Increasing evidence suggests that inflammation plays a role in the development of hypertension. Myeloperoxidase (MPO) is an enzyme linked to both inflammation and oxidative stress, but the relationship between MPO and blood pressure remains largely untested. Release of MPO by neutrophils and monocytes during inflammation plays an important role in the innate immune response, but MPO activity may also lead to tissue damage and precipitate atherogenesis. Many studies have demonstrated that systemic MPO levels predict risk throughout the spectrum of cardiovascular diseases. MPO catalyzes the production of hypochlorous acid and a range of other highly reactive species. These MPO-derived reactive substances may damage the arterial wall, thereby reducing its elasticity. In addition, by several mechanisms, MPO reduces the bioavailability of the endogenous vasodilator nitric oxide. Together, these mechanisms may lead to an increase in blood pressure. Because hydrogen peroxide is an obligate cosubstrate of MPO, the activity of MPO in the vasculature may be enhanced by increased local production of reactive oxygen species. Vascular production of superoxide and its dismutation product hydrogen peroxide has been shown to be stimulated by high glucose concentrations, resulting in increased activity of MPO. We therefore hypothesize that the relationship between MPO and blood pressure is stronger on a background of oxidative stress.

The aims of our study were to assess the relationship between plasma levels of MPO and blood pressure and to test the hypothesis that this relationship is strengthened by oxidative stress.

Methods

Subjects

The present study was conducted in the Hoorn Study follow-up examination conducted in 2000 and the Hoorn Screening Study, both of which are population-based studies in a white population. From the 822 participants, we excluded subjects with missing data on primary variables of interest, leaving 746 subjects, of whom 267...
had a normal glucose metabolism, 189 had an impaired glucose metabolism, and 290 had type 2 diabetes, according to WHO 1999 criteria. The local ethics committee approved the study, and all participants gave their written informed consent.

**Blood Pressure Measurement**

Subjects were in a sitting position and had rested for 5 minutes before measurement of systolic (SBP) and diastolic (DBP) blood pressure. A random-zero sphygmomanometer (Hawksley-Gelman, Lansing, Sussex, United Kingdom) was used for duplicate measurements, and mean values were used in analyses. Hypertension was defined as SBP >140 mm Hg or DBP >90 mm Hg, according to criteria described in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

**Biochemical Analyses**

A sandwich enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden) was used to determine MPO concentrations in EDTA-plasma, with intra- and interassay coefficients of variation of 3.9% and 5.0%, respectively. Plasma C-reactive protein (CRP) concentrations were determined with a highly sensitive in-house sandwich enzyme-linked immunosorbent assay. Circulating plasma oxidized low-density lipoprotein (LDL) was determined by competitive enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden). Hemoglobin A1c (HbA1c) was analyzed by ion-exchange high-performance liquid chromatography (reference range, 4.3 to 6.1%) on a modular monitoring system (Bio-Rad, Veenendaal, The Netherlands). Glucose was measured enzymatically (Roche, Mannheim, Germany), and insulin was determined by a 2-site immunoradiometric assay (Medgenix Diagnostics, Fleurus, Belgium). Total and high-density lipoprotein (HDL) cholesterol and triglycerides were measured by standard enzymatic methods (Roche). LDL-cholesterol concentration was determined with a direct method by the “N-geneous” assay (GenZyme, Cambridge, Mass). With this method, a triglyceride concentration up to 13.5 mmol/L does not interfere with measurement of LDL-cholesterol.

**Microalbuminuria, Metabolic Syndrome, and Cardiovascular Disease**

Microalbuminuria was defined as urinary albumin/creatinine ratio ≥2.0 mg/mmol. Metabolic syndrome was defined according to the Adult Treatment Panel III of the National Cholesterol Education Program, ie, 3 or more of the following: fasting glucose ≥6.1 mmol/L, HDL-cholesterol <1.03 mmol/L (men) or <1.29 mmol/L (women), triglycerides ≥1.7 mmol/L, waist circumference >102 cm (men) or >88 cm (women), and blood pressure ≥130/85 mm Hg. Prior cardiovascular disease was defined as Minnesota Code 1.1 to 1.3, 4.1 to 4.3, 5.1 to 5.3, or 7.1 on the ECG; coronary bypass operation or angioplasty; an ankle-brachial blood pressure index <0.9 in either leg; peripheral arterial bypass; or amputation for atherosclerotic disease.

**Statistics**

Data are presented as mean and SD or, if skewed, median and interquartile range. Bivariates were assessed by calculation of the Spearman ρ. Skewed variables were natural log transformed before trend analyses and linear regression analyses. Statistical significance for linear trend across tertiles of MPO was calculated by linear regression, with adjustment for age and sex, or by linear-by-linear χ² tests. Multivariable linear regression analysis was used to assess the relationship between (log-transformed) MPO and blood pressure. Confounding by other risk factors was investigated by adding these factors one by one to age- and sex-adjusted models and by investigating fully adjusted models including all risk factors. Regression coefficients were expressed as change in blood pressure (mm Hg) per SD increase of log-transformed MPO. Because the variance of MPO did not significantly differ (tested with the Levene test for homogeneity of variance) between the various strata investigated, the SD of the entire population was used for all stratified analyses. Data were analyzed using SPSS software, version 15 (SPSS Inc., Chicago, IL). A 2-tailed probability value <0.05 was considered to indicate statistical significance.

**Results**

**Population Characteristics**

Of the 746 study participants 432 (58%) were hypertensive. After adjustment for age and sex, it was found that blood pressure, prevalence of hypertension, and use of antihypertensive medication significantly increased across tertiles of MPO (Table 1). Higher tertiles of MPO were associated with higher CRP levels, and also, if MPO was analyzed as a continuous variable, a significant association with CRP was observed (p=0.29; P<0.001). HbA1c, fasting glucose, and insulin levels also increased in parallel with MPO, but the percentage of individuals with type 2 diabetes and impaired glucose metabolism was not significantly different between MPO tertiles. Body mass index (BMI), waist circumference, and prior cardiovascular disease significantly increased with higher MPO levels, but no significant relationships with lipid levels (including oxidized LDL) or the use of lipid-lowering medication were observed.

**Association Between MPO and Blood Pressure**

Linear regression analysis was used to investigate the relationship between MPO levels and SBP (Table 2) and DBP (Table 3). In the entire cohort, MPO was significantly associated with SBP and DBP, both in crude analysis and after adjustment for age and sex. Additional adjustment of the age- and sex-adjusted models for a range of potentially confounding risk factors, including use of antihypertensive medication and CRP, only marginally altered the strength of these associations.

**Modification of the Relationship Between MPO and Blood Pressure by Glucose**

Because we hypothesized that the adverse impact of MPO on blood pressure might be enhanced by hyperglycemia, we also examined the relationship between MPO and blood pressure in strata of fasting glucose. In individuals with glucose levels in the lowest tertile, MPO was not significantly associated with SBP (β [95% CI] of 1.04 [−1.38 to 3.46] mm Hg per 1-SD increase of MPO), but this association was stronger in individuals with intermediate glucose levels (including oxidized LDL) or the use of lipid-lowering medication and CRP, only marginally altered the strength of these associations.
The fact that the relationship between MPO and blood pressure was strongest in the presence of high levels of glucose and that oxidized LDL is associated with glucose (β=0.11; P=0.003) is in accordance with the hypothesis that MPO activity is enhanced by (glucose-induced) oxidative stress, but it does not exclude involvement of nonoxidative effects of glucose. To gain better insight in the effect of oxidative stress on the relationship between MPO and blood pressure, we repeated the analyses after stratification of the cohort according to levels of oxidized LDL, a validated marker of oxidative stress. The age- and sex-adjusted relationship between MPO and SBP by tertiles of oxidized LDL revealed a pattern similar to that observed for glucose, with the strongest association observed in individuals with high levels of oxidized LDL, ie, the third tertile (β=0.92 [1.31 to 3.14], 2.00 [0.71 to 4.70], and 3.58 [0.98 to 6.19] for increasing tertiles of oxidized LDL; Figure 2). Next, we examined whether the relationship between MPO and SBP was also modified by clinical or biochemical variables.
Table 2. Multivariable Linear Regression Models of the Relation Between MPO and SBP in Strata of Fasting Glucose

<table>
<thead>
<tr>
<th>Model</th>
<th>Overall</th>
<th>1st Tertile Glucose, &lt;5.8 mmol/L</th>
<th>2nd Tertile Glucose, 5.8–6.5 mmol/L</th>
<th>3rd Tertile Glucose, &gt;6.5 mmol/L</th>
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<td>( \beta ) (95% CI)</td>
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<td>( \beta ) (95% CI)</td>
</tr>
<tr>
<td>Crude</td>
<td>2.53 (1.06 to 3.99)</td>
<td>1.04 (−1.38 to 3.46)</td>
<td>1.88 (−0.83 to 4.59)</td>
<td>3.82 (1.39 to 6.26)</td>
</tr>
<tr>
<td>Model 1: MPO* + age + sex</td>
<td>2.10 (0.66 to 3.54)</td>
<td>0.61 (−1.70 to 2.93)</td>
<td>1.33 (−1.43 to 4.10)</td>
<td>3.42 (1.01 to 5.82)</td>
</tr>
<tr>
<td>Model 1 + CRP*</td>
<td>1.69 (0.21 to 3.17)</td>
<td>−0.03 (−2.40 to 2.34)</td>
<td>1.36 (−1.45 to 4.17)</td>
<td>3.31 (0.84 to 5.78)</td>
</tr>
<tr>
<td>Model 1 + glucose*</td>
<td>1.71 (0.28 to 3.14)</td>
<td>0.43 (−1.87 to 2.73)</td>
<td>1.32 (−1.45 to 4.10)</td>
<td>3.39 (0.96 to 5.82)</td>
</tr>
<tr>
<td>Model 1 + BMI</td>
<td>1.83 (0.40 to 3.25)</td>
<td>1.01 (−1.21 to 3.23)</td>
<td>1.03 (−1.74 to 3.79)</td>
<td>3.37 (0.95 to 5.79)</td>
</tr>
<tr>
<td>Model 1 + triglycerides*</td>
<td>2.12 (0.69 to 3.55)</td>
<td>0.64 (−1.69 to 2.96)</td>
<td>1.32 (−1.45 to 4.08)</td>
<td>3.48 (1.09 to 5.87)</td>
</tr>
<tr>
<td>Model 1 + microalbuminuria</td>
<td>2.05 (0.61 to 3.50)</td>
<td>0.57 (−1.74 to 2.88)</td>
<td>1.23 (−1.55 to 4.01)</td>
<td>3.44 (1.02 to 5.86)</td>
</tr>
<tr>
<td>Model 1 + prior cardiovascular disease</td>
<td>2.05 (0.57 to 3.53)</td>
<td>0.59 (−1.79 to 2.94)</td>
<td>1.35 (−1.48 to 4.17)</td>
<td>3.33 (0.83 to 5.83)</td>
</tr>
<tr>
<td>Model 1 + current smoker</td>
<td>2.28 (0.84 to 3.73)</td>
<td>0.80 (−1.51 to 3.11)</td>
<td>1.37 (−1.38 to 4.13)</td>
<td>3.55 (1.09 to 6.01)</td>
</tr>
<tr>
<td>Model 1 + antihypertensive medication</td>
<td>1.88 (0.44 to 3.31)</td>
<td>0.47 (−1.81 to 2.75)</td>
<td>1.22 (−1.56 to 3.99)</td>
<td>3.32 (0.91 to 5.73)</td>
</tr>
<tr>
<td>Model 1 + lipid-lowering medication</td>
<td>2.10 (0.65 to 3.55)</td>
<td>0.61 (−1.71 to 2.92)</td>
<td>1.32 (−1.46 to 4.11)</td>
<td>3.38 (0.96 to 5.80)</td>
</tr>
<tr>
<td>Fully adjusted model†</td>
<td>1.61 (0.31 to 3.10)</td>
<td>0.26 (−2.10 to 2.61)</td>
<td>1.11 (−1.77 to 4.00)</td>
<td>3.50 (0.86 to 6.14)</td>
</tr>
</tbody>
</table>

β values represent increase in systolic blood pressure (mm Hg) per SD increase of MPO. *Skewed variables were transformed by natural logarithm. †Adjusted for age, sex, CRP, glucose, BMI, triglycerides, microalbuminuria, prior cardiovascular disease, current smoking, and use of antihypertensive and lipid-lowering medication.

generally assumed to be associated with increased oxidative stress, ie, low HDL-cholesterol, obesity, and the metabolic syndrome. The concentration of HDL-cholesterol was inversely associated with oxidized LDL (\( \rho = −0.25; P<0.001 \)), whereas BMI was positively associated with oxidized LDL (\( \rho =0.13; P<0.001 \)). The association between MPO and SBP was strongest in subjects with HDL-cholesterol levels in the lowest tertile (\( \beta =3.96 \) [1.52 to 6.39]) and in subjects with a BMI in the highest tertile (\( \beta =3.52 \) [1.19 to 5.86] (Figure 2)). Levels of oxidized LDL were higher in individuals with the metabolic syndrome compared to those without the metabolic syndrome (69.9±16.1 and 60.6±13.1 U/L, respectively; \( P<0.001 \)), and in the former group, the age- and sex-adjusted association between MPO and blood pressure was strongest.

Table 3. Multivariable Linear Regression Models of the Relation Between MPO and DBP in Strata of Fasting Glucose

<table>
<thead>
<tr>
<th>Model</th>
<th>Overall</th>
<th>1st Tertile Glucose, &lt;5.8 mmol/L</th>
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<td>( \beta ) (95% CI)</td>
</tr>
<tr>
<td>Crude</td>
<td>0.85 (0.07 to 1.63)</td>
<td>0.09 (−1.25 to 1.43)</td>
<td>0.26 (−1.21 to 1.73)</td>
<td>1.66 (0.45 to 2.87)</td>
</tr>
<tr>
<td>Model 1: MPO* + age + sex</td>
<td>0.98 (0.20 to 1.76)</td>
<td>0.06 (−1.29 to 1.40)</td>
<td>0.60 (−0.89 to 2.10)</td>
<td>1.76 (0.54 to 2.98)</td>
</tr>
<tr>
<td>Model 1 + CRP*</td>
<td>0.83 (0.03 to 1.63)</td>
<td>−0.16 (−1.54 to 1.23)</td>
<td>0.71 (−0.81 to 2.23)</td>
<td>1.67 (0.42 to 2.93)</td>
</tr>
<tr>
<td>Model 1 + glucose*</td>
<td>0.77 (0.00 to 1.55)</td>
<td>0.00 (−1.35 to 1.35)</td>
<td>0.40 (−0.90 to 2.10)</td>
<td>1.67 (0.45 to 2.90)</td>
</tr>
<tr>
<td>Model 1 + BMI</td>
<td>0.79 (0.03 to 1.55)</td>
<td>0.28 (−1.01 to 1.58)</td>
<td>0.28 (−1.18 to 1.74)</td>
<td>1.68 (0.46 to 2.90)</td>
</tr>
<tr>
<td>Model 1 + triglycerides*</td>
<td>0.99 (0.22 to 1.77)</td>
<td>0.03 (−1.32 to 1.38)</td>
<td>0.57 (−0.90 to 2.04)</td>
<td>1.78 (0.57 to 3.00)</td>
</tr>
<tr>
<td>Model 1 + microalbuminuria</td>
<td>0.94 (0.16 to 1.72)</td>
<td>0.01 (−1.33 to 1.35)</td>
<td>0.57 (−0.94 to 2.08)</td>
<td>1.78 (0.57 to 3.00)</td>
</tr>
<tr>
<td>Model 1 + prior cardiovascular disease</td>
<td>0.97 (0.17 to 1.77)</td>
<td>0.05 (−1.32 to 1.42)</td>
<td>0.57 (−0.96 to 2.09)</td>
<td>1.75 (0.46 to 3.00)</td>
</tr>
<tr>
<td>Model 1 + current smoker</td>
<td>1.08 (0.30 to 1.86)</td>
<td>0.20 (−1.14 to 1.53)</td>
<td>0.61 (−0.89 to 2.12)</td>
<td>1.90 (0.66 to 3.14)</td>
</tr>
<tr>
<td>Model 1 + antihypertensive medication</td>
<td>0.87 (0.09 to 1.64)</td>
<td>0.00 (−1.34 to 1.33)</td>
<td>0.52 (−0.97 to 2.02)</td>
<td>1.72 (0.49 to 2.94)</td>
</tr>
<tr>
<td>Model 1 + lipid-lowering medication</td>
<td>0.98 (0.20 to 1.76)</td>
<td>0.05 (−1.30 to 1.39)</td>
<td>0.60 (−0.91 to 2.10)</td>
<td>1.76 (0.54 to 2.99)</td>
</tr>
<tr>
<td>Fully adjusted model†</td>
<td>0.81 (0.02 to 1.61)</td>
<td>0.07 (−1.10 to 1.43)</td>
<td>0.43 (−1.06 to 1.93)</td>
<td>1.82 (0.49 to 3.16)</td>
</tr>
</tbody>
</table>

β values represent increase in diastolic blood pressure (mm Hg) per SD increase of MPO. *Skewed variables were transformed by natural logarithm. †Adjusted for age, sex, CRP, glucose, BMI, triglycerides, microalbuminuria, prior cardiovascular disease, current smoking, and use of antihypertensive and lipid-lowering medication.
The interaction between the effects of BMI and MPO on SBP as shown in Figure 3 illustrates the clinical relevance of the MPO-associated increase in blood pressure, especially in subjects with a high BMI. The mean difference in SBP between individuals with both BMI and MPO in the highest tertile and individuals with both variables in the lowest tertile was 14 mm Hg.

**Discussion**

The main finding of the current study is that the concentration of MPO in the circulation was positively associated with both SBP and DBP. This association was independent of traditional cardiovascular risk factors, including CRP, and use of antihypertensive medication and was most prominent on a background of hyperglycemia or oxidative stress.

**Potential Mechanisms Linking MPO to Blood Pressure**

Local release by resident macrophages and transcytosis of MPO produced by activated neutrophils that are attracted and bound to sites of damaged endothelium are both sources of MPO in the vascular wall. The microenvironment of the subendothelial space of the vascular wall is especially conducive to MPO activity. Mitochondrial respiration, NAD(P)H oxidases, xanthine oxidase, and uncoupled nitric oxide synthase (NOS) are major sources of the highly reactive superoxide radical, which is actively converted into hydrogen peroxide by superoxide dismutase. Although less reactive than the superoxide radical, hydrogen peroxide is the cosubstrate for all MPO-catalyzed reactions. MPO amplifies the oxidative potential of hydrogen peroxide by producing a variety of reactive oxidants, including hypochlorous acid. Nitric oxide (NO), produced by endothelial NOS, is a powerful vasodilator and as such plays a critical role in the regulation of vascular tone. There are strong indications that MPO, by several mechanisms, may reduce the bioavailability of NO. First, NO serves as a substrate for peroxidases, and MPO may thus serve as a catalytic sink for NO. Second, scavenging of NO by MPO-derived reactive substances may further reduce the bioavailability of NO. Third, hypochlorous acid can react with nitrogen atoms of the NOS substrate arginine to produce chlorinated arginine species that are inhibitors of all isoforms of NOS and have been shown to impair endothelium-dependent relaxation of rat aortic rings. Finally, it has been demonstrated that hypochlorous acid is a potent inducer of uncoupling of endothelial NOS, thereby turning NOS into a superoxide producing enzyme.
reduction of NO bioavailability by MPO activity is a plausible mechanism for the adverse effect of MPO on blood pressure. In addition, MPO-derived reactive substances may damage the arterial wall and reduce its elasticity, thereby contributing to hypertension.

Enhancement of the Relationship Between MPO and Blood Pressure by Oxidative Stress and Hyperglycemia

Because hydrogen peroxide is an obligate cosubstrate of MPO, we hypothesized that the impact of MPO on blood pressure would be most prominent on a background of oxidative stress. This was confirmed by our observation that the relationship between MPO and blood pressure was most prominent in individuals with a high plasma concentration of oxidized LDL. Our finding that high levels of fasting glucose strengthened the association between MPO and blood pressure is also compatible with this hypothesis, because high glucose concentrations have been shown to stimulate vascular production of reactive oxygen species. HDL particles are known to have antiinflammatory and antioxidative properties. The observed decrease of the strength of the association between MPO and blood pressure with increasing levels of HDL-cholesterol is therefore also consistent with oxidative stress as a modifying factor. A high BMI, which is related to inflammation and oxidative stress, and the metabolic syndrome, which captures much of the risk associated with the above-mentioned variables, were also found to enhance the relationship between MPO and blood pressure. Notably, all conditions that strengthened the association between MPO and blood pressure were associated with increased levels of oxidized LDL. All in all, the results of these analyses point in the same direction, ie, that the impact of MPO on blood pressure is most prominent in the presence of (glucose-induced) oxidative stress.

Potential Confounding of the Relationship Between MPO and Blood Pressure by CRP

In contrast to the relationship between MPO and hypertension that has hardly been studied on the population level, in several studies an independent relationship between the inflammation marker CRP and hypertension was observed. Notably, CRP has been reported to stimulate release of MPO from polymorphonuclear cells and monocytes. This might indicate that the association between MPO and blood pressure is, at least partly, not causal but merely reflects the relationship between CRP and blood pressure. Indeed, in the present study MPO and CRP were significantly correlated, albeit with moderate strength. However, in the linear regression models, the association between MPO and blood pressure was only slightly attenuated on adjustment for CRP, indicating that confounding of this association by CRP is of minor significance. Most likely, different mechanisms are involved in the associations of MPO and CRP with hypertension. This is consistent with CRP being mainly produced by the liver on stimulation by inflammatory cytokines, whereas MPO is locally produced at sites of inflammation including the vasculature.

Study Limitations

First, although a causal relationship between MPO and blood pressure is plausible, we used a cross-sectional design, which does not allow us to draw definitive conclusions on causality. Second, although the original study population was recruited from the general population, for the present study a selection was made on the basis of glucose metabolism, ie, individuals with impaired glucose metabolism and type 2 diabetes were overrepresented. This design made this cohort very suitable to investigate the impact of (glucose-induced) oxidative stress on the relationship between MPO and hypertension. However, we cannot exclude the possibility that selection bias has influenced the relationship between MPO and blood pressure. Third, the study was performed in elderly white subjects, and the association between MPO and blood pressure may be different in younger individuals and other races. Fourth, MPO was measured in the circulation, and it is currently not known to what extent this measure reflects MPO in the vasculature.

Finally, we measured MPO mass and not activity. However, a strong correlation between MPO mass and MPO activity \( r=0.95 \) has been reported.

Perspectives

The current study demonstrates that a high plasma level of MPO is associated with a clinically relevant increase in both SBP and DBP. The relationship between MPO and blood pressure is particularly prominent on a background of hyperglycemia or oxidative stress, consistent with the ability of MPO to amplify oxidative stress, eg, by using hydrogen peroxide as a cosubstrate to form more reactive oxidant species. The relationship between MPO and hypertension, together with emerging evidence that MPO-derived oxidants contribute to initiation and propagation of acute and chronic vascular disease, identifies MPO as an interesting target for drug development. However, because MPO plays an important role in the innate immune system, a suitable inhibitor should specifically target activity of MPO in the vascular wall, without interfering with its bactericidal activity. Possibly, this selectivity may be achieved by lowering vascular oxidative stress and thereby the local concentration of hydrogen peroxide, the cosubstrate of MPO.

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Disclosures

None.

References


Hyperglycemia and Oxidative Stress Strengthen the Association Between Myeloperoxidase and Blood Pressure

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