesions in patients acute MI and stable CAD and found an active infiltration of complicated lesions (eroded or ruptured) by MPO-positive neutrophils. A coronary ultrasound study showed an association between MPO and percent atheroma volume in diabetic patients but not in nondiabetic patients [186]. A recent study in apolipoprotein E gene knockout mice by Rashid et al. [187] showed that MPO activity was two-fold higher in unstable plaques compared with stable ones. Of note, genetic deletion of MPO or MPO inhibition with AZM198 inhibitor significantly increased fibrous cap thickness and decreased the content of fibrin and hemosiderin in unstable phenotypes. The study strongly suggested that MPO participates in fibrous cap thinning and intraplaque hemorrhage, known to be key features of unstable atherosclerotic plaques and emphasized the need to consider MPO inhibition or other novel therapies to attenuate vascular inflammation in patients with ACS. There are several mechanisms through which MPO-generated products may promote atherosclerotic plaque instability. First, MPO-generated products (primarily HOCl) degrade fibrous cap constituents, collagen and elastin by activation a latent collagenase [188] and metalloproteinase-7 and inactivation of tissue inhibitor of metalloproteinase-1 [61,189]. Second, the MPO product HOCl causes desquamation and detachment of endothelial cells and endothelial cell death via either apoptotic or oncotic cell-death pathways [190]. Third, nitrated and chlorinated HDL inhibit smooth muscle cell proliferation and migration [191]. Thus degradation of elastin and collagen, apoptosis of endothelial cells and inhibition of vascular smooth muscle cell proliferation lead to plaque thinning increasing the plaque propensity to erosion/rupture. Finally, MPO-generated products within the atherosclerotic plaque create a prothrombotic milieu increasing the risk of local thrombosis. It has been shown in vitro that sublethal concentrations of HOCl increased tissue factor in endothelial cells [190] increasing thrombogeneicity in vicinity of atherosclerotic plaques and the risk of vascular thrombosis (Fig. 2).

5. Concluding remarks

Multiple lines of evidence suggest an association between elevated MPO levels and the risk for CVD or adverse vascular events in subjects with CVD including CAD, CVD-related mortality, CHF, arterial hypertension, pulmonary arterial hypertension, PAD, ischemia/reperfusion injury, stroke, cardiac arrhythmia and venous thrombosis. Although, an association between MPO and these conditions was consistently found, causality between MPO and CVD or CVD-related outcomes remains unproven. Mechanistically elevated MPO may signify an increased risk for CVD for at least 2 reasons. First, since low-grade inflammation and increased oxidative stress coexist with many metabolic abnormalities and comorbidities, an elevated MPO level may represent an increased cardiometabolic risk in general. Second, MPO produces a large number of highly reactive species which can attack, destroy or modify the function of every known cellular component. The most common MPO actions relevant to CVD are generation of dysfunctional lipoproteins, reduced NO availability, endothelial dysfunction, impaired vasoreactivity and atherosclerotic plaque instability. These actions strongly suggest that MPO is directly involved in the pathophysiology of CVD. In this regard MPO may be seen as an instrument through which inflammation promotes CVD at molecular and cellular level. A further investigation of MPO participation in the pathophysiology of CVD, standardization of MPO measurement methods, indications for MPO measurement, performance of dedicated epidemiological studies to prove causality in the MPO-CVD relationship and the use of MPO inhibitors to attenuate MPO deleterious effects in clinical setting remain duties of future research.

Conflict of interest

None.

Funding

None.

References

[1] C.F. Schoenbein, Verh. Naturforsch. Ges. Basel 1 (1855) 339–355.
[2] E. Klebs, Die pyrogene substanz. Vorleufige Mitteilung, Cbl. Med. Wiss. 6 (1868) 417–418.
[3] G. Linossier, Contribution a l'etude des ferments oxydants. Sur la peroxidase du pus, C. R. Soc. Biol. Paris 50 (1898) 373–375.
[4] G.S. Graham, The neutrophilic granules of the circulating blood in health and in disease. A preliminary report, N. Y. State J. Med. 20 (1920) 46–55.
[5] K. Agner, Verdoperoxidase: a ferment isolated from leucocytes, Acta Physiol. Scand. 2 (1941) 1–64.
[6] H. Theorell, A. Akeson, Highly purified milk peroxidase, Arkiv Kemi Mineralogi Geologi 17B, (1943).
[7] J.G. Hirsch, Z.A. Cohn, Degranulation of polymorphonuclear leucocytes following phagocytosis of microorganisms, J. Exp. Med. 112 (1960) 1005–1014.
[8] J. Schultz, K. Kaminker, Myeloperoxidase of the leucocyte of normal human blood. I. Content and localization, Arch. Biochem. Biophys. 96 (1962) 465–467.
[9] J.M. Zgliczynski, T. Stelmaszynska, J. Domanski, W. Ostrowski, Chloramines as intermediates of oxidation reaction of amino acids by myeloperoxidase, Biochim. Biophys. Acta 235 (1971) 419–424.
[10] S.J. Klebanoff, Iodination of bacteria: a bactericidal mechanism, J. Exp. Med. 126 (1967) 1063–1078.
[11] S.J. Klebanoff, Myeloperoxidase-halide-hydrogen peroxide antibacterial system, J. Bacteriol. 95 (1968) 2131–2138.
[12] B.S. van der Veen, M.P. de Winther, P. Heeringa, Myeloperoxidase: molecular mechanisms of action and their relevance to human health and disease, Antioxid. Redox Signal. 11 (2009) 2899–2937.
[13] T.J. Fiedler, C.A. Davey, R.E. Fenna, X-ray crystal structure and characterization of halide-binding sites of human myeloperoxidase at 1.8 A resolution, J. Biol. Chem. 275 (2000) 11964–11971.
[14] P.G. Furtmuller, M. Zederbauer, W. Jantschko, J. Helm, M. Bogner, C. Jakopitsch, C. Obinger, Active site structure and catalytic mechanisms of human peroxidases, Arch. Biochem. Biophys. 445 (2006) 199–213.
[15] K.T. Miyasaki, J.J. Zambon, C.A. Jones, M.E. Wilson, Role of high-avidity binding of human neutrophil myeloperoxidase in the killing of Actinobacillus actinomycetemcomitans, Infect. Immun. 55 (1987) 1029–1036.
[16] B.E. Ballieux, K.T. Zondervan, P. Kievit, E.C. Hagen, L.A. van Es, F.J. van der Woude, M.R. Daha, Binding of proteinase 3 and myeloperoxidase to endothelial cells: ANCA-mediated endothelial damage through ADCC? Clin. Exp. Immunol. 97 (1994) 52–60.
[17] E.M. Daphna, S. Michaela, P. Eynat, A. Irit, S. Rimon, Association of myeloperoxidase with heparin: oxidative inactivation of proteins on the surface of endothelial cells by the bound enzyme, Mol. Cell. Biochem. 183 (1998) 55–61.
[18] M.D. Rees, J.M. Whitelock, E. Malle, C.Y. Chuang, R.V. Iozzo, A. Nilasaroya, M.J. Davies, Myeloperoxidase-derived oxidants selectively disrupt the protein core of the heparan sulfate proteoglycan perlecan, Matrix Biol. 29 (2010) 63–73.
[19] A.C. Carr, M.C. Myzak, R. Stocker, M.R. McCall, B. Frei, Myeloperoxidase binds to low-density lipoprotein: potential implications for atherosclerosis, FEBS Lett. 487 (2000) 176–180.
[20] L. Zheng, B. Nukuna, M.L. Brennan, M. Sun, M. Goormastic, M. Settle, D. Schmitt, X. Fu, L. Thomson, P.L. Fox, H. Ischiropoulos, J.D. Smith, M. Kinter, S.L. Hazen, Apolipoprotein A-I is a selective target for myeloperoxidase-catalyzed oxidation and functional impairment in subjects with cardiovascular disease, J. Clin. Invest. 114 (2004) 529–541.
[21] C. Tiruppathi, T. Naqvi, Y. Wu, S.M. Vogel, R.D. Minshall, A.B. Malik, Albumin mediates the transcytosis of myeloperoxidase by means of caveolae in endothelial cells, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 7699–7704.
[22] J.M. Astern, W.F. Pendergraft 3rd, R.J. Falk, J.C. Jennette, A.H. Schmaier, F. Mahdi, G.A. Preston, Myeloperoxidase interacts with endothelial cell-surface cytokeratin 1 and modulates bradykinin production by the plasma Kallikrein-Kinin system, Am. J. Pathol. 171 (2007) 349–360.
[23] H. Bouriche, P. Salavei, J. Lessig, J. Arnhold, Differential effects of flavonols on

inactivation of alpha1-antitrypsin induced by hypohalous acids and the myeloperoxidase-hydrogen peroxide-halide system, Arch. Biochem. Biophys. 459 (2007) 137–142.
[24] M. Segelmark, B. Persson, T. Hellmark, J. Wieslander, Binding and inhibition of myeloperoxidase (MPO): a major function of ceruloplasmin? Clin. Exp. Immunol. 108 (1997) 167–174.
[25] S. Baldus, V. Rudolph, M. Roiss, W.D. Ito, T.K. Rudolph, J.P. Eiserich, K. Sydow, D. Lau, K. Szocs, A. Klinke, L. Kubala, L. Berglund, S. Schrepfer, T. Deuse, M. Haddad, T. Risius, H. Klemm, H.C. Reichenspurner, T. Meinertz, T. Heitzer, Heparins increase endothelial nitric oxide bioavailability by liberating vessel-immobilized myeloperoxidase, Circulation 113 (2006) 1871–1878.
[26] G. de la Rebiere, T. Franck, G. Deby-Dupont, A. Salciccia, S. Grulke, F. Peters, D. Serteyn, Effects of unfractionated and fractionated heparins on myeloperoxidase activity and interactions with endothelial cells: possible effects on the pathophysiology of equine laminitis, Vet. J. 178 (2008) 62–69.
[27] J. Inazawa, K. Inoue, H. Nishigaki, S. Tsuda, M. Taniwaki, S. Misawa, T. Abe, Assignment of the human myeloperoxidase gene (MPO) to bands q21.3—q23 of chromosome 17, Cytogenet. Cell Genet. 50 (1989) 135–136.
[28] A. Latos-Bielenska, C. Klett, W. Just, H. Hameister, Refinement of localization of the human genes for myeloperoxidase (MPO), protein kinase C, alpha polypeptide, PRKCA, and the DNA fragment D17S21 on chromosome 17q, Hereditas 115 (1991) 69–72.
[29] P. van Tuinen, K.R. Johnson, S.A. Ledbetter, R.L. Nussbaum, G. Rovera, D.H. Ledbetter, Localization of myeloperoxidase to the long arm of human chromosome 17: relationship to the 15; 17 translocation of acute promyelocytic leukemia, Oncogene 1 (1987) 319–322.
[30] W.F. Reynolds, E. Chang, D. Douer, E.D. Ball, V. Kanda, An allelic association implicates myeloperoxidase in the etiology of acute promyelocytic leukemia, Blood 90 (1997) 2730–2737.
[31] A.P. Kumar, F.J. Piedrafita, W.F. Reynolds, Peroxisome proliferator-activated receptor gamma ligands regulate myeloperoxidase expression in macrophages by an estrogen-dependent mechanism involving the -463GA promoter polymorphism, J. Biol. Chem. 279 (2004) 8300–8315.
[32] R.A. Maki, V.A. Tyurin, R.C. Lyon, R.L. Hamilton, S.T. DeKosky, V.E. Kagan, W.F. Reynolds, Aberrant expression of myeloperoxidase in astrocytes promotes phospholipid oxidation and memory deficits in a mouse model of Alzheimer disease, J. Biol. Chem. 284 (2009) 3158–3169.
[33] W.F. Reynolds, A.P. Kumar, F.J. Piedrafita, The human myeloperoxidase gene is regulated by LXR and PPARalpha ligands, Biochem. Biophys. Res. Commun. 349 (2006) 846–854.
[34] A. Hoy, D. Tregouet, B. Leininger-Muller, O. Poirier, M. Maurice, C. Sass, G. Siest, L. Tiret, S. Visvikis, Serum myeloperoxidase concentration in a healthy population: biological variations, familial resemblance and new genetic polymorphisms, Eur. J. Hum. Genet. 9 (2001) 780–786.
[35] I. Chevrier, D.A. Tregouet, S. Massonnet-Castel, P. Beaune, M.A. Loriot, Myeloperoxidase genetic polymorphisms modulate human neutrophil enzyme activity: genetic determinants for atherosclerosis? Atherosclerosis 188 (2006) 150–154.
[36] W.M. Nauseef, Biosynthesis of human myeloperoxidase, Arch. Biochem. Biophys. 642 (2018) 1–9.
[37] A. Bos, R. Wever, D. Roos, Characterization and quantification of the peroxidase in human monocytes, Biochim. Biophys. Acta 525 (1978) 37–44.
[38] M. Hansson, I. Olsson, W.M. Nauseef, Biosynthesis, processing, and sorting of human myeloperoxidase, Arch. Biochem. Biophys. 445 (2006) 214–224.
[39] S.S. Okada, E.M. de Oliveira, T.H. de Araujo, M.R. Rodrigues, R.C. Albuquerque, R.A. Mortara, N.N. Taniwaki, H.I. Nakaya, A. Campa, A.C. Moreno, Myeloperoxidase in human peripheral blood lymphocytes: production and subcellular localization, Cell. Immunol. 300 (2016) 18–25.
[40] K.E. Brown, E.M. Brunt, J.W. Heinecke, Immunohistochemical detection of myeloperoxidase and its oxidation products in Kupffer cells of human liver, Am. J. Pathol. 159 (2001) 2081–2088.
[41] M.R. Rodrigues, D. Rodriguez, M. Russo, A. Campa, Macrophage activation includes high intracellular myeloperoxidase activity, Biochem. Biophys. Res. Commun. 292 (2002) 869–873.
[42] R.M. Nagra, B. Becher, W.W. Tourtellotte, J.P. Antel, D. Gold, T. Paladino, R.A. Smith, J.R. Nelson, W.F. Reynolds, Immunohistochemical and genetic evidence of myeloperoxidase involvement in multiple sclerosis, J. Neuroimmunol. 78 (1997) 97–107.
[43] E. Malle, G. Waeg, R. Schreiber, E.F. Grone, W. Sattler, H.J. Grone, Immunohistochemical evidence for the myeloperoxidase/H2O2/halide system in human atherosclerotic lesions: colocalization of myeloperoxidase and hypochlorite-modified proteins, Eur. J. Biochem. 267 (2000) 4495–4503.
[44] K.M. O'Sullivan, C.Y. Lo, S.A. Summers, K.D. Elgass, P.J. McMillan, A. Longano, S.L. Ford, P.Y. Gan, P.G. Kerr, A.R. Kitching, S.R. Holdsworth, Renal participation of myeloperoxidase in antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis, Kidney Int. 88 (2015) 1030–1046.
[45] T. Roumeguere, P. Delree, P. Van Antwerpen, S. Rorive, L. Vanhamme, L. de Ryhove Lde, D. Serteyn, E. Wespes, M. Vanhaerverbeek, K.Z. Boudjeltia, Intriguing location of myeloperoxidase in the prostate: a preliminary immunohistochemical study, Prostate 72 (2012) 507–513.
[46] P.S. Green, A.J. Mendez, J.S. Jacob, J.R. Crowley, W. Growdon, B.T. Hyman, J.W. Heinecke, Neuronal expression of myeloperoxidase is increased in Alzheimer's disease, J. Neurochem. 90 (2004) 724–733.
[47] G. La Rocca, A. Di Stefano, E. Eleuteri, R. Anzalone, F. Magno, S. Corrao, T. Loria, A. Martorana, C. Di Gangi, M. Colombo, F. Sansone, F. Patane, F. Farina, M. Rinaldi, F. Cappello, P. Giannuzzi, G. Zummo, Oxidative stress induces myeloperoxidase expression in endocardial endothelial cells from patients with chronic heart failure, Basic Res. Cardiol. 104 (2009) 307–320.
[48] A. Khalil, H. Medfai, P. Poelvoorde, M. Fayyad-Kazan, C. Delporte, P. Van Antwerpen, Y. El-Makhour, P. Biston, P. Delree, B. Badran, L. Vanhamme, K.Z. Boudjeltia, Myeloperoxidase promotes tube formation, triggers ERK1/2 and Akt pathways and is expressed endogenously in endothelial cells, Arch. Biochem. Biophys. 654 (2018) 55–69.
[49] S. Sugiyama, Y. Okada, G.K. Sukhova, R. Virmani, J.W. Heinecke, P. Libby, Macrophage myeloperoxidase regulation by granulocyte macrophage colony-stimulating factor in human atherosclerosis and implications in acute coronary syndromes, Am. J. Pathol. 158 (2001) 879–891.
[50] L. Vanhamme, K. Zouaoui Boudjeltia, P. Van Antwerpen, C. Delporte, The other myeloperoxidase: emerging functions, Arch. Biochem. Biophys. 649 (2018) 1–14.
[51] N. Teng, G.J. Maghzal, J. Talib, I. Rashid, A.K. Lau, R. Stocker, The roles of myeloperoxidase in coronary artery disease and its potential implication in plaque rupture, Redox Rep. 22 (2017) 51–73.
[52] W. Jantschko, P.G. Furtmuller, M. Zederbauer, K. Neugschwandtner, I. Lehner, C. Jakopitsch, J. Arnhold, C. Obinger, Exploitation of the unusual thermodynamic properties of human myeloperoxidase in inhibitor design, Biochem. Pharmacol. 69 (2005) 1149–1157.
[53] P.E. Morgan, D.I. Pattison, J. Talib, F.A. Summers, J.A. Harmer, D.S. Celermajer, C.L. Hawkins, M.J. Davies, High plasma thiocyanate levels in smokers are a key determinant of thiol oxidation induced by myeloperoxidase, Free Radic. Biol. Med. 51 (2011) 1815–1822.
[54] N. Anatoliotakis, S. Deftereos, G. Bouras, G. Giannopoulos, D. Tsounis, C. Angelidis, A. Kaoukis, C. Stefanadis, Myeloperoxidase: expressing inflammation and oxidative stress in cardiovascular disease, Curr. Top. Med. Chem. 13 (2013) 115–138.
[55] M.J. Davies, C.L. Hawkins, D.I. Pattison, M.D. Rees, Mammalian heme peroxidases: from molecular mechanisms to health implications, Antioxid. Redox Signal. 10 (2008) 1199–1234.
[56] L.A. Marquez, H.B. Dunford, Reaction of compound III of myeloperoxidase with ascorbic acid, J. Biol. Chem. 265 (1990) 6074–6078.
[57] L.A. Marquez, H.B. Dunford, Interaction of acetaminophen with myeloperoxidase intermediates: optimum stimulation of enzyme activity, Arch. Biochem. Biophys. 305 (1993) 414–420.
[58] M.J. Davies, Myeloperoxidase-derived oxidation: mechanisms of biological damage and its prevention, J. Clin. Biochem. Nutr. 48 (2011) 8–19.
[59] A.V. Peskin, C.C. Winterbourn, Taurine chloramine is more selective than hypochlorous acid at targeting critical cysteines and inactivating creatine kinase and glyceraldehyde-3-phosphate dehydrogenase, Free Radic. Biol. Med. 40 (2006) 45–53.
[60] J. Xu, Z. Xie, R. Reece, D. Pimental, M.H. Zou, Uncoupling of endothelial nitric oxidase synthase by hypochlorous acid: role of NAD(P)H oxidase-derived superoxide and peroxynitrite, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 2688–2695.
[61] X. Fu, S.Y. Kassim, W.C. Parks, J.W. Heinecke, Hypochlorous acid oxygenates the cysteine switch domain of pro-matrilysin (MMP-7). A mechanism for matrix metalloproteinase activation and atherosclerotic plaque rupture by myeloperoxidase, J. Biol. Chem. 276 (2001) 41279–41287.
[62] M.M. Lloyd, D.M. van Reyk, M.J. Davies, C.L. Hawkins, Hypothiocyanous acid is a more potent inducer of apoptosis and protein thiol depletion in murine macrophage cells than hypochlorous acid or hypobromous acid, Biochem. J. 414 (2008) 271–280.
[63] A.E. Lane, J.T. Tan, C.L. Hawkins, A.K. Heather, M.J. Davies, The myeloperoxidase-derived oxidant HOSCN inhibits protein tyrosine phosphatases and modulates cell signalling via the mitogen-activated protein kinase (MAPK) pathway in macrophages, Biochem. J. 430 (2010) 161–169.
[64] M. Exner, M. Hermann, R. Hofbauer, B. Hartmann, S. Kapiotis, B. Gmeiner, Thiocyanate catalyzes myeloperoxidase-initiated lipid oxidation in LDL, Free Radic. Biol. Med. 37 (2004) 146–155.
[65] Z. Wang, S.J. Nicholls, E.R. Rodriguez, O. Kummu, S. Horkko, J. Barnard, W.F. Reynolds, E.J. Topol, J.A. DiDonato, S.L. Hazen, Protein carbamylation links inflammation, smoking, uremia and atherogenesis, Nat. Med. 13 (2007) 1176–1184.
[66] E.A. Podrez, D. Schmitt, H.F. Hoff, S.L. Hazen, Myeloperoxidase-generated reactive nitrogen species convert LDL into an atherogenic form in vitro, J. Clin. Invest. 103 (1999) 1547–1560.
[67] V. Brinkmann, U. Reichard, C. Goosmann, B. Fauler, Y. Uhlemann, D.S. Weiss, Y. Weinrauch, A. Zychlinsky, Neutrophil extracellular traps kill bacteria, Science 303 (2004) 1532–1535.
[68] O. Soehnlein, Multiple roles for neutrophils in atherosclerosis, Circ. Res. 110 (2012) 875–888.
[69] Y. Doring, O. Soehnlein, C. Weber, Neutrophil Extracellular Traps in Atherosclerosis and Atherothrombosis, Circ. Res. 120 (2017) 736–743.
[70] M.S. Langseth, T.B. Opstad, V. Bratseth, S. Solheim, H. Arnesen, A.A. Pettersen, I. Seljeflot, R. Helseth, Markers of neutrophil extracellular traps are associated with adverse clinical outcome in stable coronary artery disease, Eur. J. Prev. Cardiol. 25 (2018) 762–769.
[71] M. Kitahara, H.J. Eyre, Y. Simonian, C.L. Atkin, S.J. Hasstedt, Hereditary myeloperoxidase deficiency, Blood 57 (1981) 888–893.
[72] R. Zhang, M.L. Brennan, X. Fu, R.J. Aviles, G.L. Pearce, M.S. Penn, E.J. Topol, D.L. Sprecher, S.L. Hazen, Association between myeloperoxidase levels and risk of coronary artery disease, JAMA 286 (2001) 2136–2142.
[73] G. Ndrepepa, S. Braun, J. Mehilli, N. von Beckerath, A. Schomig, A. Kastrati, Myeloperoxidase level in patients with stable coronary artery disease and acute coronary syndromes, Eur. J. Clin. Investig. 38 (2008) 90–96.

[74] B.U. Goldmann, V. Rudolph, T.K. Rudolph, A.K. Holle, M. Hillebrandt, T. Meinertz, S. Baldus, Neutrophil activation precedes myocardial injury in patients with acute myocardial infarction, Free Radic. Biol. Med. 47 (2009) 79–83.
[75] C.L. Heslop, J.J. Frohlich, J.S. Hill, Myeloperoxidase and C-reactive protein have combined utility for long-term prediction of cardiovascular mortality after coronary angiography, J. Am. Coll. Cardiol. 55 (2010) 1102–1109.
[76] A.G. Rebeiz, H.M. Tamim, R.M. Sleiman, A.G. Abchee, Z. Ibrahim, M.Y. Khoury, S. Youhanna, H.N. Skouri, S.E. Alam, Plasma myeloperoxidase concentration predicts the presence and severity of coronary disease in patients with chest pain and negative troponin-T, Coron. Artery Dis. 22 (2011) 553–558.
[77] O. Duzguncinar, B. Yavuz, T. Hazirolan, A. Deniz, S.L. Tokgozoglu, D. Akata, E. Demirpence, Plasma myeloperoxidase is related to the severity of coronary artery disease, Acta Cardiol. 63 (2008) 147–152.
[78] M.C. Meuwese, E.S. Stroes, S.L. Hazen, J.N. van Miert, J.A. Kuivenhoven, R.G. Schaub, N.J. Wareham, R. Luben, J.J. Kastelein, K.T. Khaw, S.M. Boekholdt, Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals: the EPIC-Norfolk Prospective Population Study, J. Am. Coll. Cardiol. 50 (2007) 159–165.
[79] L. Kubala, G. Lu, S. Baldus, L. Berglund, J.P. Eiserich, Plasma levels of myeloperoxidase are not elevated in patients with stable coronary artery disease, Clin. Chim. Acta 394 (2008) 59–62.
[80] L.Q. Chen, A. Rohatgi, C.R. Ayers, S.R. Das, A. Khera, J.D. Berry, D.K. McGuire, J.A. de Lemos, Race-specific associations of myeloperoxidase with atherosclerosis in a population-based sample: the Dallas Heart Study, Atherosclerosis 219 (2011) 833–838.
[81] R.V. Wainstein, M.V. Wainstein, J.P. Ribeiro, L.V. Dornelles, P. Tozzati, P. Ashton-Prolla, I.P. Ewald, G. Vietta, C.A. Polanczyk, Association between myeloperoxidase polymorphisms and its plasma levels with severity of coronary artery disease, Clin. Biochem. 43 (2010) 57–62.
[82] H. Scharnagl, M.E. Kleber, B. Genser, S. Kickmaier, W. Renner, G. Weihrauch, T. Grammer, C. Rossmann, B.R. Winkelmann, B.O. Boehm, W. Sattler, W. Marz, E. Malle, Association of myeloperoxidase with total and cardiovascular mortality in individuals undergoing coronary angiography–the LURIC study, Int. J. Cardiol. 174 (2014) 96–105.
[83] A.O. Oyenuga, D. Couper, K. Matsushita, E. Boerwinkle, A.R. Folsom, Association of monocyte myeloperoxidase with incident cardiovascular disease: the Atherosclerosis Risk in Communities Study, PLoS One 13 (2018) e0205310.
[84] H.W. Khine, J.F. Teiber, R.W. Haley, A. Khera, C.R. Ayers, A. Rohatgi, Association of the serum myeloperoxidase/high-density lipoprotein particle ratio and incident cardiovascular events in a multi-ethnic population: observations from the Dallas Heart Study, Atherosclerosis 263 (2017) 156–162.
[85] S. Baldus, C. Heeschen, T. Meinertz, A.M. Zeiher, J.P. Eiserich, T. Munzel, M.L. Simoons, C.W. Hamm, CAPTURE Investigators, Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes, Circulation 108 (2003) 1440–1445.
[86] M.L. Brennan, M.S. Penn, F. Van Lente, V. Nambi, M.H. Shishehbor, R.J. Aviles, M. Goormastic, M.L. Pepoy, E.S. McErlean, E.J. Topol, S.E. Nissen, S.L. Hazen, Prognostic value of myeloperoxidase in patients with chest pain, N. Engl. J. Med. 349 (2003) 1595–1604.
[87] E. Cavusoglu, C. Ruwende, C. Eng, V. Chopra, S. Yanamadala, L.T. Clark, D.J. Pinsky, J.D. Marmur, Usefulness of baseline plasma myeloperoxidase levels as an independent predictor of myocardial infarction at two years in patients presenting with acute coronary syndrome, Am. J. Cardiol. 99 (2007) 1364–1368.
[88] D.A. Morrow, M.S. Sabatine, M.L. Brennan, J.A. de Lemos, S.A. Murphy, C.T. Ruff, N. Rifai, C.P. Cannon, S.L. Hazen, Concurrent evaluation of novel cardiac biomarkers in acute coronary syndrome: myeloperoxidase and soluble CD40 ligand and the risk of recurrent ischaemic events in TACTICS-TIMI 18, Eur. Heart J. 29 (2008) 1096–1102.
[89] K. Kalantar-Zadeh, M.L. Brennan, S.L. Hazen, Serum myeloperoxidase and mortality in maintenance hemodialysis patients, Am. J. Kidney Dis. 48 (2006) 59–68.
[90] R.M. Roman, P.V. Camargo, F.K. Borges, A.P. Rossini, C.A. Polanczyk, Prognostic value of myeloperoxidase in coronary artery disease: comparison of unstable and stable angina patients, Coron. Artery Dis. 21 (2010) 129–136.
[91] N.D. Wong, H. Gransar, J. Narula, L. Shaw, J.H. Moon, R. Miranda-Peats, A. Rozanski, S.W. Hayes, L.E. Thomson, J.D. Friedman, D.S. Berman, Myeloperoxidase, subclinical atherosclerosis, and cardiovascular disease events, JACC Cardiovasc. Imaging 2 (2009) 1093–1099.
[92] T.J. Mocatta, A.P. Pilbrow, V.A. Cameron, R. Senthilmohan, C.M. Frampton, A.M. Richards, C.C. Winterbourn, Plasma concentrations of myeloperoxidase predict mortality after myocardial infarction, J. Am. Coll. Cardiol. 49 (2007) 1993–2000.
[93] W.H. Tang, Y. Wu, S.J. Nicholls, S.L. Hazen, Plasma myeloperoxidase predicts incident cardiovascular risks in stable patients undergoing medical management for coronary artery disease, Clin. Chem. 57 (2011) 33–39.
[94] W.H. Tang, N. Iqbal, Y. Wu, S.L. Hazen, Usefulness of cardiac biomarker score for risk stratification in stable patients undergoing elective cardiac evaluation across glycemic status, Am. J. Cardiol. 111 (2013) 465–470.
[95] S.J. Nicholls, W.H. Tang, D. Brennan, M.L. Brennan, S. Mann, S.E. Nissen, S.L. Hazen, Risk prediction with serial myeloperoxidase monitoring in patients with acute chest pain, Clin. Chem. 57 (2011) 1762–1770.
[96] M. Exner, E. Minar, W. Mlekusch, S. Sabeti, J. Amighi, W. Lalouschek, G. Maurer, C. Bieglmayer, H. Kieweg, O. Wagner, M. Schillinger, Myeloperoxidase predicts progression of carotid stenosis in states of low high-density lipoprotein cholesterol, J. Am. Coll. Cardiol. 47 (2006) 2212–2218.
[97] F.S. Apple, L.A. Pearce, A. Chung, R. Ler, M.M. Murakami, Multiple biomarker use for detection of adverse events in patients presenting with symptoms suggestive of acute coronary syndrome, Clin. Chem. 53 (2007) 874–881.
[98] A. Stefanescu, S. Braun, G. Ndrepepa, T. Koppara, H. Pavaci, J. Mehilli, A. Schomig, A. Kastrati, Prognostic value of plasma myeloperoxidase concentration in patients with stable coronary artery disease, Am. Heart J. 155 (2008) 356–360.
[99] K.M. Eggers, M. Dellborg, N. Johnston, J. Oldgren, E. Swahn, P. Venge, B. Lindahl, Myeloperoxidase is not useful for the early assessment of patients with chest pain, Clin. Biochem. 43 (2010) 240–245.
[100] B.M. Scirica, M.S. Sabatine, P. Jarolim, S.A. Murphy, J.L. de Lemos, E. Braunwald, D.A. Morrow, Assessment of multiple cardiac biomarkers in non-ST-segment elevation acute coronary syndromes: observations from the MERLIN-TIMI 36 trial, Eur. Heart J. 32 (2011) 697–705.
[101] V. Rudolph, T. Keller, A. Schulz, F. Ojeda, T.K. Rudolph, S. Tzikas, C. Bickel, T. Meinertz, T. Munzel, S. Blankenberg, S. Baldus, Diagnostic and prognostic performance of myeloperoxidase plasma levels compared with sensitive troponins in patients admitted with acute onset chest pain, Circ. Cardiovasc. Genet. 5 (2012) 561–568.
[102] A.T. Askari, M.L. Brennan, X. Zhou, J. Drinko, A. Morehead, J.D. Thomas, E.J. Topol, S.L. Hazen, M.S. Penn, Myeloperoxidase and plasminogen activator inhibitor 1 play a central role in ventricular remodeling after myocardial infarction, J. Exp. Med. 197 (2003) 615–624.
[103] N. Vasilyev, T. Williams, M.L. Brennan, S. Unzek, X. Zhou, J.W. Heinecke, D.R. Spitz, E.J. Topol, S.L. Hazen, M.S. Penn, Myeloperoxidase-generated oxidants modulate left ventricular remodeling but not infarct size after myocardial infarction, Circulation 112 (2005) 2812–2820.
[104] W.H. Tang, M.L. Brennan, K. Philip, W. Tong, S. Mann, F. Van Lente, S.L. Hazen, Plasma myeloperoxidase levels in patients with chronic heart failure, Am. J. Cardiol. 98 (2006) 796–799.
[105] W.H. Tang, R. Katz, M.L. Brennan, R.J. Aviles, R.P. Tracy, B.M. Psaty, S.L. Hazen, Usefulness of myeloperoxidase levels in healthy elderly subjects to predict risk of developing heart failure, Am. J. Cardiol. 103 (2009) 1269–1274.
[106] L.L. Ng, B. Pathik, I.W. Loke, I.B. Squire, J.E. Davies, Myeloperoxidase and C-reactive protein augment the specificity of B-type natriuretic peptide in community screening for systolic heart failure, Am. Heart J. 152 (2006) 94–101.
[107] V. Rudolph, T.K. Rudolph, J.C. Hennings, S. Blankenberg, R. Schnabel, D. Steven, M. Haddad, K. Knittel, S. Wende, J. Wenzel, T. Munzel, T. Heitzer, T. Meinertz, C. Hubner, S. Baldus, Activation of polymorphonuclear neutrophils in patients with impaired left ventricular function, Free Radic. Biol. Med. 43 (2007) 1189–1196.
[108] W.H. Tang, W. Tong, R.W. Troughton, M.G. Martin, K. Shrestha, A. Borowski, S. Jasper, S.L. Hazen, A.L. Klein, Prognostic value and echocardiographic determinants of plasma myeloperoxidase levels in chronic heart failure, J. Am. Coll. Cardiol. 49 (2007) 2364–2370.
[109] T. Reichlin, T. Socrates, P. Egli, M. Potocki, T. Breidthardt, N. Arenja, J. Meissner, M. Noveanu, M. Reiter, R. Twerenbold, N. Schaub, A. Buser, C. Mueller, Use of myeloperoxidase for risk stratification in acute heart failure, Clin. Chem. 56 (2010) 944–951.
[110] Y. Michowitz, S. Kisil, H. Guzner-Gur, A. Rubinstein, D. Wexler, D. Sheps, G. Keren, J. George, Usefulness of serum myeloperoxidase in prediction of mortality in patients with severe heart failure, Isr. Med. Assoc. J. 10 (2008) 884–888.
[111] V. Rudolph, T.K. Rudolph, L. Kubala, N. Clauberg, R. Maas, M. Pekarova, A. Klinke, D. Lau, K. Szocs, T. Meinertz, R.H. Boger, S. Baldus, A myeloperoxidase promoter polymorphism is independently associated with mortality in patients with impaired left ventricular function, Free Radic. Biol. Med. 47 (2009) 1584–1590.
[112] M. Ali, B. Pulli, G. Courties, B. Tricot, M. Sebas, Y. Iwamoto, I. Hilgendorf, S. Schob, A. Dong, W. Zheng, A. Skoura, A. Kalgukar, C. Cortes, R. Ruggeri, F.K. Swirski, M. Nahrendorf, L. Buckbinder, J.W. Chen, Myeloperoxidase inhibition improves ventricular function and remodeling after experimental myocardial infarction, JACC Basic Transl. Sci. 1 (2016) 633–643.
[113] K.B. Shah, W.J. Kop, R.H. Christenson, D.B. Diercks, D. Kuo, S. Henderson, K. Hanson, M.R. Mehra, C.R. deFilippi, Lack of diagnostic and prognostic utility of circulating plasma myeloperoxidase concentrations in patients presenting with dyspnea, Clin. Chem. 55 (2009) 59–67.
[114] T.K. Rudolph, S. Wipper, B. Reiter, V. Rudolph, A. Coym, C. Detter, D. Lau, A. Klinke, K. Friedrichs, T. Rau, M. Pekarova, D. Russ, K. Knoll, M. Kolk, B. Schroeder, K. Wegscheider, H. Andresen, E. Schwedhelm, R. Boeger, H. Ehmke, S. Baldus, Myeloperoxidase deficiency preserves vasomotor function in humans, Eur. Heart J. 33 (2012) 1625–1634.
[115] L.P. Van der Zwan, P.G. Scheffer, J.M. Dekker, C.D. Stehouwer, R.J. Heine, T. Teerlink, Hyperglycemia and oxidative stress strengthen the association between myeloperoxidase and blood pressure, Hypertension 55 (2010) 1366–1372.
[116] V.A. Cameron, T.J. Mocatta, A.P. Pilbrow, C.M. Frampton, R.W. Troughton, A.M. Richards, C.C. Winterbourn, Angiotensin type-1 receptor A1166C gene polymorphism correlates with oxidative stress levels in human heart failure, Hypertension 47 (2006) 1155–1161.
[117] L. Aldabbous, V. Abdul-Salam, T. McKinnon, L. Duluc, J. Pepke-Zaba, M. Southwood, A.J. Ainscough, C. Hadinnapola, M.R. Wilkins, M. Toshner, B. Wojciak-Stothard, Neutrophil extracellular traps promote angiogenesis: evidence from vascular pathology in pulmonary hypertension, Arterioscler. Thromb. Vasc. Biol. 36 (2016) 2078–2087.
[118] A. Klinke, E. Berghausen, K. Friedrichs, S. Molz, D. Lau, L. Remane, M. Berlin, C. Kaltwasser, M. Adam, D. Mehrkens, M. Mollenhauer, K. Manchanda, T. Ravekes, G.A. Heresi, M. Aytekin, R.A. Dweik, J.K. Hennigs, L. Kubala, E. Michaelsson, S. Rosenkranz, T.K. Rudolph, S.L. Hazen, H. Klose, R.T. Schermuly, V. Rudolph, S. Baldus, Myeloperoxidase aggravates pulmonary

arterial hypertension by activation of vascular Rho-kinase, JCI Insight 3 (2018).
[119] J.E. Jordan, Z.Q. Zhao, J. Vinten-Johansen, The role of neutrophils in myocardial ischemia-reperfusion injury, Cardiovasc. Res. 43 (1999) 860–878.
[120] J. Vinten-Johansen, Involvement of neutrophils in the pathogenesis of lethal myocardial reperfusion injury, Cardiovasc. Res. 61 (2004) 481–497.
[121] S. Baldus, T. Heitzer, J.P. Eiserich, D. Lau, H. Mollnau, M. Ortak, S. Petri, B. Goldmann, H.J. Duchstein, J. Berger, U. Helmchen, B.A. Freeman, T. Meinertz, T. Munzel, Myeloperoxidase enhances nitric oxide catabolism during myocardial ischemia and reperfusion, Free Radic. Biol. Med. 37 (2004) 902–911.
[122] R.M. Roman, A.E. Wendland, C.A. Polanczyk, Myeloperoxidase and coronary arterial disease: from research to clinical practice, Arq. Bras. Cardiol. 91 (2008) e11–e19.
[123] K. Stamboul, M. Zeller, L. Rochette, Y. Cottin, A. Cochet, T. Leclercq, G. Porot, C. Guenancia, M. Fichot, N. Maillot, C. Vergely, L. Lorgis, Relation between high levels of myeloperoxidase in the culprit artery and microvascular obstruction, infarct size and reverse remodeling in ST-elevation myocardial infarction, PLoS One 12 (2017) e0179929.
[124] J.S. Berger, C.M. Ballantyne, M.H. Davidson, J.L. Johnson, E.A. Tarka, D. Lawrence, T. Trivedi, A. Zalewski, E.R. Mohler III, Peripheral artery disease, biomarkers, and darapladib, Am. Heart J. 161 (2011) 972–978.
[125] N. Matijevic, K.K. Wu, N. Nidkarni, G. Heiss, A.R. Folsom, The ARIC carotid MRI study of blood cellular markers: an inverse association of monocyte myeloperoxidase content with peripheral arterial disease, Angiology 62 (2011) 237–244.
[126] M. Wildgruber, T. Aschenbrenner, H. Wendorff, M. Czubba, A. Glinzer, B. Haller, M. Schiemann, A. Zimmermann, H. Berger, H.H. Eckstein, R. Meier, W.A. Wohlgemuth, P. Libby, A. Zernecke, The "Intermediate" CD14(++)CD16(+) monocyte subset increases in severe peripheral artery disease in humans, Sci. Rep. 6 (2016) 39483.
[127] H. Maezawa, A. Maeda, Y. Iso, T. Sakai, H. Suzuki, The histological characteristics and virtual histology findings of the tissues obtained by a distal protection device during endovascular therapy for peripheral artery disease, J. Cardiol. 69 (2017) 125–130.
[128] G. Brevetti, F. Piscione, P. Cirillo, G. Galasso, V. Schiano, E. Barbato, F. Scopacasa, M. Chiariello, In concomitant coronary and peripheral arterial disease, inflammation of the affected limbs predicts coronary artery endothelial dysfunction, Atherosclerosis 201 (2008) 440–446.
[129] J. Chen, E.R. Mohler, D. Xie, M. Shlipak, R.R. Townsend, L.J. Appel, A. Ojo, M. Schreiber, L. Nessel, X. Zhang, D. Raj, L. Strauss, C.M. Lora, M. Rahman, L.L. Hamm, J. He, C.S. Investigators, Traditional and non-traditional risk factors for incident peripheral arterial disease among patients with chronic kidney disease, Nephrol. Dial. Transplant. 31 (2016) 1145–1151.
[130] Z. Ali, P. Sarcia, T.H. Mosley Jr., V. Kondragunta, I.J. Kullo, Association of serum myeloperoxidase with the ankle-brachial index and peripheral arterial disease, Vasc. Med. 14 (2009) 215–220.
[131] Z. Ye, Z. Ali, G.G. Klee, T.H. Mosley Jr., I.J. Kullo, Associations of candidate biomarkers of vascular disease with the ankle-brachial index and peripheral arterial disease, Am. J. Hypertens. 26 (2013) 495–502.
[132] G. Brevetti, V. Schiano, E. Laurenzano, G. Giugliano, M. Petretta, F. Scopacasa, M. Chiariello, Myeloperoxidase, but not C-reactive protein, predicts cardiovascular risk in peripheral arterial disease, Eur. Heart J. 29 (2008) 224–230.
[133] H. Haslacher, T. Perkmann, J. Gruenewald, M. Exner, G. Endler, V. Scheichenberger, O. Wagner, M. Schillinger, Plasma myeloperoxidase level and peripheral arterial disease, Eur. J. Clin. Investig. 42 (2012) 463–469.
[134] Y. Matsuo, H. Onodera, Y. Shiga, M. Nakamura, M. Ninomiya, T. Kihara, K. Kogure, Correlation between myeloperoxidase-quantified neutrophil accumulation and ischemic brain injury in the rat. Effects of neutrophil depletion, Stroke 25 (1994) 1469–1475.
[135] R. Forghani, H.J. Kim, G.R. Wojtkiewicz, L. Bure, Y. Wu, M. Hayase, Y. Wei, Y. Zheng, M.A. Moskowitz, J.W. Chen, Myeloperoxidase propagates damage and is a potential therapeutic target for subacute stroke, J. Cereb. Blood Flow Metab. 35 (2015) 485–493.
[136] H.J. Kim, Y. Wei, G.R. Wojtkiewicz, J.Y. Lee, M.A. Moskowitz, J.W. Chen, Reducing myeloperoxidase activity decreases inflammation and increases cellular protection in ischemic stroke, J. Cereb. Blood Flow Metab. (2018), https://doi.org/10.1177/0271678X18771978 (271678X18771978).
[137] H. Kim, Y. Wei, J.Y. Lee, Y. Wu, Y. Zheng, M.A. Moskowitz, J.W. Chen, Myeloperoxidase inhibition increases neurogenesis after ischemic stroke, J. Pharmacol. Exp. Ther. 359 (2016) 262–272.
[138] G.R. Zheng, B. Chen, J. Shen, S.Z. Qiu, H.M. Yin, W. Mao, H.X. Wang, J.B. Gao, Serum myeloperoxidase concentrations for outcome prediction in acute intracerebral hemorrhage, Clin. Chim. Acta 487 (2018) 330–336.
[139] F. Palm, P.J. Pussinen, A. Safer, T. Tervahartiala, T. Sorsa, C. Urbanek, H. Becher, A.J. Grau, Serum matrix metalloproteinase-8, tissue inhibitor of metalloproteinase and myeloperoxidase in ischemic stroke, Atherosclerosis 271 (2018) 9–14.
[140] A. Hoy, B. Leininger-Muller, O. Poirier, G. Siest, M. Gautier, A. Elbaz, P. Amarenco, S. Visvikis, Myeloperoxidase polymorphisms in brain infarction. Association with infarct size and functional outcome, Atherosclerosis 167 (2003) 223–230.
[141] C.L. Phuah, T. Dave, R. Malik, M.R. Raffeld, A.M. Ayres, J.N. Goldstein, A. Viswanathan, S.M. Greenberg, J.M. Jagiella, B.M. Hansen, B. Norrving, J. Jimenez-Conde, J. Roquer, A. Pichler, C. Enzinger, J. Montaner, I. Fernandez-Cadenas, A. Lindgren, A. Slowik, R. Schmidt, A. Biffi, N. Rost, C.D. Langefeld, H.S. Markus, B.D. Mitchell, B.B. Worrall, S.J. Kittner, D. Woo, M. Dichgans, J. Rosand, C.D. Anderson, METASTROKE, NINDS-SiGN Consortium, International Stroke Genetics Consortium, Genetic variants influencing elevated myeloperoxidase levels increase risk of stroke, Brain 140 (2017) 2663–2672.
[142] C.B. Wright, Y. Moon, M.C. Paik, T.R. Brown, L. Rabbani, M. Yoshita, C. DeCarli, R. Sacco, M.S. Elkind, Inflammatory biomarkers of vascular risk as correlates of leukoariosis, Stroke 40 (2009) 3466–3471.
[143] P. Ganz, P. Amarenco, L.B. Goldstein, H. Sillesen, W. Bao, G.M. Preston, K.M.A. Welch, SPARCL Steering Committee, Association of osteopontin, neopterin, and myeloperoxidase with stroke risk in patients with prior stroke or transient ischemic attacks: results of an analysis of 13 biomarkers from the stroke prevention by aggressive reduction in cholesterol levels trial, Stroke 48 (2017) 3223–3231.
[144] M.J. Gounis, S. Vedantham, J.P. Weaver, A.S. Puri, C.S. Brooks, A.K. Wakhloo, A.A. Bogdanov Jr., Myeloperoxidase in human intracranial aneurysms: preliminary evidence, Stroke 45 (2014) 1474–1477.
[145] Y. Chu, K. Wilson, H. Gu, L. Wegman-Points, S.A. Dooley, G.L. Pierce, G. Cheng, R.A. Pena Silva, D.D. Heistad, D. Hasan, Myeloperoxidase is increased in human cerebral aneurysms and increases formation and rupture of cerebral aneurysms in mice, Stroke 46 (2015) 1651–1656.
[146] K. Friedrichs, S. Baldus, A. Klinke, Fibrosis in atrial fibrillation - role of reactive species and MPO, Front. Physiol. 3 (2012) 214.
[147] Y. Ishii, R.B. Schuessler, S.L. Gaynor, K. Yamada, A.S. Fu, J.P. Boineau, R.J. Damiano Jr., Inflammation of atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and atrial fibrillation, Circulation 111 (2005) 2881–2888.
[148] B. Richter, M. Gwechenberger, A. Socas, G. Zorn, S. Albinni, M. Marx, J. Bergler-Klein, T. Binder, J. Wojta, H.D. Gossinger, Markers of oxidative stress after ablation of atrial fibrillation are associated with inflammation, delivered radiofrequency energy and early recurrence of atrial fibrillation, Clin. Res. Cardiol. 101 (2012) 217–225.
[149] V. Rudolph, R.P. Andrie, T.K. Rudolph, K. Friedrichs, A. Klinke, B. Hirsch-Hoffmann, A.P. Schwoerer, D. Lau, X. Fu, K. Klingel, K. Sydow, M. Didie, A. Seniuk, E.C. von Leitner, K. Szoecs, J.W. Schrickel, H. Treede, U. Wenzel, T. Lewalter, G. Nickenig, W.H. Zimmermann, T. Meinertz, R.H. Boger, H. Reichenspurner, B.A. Freeman, T. Eschenhagen, H. Ehmke, S.L. Hazen, S. Willems, S. Baldus, Myeloperoxidase acts as a profibrotic mediator of atrial fibrillation, Nat. Med. 16 (2010) 470–474.
[150] N.E. Procter, J. Ball, D.T. Ngo, Y.Y. Chirkov, J.S. Isenberg, E.M. Hylek, S. Stewart, J.D. Horowitz, Platelet hyperaggregability in patients with atrial fibrillation. Evidence of a background proinflammatory milieu, Herz 41 (2016) 57–62.
[151] R.B. Schnabel, P.S. Wild, S. Wilde, F.M. Ojeda, A. Schulz, T. Zeller, C.R. Sinning, J. Kunde, K.J. Lackner, T. Munzel, S. Blankenberg, Multiple biomarkers and atrial fibrillation in the general population, PLoS One 9 (2014) e112486.
[152] M. Mollenhauer, K. Friedrichs, M. Lange, J. Gesenberg, L. Remane, C. Kerkenpass, J. Krause, J. Schneider, T. Ravekes, M. Maass, M. Halbach, G. Peinkofer, T. Saric, D. Mehrkens, M. Adam, F.G. Deuschl, D. Lau, B. Geertz, K. Manchanda, T. Eschenhagen, L. Kubala, T.K. Rudolph, Y. Wu, W.H.W. Tang, S.L. Hazen, S. Baldus, A. Klinke, V. Rudolph, Myeloperoxidase mediates postischemic arrhythmogenic ventricular remodeling, Circ. Res. 121 (2017) 56–70.
[153] M. Sadowski, M. Zabczyk, A. Undas, Coronary thrombus composition: links with inflammation, platelet and endothelial markers, Atherosclerosis 237 (2014) 555–561.
[154] M. Nosaka, Y. Ishida, A. Kimura, T. Kondo, Time-dependent appearance of intrathrombus neutrophils and macrophages in a stasis-induced deep vein thrombosis model and its application to thrombus age determination, Int. J. Legal Med. 123 (2009) 235–240.
[155] L.J. Downing, R.M. Strieter, A.M. Kadell, C.A. Wilke, S.L. Brown, S.K. Wrobleski, M.D. Burdick, M.S. Hulin, J.B. Fowlkes, L.J. Greenfield, T.W. Wakefield, Neutrophils are the initial cell type identified in deep venous thrombosis induced vein wall inflammation, ASAIO J. 42 (1996) M677–M682.
[156] A.M. Mitchell, K.E. Nordenholz, J.A. Kline, Tandem measurement of D-dimer and myeloperoxidase or C-reactive protein to effectively screen for pulmonary embolism in the emergency department, Acad. Emerg. Med. 15 (2008) 800–805.
[157] G. Ndrepepa, S. Braun, A. Schomig, A. Kastrati, Impact of therapy with statins, beta-blockers and angiotensin-converting enzyme inhibitors on plasma myeloperoxidase in patients with coronary artery disease, Clin. Res. Cardiol. 100 (2011) 327–333.
[158] H. Beril Gok, I. Solaroglu, O. Okutan, B. Cimen, E. Kaptanoglu, S. Palaoglu, Metoprolol treatment decreases tissue myeloperoxidase activity after spinal cord injury in rats, J. Clin. Neurosci. 14 (2007) 138–142.
[159] F. Gao, J. Chen, B.L. Lopez, T.A. Christopher, J. Gu, P. Lysko, R.R. Ruffolo Jr., E.H. Ohlstein, X.L. Ma, T.L. Yue, Comparison of bisoprolol and carvedilol cardioprotection in a rabbit ischemia and reperfusion model, Eur. J. Pharmacol. 406 (2000) 109–116.
[160] T. Macickova, J. Pecivova, R. Nosal, A. Lojek, M. Pekarova, D. Cupanikova, Inhibition of superoxide generation and myeloperoxidase release by carvedilol after receptor and nonreceptor stimulation of human neutrophils, Neuro Endocrinol. Lett. 29 (2008) 790–793.
[161] P.A. Cowled, A. Khanna, P.E. Laws, J.B. Field, A. Varelias, R.A. Fitridge, Statins inhibit neutrophil infiltration in skeletal muscle reperfusion injury, J. Surg. Res. 141 (2007) 267–276.
[162] A.P. Kumar, W.F. Reynolds, Statins downregulate myeloperoxidase gene expression in macrophages, Biochem. Biophys. Res. Commun. 331 (2005) 442–451.
[163] I. Andreou, D. Tousoulis, A. Miliou, C. Tentolouris, K. Zisimos, P. Gounari, G. Siasos, N. Papageorgiou, C.A. Papadimitriou, M.A. Dimopoulos, C. Stefanadis, Effects of rosuvastatin on myeloperoxidase levels in patients with chronic heart failure: a randomized placebo-controlled study, Atherosclerosis 210 (2010) 194–198.
[164] T. Zhou, S.H. Zhou, S.S. Qi, X.Q. Shen, G.F. Zeng, H.N. Zhou, The effect of

atorvastatin on serum myeloperoxidase and CRP levels in patients with acute coronary syndrome, Clin. Chim. Acta 368 (2006) 168–172.
[165] P. Stenvinkel, E. Rodriguez-Ayala, Z.A. Massy, A.R. Qureshi, P. Barany, B. Fellstrom, O. Heimburger, B. Lindholm, A. Alvestrand, Statin treatment and diabetes affect myeloperoxidase activity in maintenance hemodialysis patients, Clin. J. Am. Soc. Nephrol. 1 (2006) 281–287.
[166] S. Husted, R.F. Storey, R.A. Harrington, H. Emanuelsson, C.P. Cannon, Changes in inflammatory biomarkers in patients treated with ticagrelor or clopidogrel, Clin. Cardiol. 33 (2010) 206–212.
[167] S.L. Hazen, J.W. Heinecke, 3-Chlorotyrosine, a specific marker of myeloperoxidase-catalyzed oxidation, is markedly elevated in low density lipoprotein isolated from human atherosclerotic intima, J. Clin. Invest. 99 (1997) 2075–2081.
[168] G. Marsche, R. Zimmermann, S. Horiuchi, N.N. Tandon, W. Sattler, E. Malle, Class B scavenger receptors CD36 and SR-BI are receptors for hypochlorite-modified low density lipoprotein, J. Biol. Chem. 278 (2003) 47562–47570.
[169] C. Leeuwenburgh, M.M. Hardy, S.L. Hazen, P. Wagner, S. Oh-ishi, U.P. Steinbrecher, J.W. Heinecke, Reactive nitrogen intermediates promote low density lipoprotein oxidation in human atherosclerotic intima, J. Biol. Chem. 272 (1997) 1433–1436.
[170] S. Sirpal, Myeloperoxidase-mediated lipoprotein carbamylation as a mechanistic pathway for atherosclerotic vascular disease, Clin. Sci. (Lond.) 116 (2009) 681–695.
[171] D. El-Bejjani, S.L. Hazen, W. Mackay, N.E. Glass, T. Hulgan, M. Tungsiripat, G.A. McComsey, Higher plasma myeloperoxidase levels are not associated with an increased risk for cardiovascular events in HIV-infected adults, HIV Clin. Trials 9 (2008) 207–211.
[172] A.I. Abdo, B.S. Rayner, D.M. van Reyk, C.L. Hawkins, Low-density lipoprotein modified by myeloperoxidase oxidants induces endothelial dysfunction, Redox Biol. 13 (2017) 623–632.
[173] G. Marsche, R. Heller, G. Fauler, A. Kovacevic, A. Nuszkowski, W. Graier, W. Sattler, E. Malle, 2-chlorohexadecanal derived from hypochlorite-modified high-density lipoprotein-associated plasmalogen is a natural inhibitor of endothelial nitric oxide biosynthesis, Arterioscler. Thromb. Vasc. Biol. 24 (2004) 2302–2306.
[174] A. Mertens, P. Holvoet, Oxidized LDL and HDL: antagonists in atherothrombosis, FASEB J. 15 (2001) 2073–2084.
[175] K.A. Rye, P.J. Barter, Cardioprotective functions of HDLs, J. Lipid Res. 55 (2014) 168–179.
[176] H. Feng, X.A. Li, Dysfunctional high-density lipoprotein, Curr. Opin. Endocrinol. Diabetes Obes. 16 (2009) 156–162.
[177] C. Bergt, S. Pennathur, X. Fu, J. Byun, K. O'Brien, T.O. McDonald, P. Singh, G.M. Anantharamaiah, A. Chait, J. Brunzell, R.L. Geary, J.F. Oram, J.W. Heinecke, The myeloperoxidase product hypochlorous acid oxidizes HDL in the human artery wall and impairs ABCA1-dependent cholesterol transport, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 13032–13037.
[178] L. Zheng, M. Settle, G. Brubaker, D. Schmitt, S.L. Hazen, J.D. Smith, M. Kinter, Localization of nitration and chlorination sites on apolipoprotein A-I catalyzed by myeloperoxidase in human atheroma and associated oxidative impairment in ABCA1-dependent cholesterol efflux from macrophages, J. Biol. Chem. 280 (2005) 38–47.
[179] B. Shao, M.N. Oda, J.F. Oram, J.W. Heinecke, Myeloperoxidase: an oxidative pathway for generating dysfunctional high-density lipoprotein, Chem. Res. Toxicol. 23 (2010) 447–454.
[180] A. Undurti, Y. Huang, J.A. Lupica, J.D. Smith, J.A. DiDonato, S.L. Hazen, Modification of high density lipoprotein by myeloperoxidase generates a pro-inflammatory particle, J. Biol. Chem. 284 (2009) 30825–30835.
[181] S.J. Nicholls, S.L. Hazen, Myeloperoxidase and cardiovascular disease, Arterioscler. Thromb. Vasc. Biol. 25 (2005) 1102–1111.
[182] J.A. Vita, M.L. Brennan, N. Gokce, S.A. Mann, M. Goormastic, M.H. Shishehbor, M.S. Penn, J.F. Keaney Jr., S.L. Hazen, Serum myeloperoxidase levels independently predict endothelial dysfunction in humans, Circulation 110 (2004) 1134–1139.
[183] S. Tsimikas, Oxidative biomarkers in the diagnosis and prognosis of cardiovascular disease, Am. J. Cardiol. 98 (2006) 9P–17P.
[184] A. Daugherty, J.L. Dunn, D.L. Rateri, J.W. Heinecke, Myeloperoxidase, a catalyst for lipoprotein oxidation, is expressed in human atherosclerotic lesions, J. Clin. Invest. 94 (1994) 437–444.
[185] T. Naruko, M. Ueda, K. Haze, A.C. van der Wal, C.M. van der Loos, A. Itoh, R. Komatsu, Y. Ikura, M. Ogami, Y. Shimada, S. Ehara, M. Yoshiyama, K. Takeuchi, J. Yoshikawa, A.E. Becker, Neutrophil infiltration of culprit lesions in acute coronary syndromes, Circulation 106 (2002) 2894–2900.
[186] Y. Kataoka, M. Shao, K. Wolski, K. Uno, R. Puri, E. Murat Tuzcu, S.L. Hazen, S.E. Nissen, S.J. Nicholls, Myeloperoxidase levels predict accelerated progression of coronary atherosclerosis in diabetic patients: insights from intravascular ultrasound, Atherosclerosis 232 (2014) 377–383.
[187] I. Rashid, G.J. Maghzal, Y.C. Chen, D. Cheng, J. Talib, D. Newington, M. Ren, S.K. Vajandar, A. Searle, A. Maluenda, E.L. Lindstedt, A. Jabbour, A.J. Kettle, A. Bongers, C. Power, E. Michaelsson, K. Peter, R. Stocker, Myeloperoxidase is a potential molecular imaging and therapeutic target for the identification and stabilization of high-risk atherosclerotic plaque, Eur. Heart J. 39 (2018) 3301–3310.
[188] S.J. Weiss, G. Peppin, X. Ortiz, C. Ragsdale, S.T. Test, Oxidative autoactivation of latent collagenase by human neutrophils, Science 227 (1985) 747–749.
[189] Y. Wang, H. Rosen, D.K. Madtes, B. Shao, T.R. Martin, J.W. Heinecke, X. Fu, Myeloperoxidase inactivates TIMP-1 by oxidizing its N-terminal cysteine residue: an oxidative mechanism for regulating proteolysis during inflammation, J. Biol. Chem. 282 (2007) 31826–31834.
[190] S. Sugiyama, K. Kugiyama, M. Aikawa, S. Nakamura, H. Ogawa, P. Libby, Hypochlorous acid, a macrophage product, induces endothelial apoptosis and tissue factor expression: involvement of myeloperoxidase-mediated oxidant in plaque erosion and thrombogenesis, Arterioscler. Thromb. Vasc. Biol. 24 (2004) 1309–1314.
[191] B. Zhou, L. Zu, Y. Chen, X. Zheng, Y. Wang, B. Pan, M. Dong, E. Zhou, M. Zhao, Y. Zhang, L. Zheng, W. Gao, Myeloperoxidase-oxidized high density lipoprotein impairs atherosclerotic plaque stability by inhibiting smooth muscle cell migration, Lipids Health Dis. 16 (2017) 3.