Myeloperoxidase aids prognostication together with NT-BNP in high-risk patients with acute ST elevation myocardial infarction

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Abstract

**Background** Inflammation plays a critical role in acute myocardial infarction. One such inflammatory marker is myeloperoxidase (MPO). Its role as a predictor of death or MI in patients with ST segment elevation myocardial infarction (STEMI) is unclear. We sought to investigate this and compared it to N terminal pro B type natriuretic peptide (NT-BNP).

**Method** We studied 384 post STEMI patients. Patients were followed-up for the combined endpoint of death or readmission with non-fatal MI.

**Results** There were 40 deaths and 37 readmissions with MI. Median MPO was raised in patients experiencing death or MI compared to survivors (median [range] ng/ml, 50.6[15.3-124.1] vs. 33.5[6.6-400.2], p=0.001). Using a Cox proportional hazards model log median MPO (HR 6.91, 95% CI: 1.79-26.73, p=0.005) and log median NT-BNP (HR 4.21, 95% CI: 1.53-11.58, p=0.005) independently predicted death or non-fatal MI. MPO had predictive power in both below and above median NT-BNP levels (log rank 5.60, p=0.020, log rank 5.12, p=0.024 respectively). The receiver-operating curve for median NT-BNP yielded an area under the curve (AUC) of 0.72 (95% CI: 0.65-0.79, p<0.001); for median MPO the AUC was 0.62 (95% CI: 0.55-0.69, p=0.001). The logistic model combining the 2 markers yielded an AUC of 0.76 (95% CI: 0.69-0.82, p<0.001). **Conclusion** MPO and NT-BNP may be useful tools for risk stratification of all acute coronary syndromes, including higher risk STEMI patients.

**Keywords** Myocardial infarction; peptides, myeloperoxidase, prognosis
Introduction

Inflammatory mechanisms play a central role in atherosclerosis. Acute myocardial infarction (AMI) occurs when an underlying atherosclerotic plaque ruptures leading to thrombus formation and occlusion of a coronary vessel. As our understanding of this process has increased the importance of the leucocyte as being pivotal in this process has also increased. Indeed the association of the leucocyte with the extent of coronary artery disease has been known for some years. The importance of the white cell enzymes however is only recently being investigated. One such enzyme is myeloperoxidase (MPO) which is present in the granules of the leucocyte. Immunohistochemical studies have demonstrated the presence of MPO in atheromatous plaques. MPO can also activate metalloproteinases and inactivate plasminogen activator inhibitor, promoting destabilization and rupture of the atherosclerotic plaque surface. Furthermore, MPO catalytically consumes endothelium-derived nitric oxide, thereby reducing nitric oxide bioavailability, leading to vasoconstriction and endothelial dysfunction. Indeed MPO is emerging as a useful marker for prognostication in a variety of clinical settings. Recently it was shown to be of prognostic value in patients presenting with chest pain to the emergency room and there is also association between myeloperoxidase levels and risk of coronary artery disease. The inflammation in acute coronary syndromes is thought to be widespread. Its role however in the prognostication of AMI is unknown. In this study we investigated whether MPO would be of benefit in determining the prognosis of AMI, particularly death and reinfarction which remain a leading cause of mortality and morbidity. We compared this with N terminal pro B type natriuretic peptide (NT-BNP) which has been shown to be of prognostic benefit in this group of patients.
Methods

Study population

We studied 384 consecutive post ST segment elevation myocardial infarction (STEMI) patient who were admitted to the Coronary Care Unit of Leicester Royal Infirmary. The study complied with the Declaration of Helsinki, was approved by the local ethics committee and written informed consent was obtained from patients. Myocardial infarction (MI) was diagnosed if a patient had chest pain lasting >20 minutes, diagnostic serial electrocardiographic (ECG) changes consisting of new pathological Q waves or ST-segment elevation changes, and a plasma creatine kinase-MB elevation greater than twice normal or cardiac troponin I level >0.1 ng/mL.\textsuperscript{13} Exclusion criteria were known malignancy, or surgery in the previous month. Patients with ST-segment elevation of >0.1 mV in two contiguous ECG leads received thrombolytic therapy (tissue plasminogen activator or streptokinase) if they presented within a suitable time frame. Control subjects were age and gender matched and recruited from University of Leicester and had peptide measurements made once.

Plasma samples

Serial blood measurements were made at 0-24, 25-48, 49-72, 73-96, 97-120 hr after onset of chest pain for determination of plasma MPO and NT-BNP. A single median value over the 5 days was used in analysis. After 15 minutes bed rest, 20mL blood was collected into tubes containing EDTA and aprotinin. All plasma was stored at -70°C until assayed in a single batch.
Echocardiography

Transthoracic echocardiography was performed in patients using a Sonos 5500 instrument (Philips Medical Systems, Reigate, UK). A 16-segment left ventricular wall motion index (LVWMI) based on the American Society of Echocardiography model was derived by scoring each LV segment (1=normal, 2=hypokinesis, 3=akinesis and 4=dyskinesis (Paradoxical Motion), and dividing the total by the number of segments scored. Left ventricular ejection fraction (LVEF) was calculated using the biplane method of discs formula.

NT-BNP assay

Our NT-BNP assay was based on a non-competitive assay. Sheep antibodies were raised to the N-terminal of human NT-BNP and monoclonal mouse antibodies were raised to the C-terminal. The N-terminal IgG was affinity-purified and biotinylated. Samples or NT-BNP standards were incubated in C-terminal IgG–coated wells with the biotinylated antibody for 24 hours at 4°C. Detection was with methyl-acridinium ester (MAE)–labelled streptavidin. The lower limit of detection was 0.3 fmol/ml. There was no cross reactivity with atrial natriuretic peptide, BNP, or C-type natriuretic peptide. The results from this in-house assay are highly correlated (r=0.90, P<0.0001, n=86) to those obtained on the NTproBNP assay marketed by Roche Diagnostics Ltd. (Lewes, East Sussex, UK).

MPO assay

The MPO assay was based on a non-competitive assay. Capture antibody was 100ng of a monoclonal anti-MPO (Research Diagnostics Inc., Flanders, NJ) coated onto ELISA plates, and detection was with a rabbit anti-MPO antibody (Merck Biosciences
Ltd., Nottingham, UK). Samples or MPO standards were incubated for 24 hours at
4°C. Following washes, detection was performed using sequential incubations with
biotinylated goat anti-rabbit IgG and methyl-acridinium ester (MAE)–labelled
streptavidin. Intra and inter-assay coefficients of variation which were found to be
less than 10%.

End points
We assessed the value of both MPO and NT-BNP for the prediction of mortality. We
used a combined primary endpoint consisting of death and non-fatal MI and also
investigated death and non-fatal MI as individual secondary endpoints.
Hospitalisation for AMI was defined as above. We also investigated the secondary
endpoint of heart failure. Hospitalization for heart failure was defined as a hospital
admission for which heart failure was the primary reason. Endpoints were obtained by
reviewing the Office of National Statistics Registry, and by contacting each patient.
There was a minimum 30-day follow-up of all patients.

Statistical analysis
Statistical analyses were performed on SPSS Version 12 (SPSS Inc, Chicago,
Illinois). The continuous variables in the two independent groups were compared
using the Mann Whitney U test. Spearman’s correlations were performed and Cox
proportional hazards analyses were conducted which included baseline patient
characteristics (age, sex, serum creatinine, Killip class, territory of AMI, LVWMI and
whether the patient received thrombolysis or not) and peptide markers (including
troponin I), to test the independent predictive power of the peptides above and below
the median for death or non-fatal MI as defined above. NT-BNP and MPO were
normalised by log transformation. Thus hazard ratios refer to a tenfold rise in the levels of these markers. Kaplan-Meier survival curves were generated to visualise the relationship between the peptides NT-BNP and MPO and the composite endpoints. To compare the predictive value of NT-BNP and MPO, receiver-operating characteristic (ROC) curves were generated and the area under the curves (AUC) was calculated. A p value below 0.05 was deemed to be statistically significant. Power calculations suggest that 318 patients recruited over 24 months and a follow-up period of at least 1 month, with median survival probabilities of 0.8 or 0.7 at 12 months in the groups stratified by the biomarker median, would enable the hypothesis to be tested with a power of 95% at P<0.01 (2-sided test). We recruited 20% more patients in case follow-up was incomplete in some cases.

Results

Patient characteristics

The demographic features of the patient population separated into quartiles are shown in Table 1. There were 257 controls (132 male), age 61.8 ± 14.3. Median length of follow-up was 330 days with a range of 0–644 days (0 was due to death). Of the patients enrolled, 70.8 % received thrombolysis during the index admission. No patient was lost to follow-up. During follow-up, 40 (10.4%) patients died 37 (9.6%) were readmitted with AMI and there were 23 (6.0%) readmissions with heart failure. Echocardiographic data was available for 334 (87.0%) of the 384 patients and performed at a median of 3.5 days (range 2-5) after presentation with AMI. 39 echocardiograms were unanalysable (due to off axis apical views, and/or poor image quality) and 11 patients did not receive an echocardiogram.
MPO levels in patients and controls

Plasma levels of MPO in patients with AMI ranged from 4.0-405.2 ng/ml. Median level over the 5 days was 35.9 ng/ml, 25\textsuperscript{th} and 75\textsuperscript{th} centile 18.0 and 61.2 ng/ml. These levels were significantly higher than those observed in the control subjects (median 26.7 ng/ml range 8.0-79.0 ng/ml p<0.005). Plasma median MPO was raised in patients experiencing the primary endpoint of death or MI compared to survivors without recurrent MI (median [range] ng/ml, 50.6[15.3-124.1] vs. 34.5[6.6-400.2], p=0.001). The time course of secretion of MPO revealed a significant difference over the 5 days (p<0.0001) and is shown in figure 1.

Although MPO levels in the first 48 hrs after an AMI weakly correlated with peak troponin I levels (r= 0.183, p=0.025), this was not true for the later plasma levels (r=0.109, p=0.179). There was no correlation of MPO with age (r= -0.04, p> 0.247), LVWMI (r= 0.131, p> 0.147) or presentation neutrophil count (r= 0.089, p> 0.307), MPO did not differ significantly according to gender, smoking status, the presence or absence of diabetes mellitus, hypertension, previous MI diagnosis, hypercholesterolemia or whether a patient received thrombolyis or not. There was no correlation however between NT-BNP and MPO (r=0.068, p=0.401).

NT-BNP levels in patients and controls

NT-BNP was significantly elevated in AMI compared with controls (Median [Range], fmol/ml, 1459.94; [0.3–11779.03] vs. 10.1; [0.3– 134.4]; p<0.001) and was significantly higher in patients who died (5815.86; [20.1–11269.92] vs. 767.6; [0.30–11779.03]; p<0.001) or reinfarcted in the first 72 hours (1271.104; [2.64– 11779.03] vs. 767.6; [0.30–11779.03]; p=0.031). The time course of secretion of NT-BNP revealed a significant difference over the 5 days (p<0.0001) and is shown in figure 2.
Relationship between MPO and echocardiographic parameters

For the whole population, mean LVWMI was 1.53 (range 1.08-2.83) and EF was 36% (range 8-49%). The LVWMI score in those subjects with anterior AMI was higher than in those with inferior AMI (1.8 [1.08-2.75] vs. 1.4 [1.00-2.83], p<0.001) and LVEF was lower in anterior AMI than inferior AMI (37 [8-48] vs. 40.1 [14-49]) %, p=0.05). There was no correlation of MPO with LVWMI (r=0.104, p>0.147).

However NT-BNP correlated with LVWMI (r=0.434, p<0.0001) at all time points.

MPO and NT-BNP as predictors of death or non-fatal MI

When clinical and demographic characteristics (age, sex, serum creatinine, Killip class, territory of AMI, LVWMI, whether the patient received thrombolysis or not, troponin I, MPO and NT-BNP) entered into a Cox proportional hazards model the independent predictors of the primary endpoint were log median MPO (HR 6.91, 95% CI: 1.79-26.73, p=0.005) and log median NT-BNP (HR 4.21, 95% CI: 1.53-11.58, p=0.005, table 2) The Kaplan-Meier survival curve revealed a significantly better clinical outcome in patients with median MPO below the median compared with those with median MPO above the median (log rank 12.62, p=0.0004, figure 3); this was also true for NT-BNP (log rank 20.24, p<0.0001, figure 4). MPO had predictive power in patients with NT-BNP levels below or above the median (log rank 5.60, p=0.020, log rank 5.12, p=0.024 respectively). In addition there was a grading to the primary endpoint, which increased as the levels of MPO or NT-BNP increased. A positive MPO and NT-BNP (i.e. both above their respective median values) was associated with a significantly higher rate of the primary endpoint than having either peptide level above their medians, or both peptides below their medians (log rank 30.73, p<0.00001, figure 5). When patients were examined for one or more raised
MPO or NT-BNP peptide levels the receiver-operating curve for median NT-BNP yielded an area under the curve (AUC) of 0.72 (95% CI: 0.65-0.79, p<0.001); for median MPO the AUC was 0.62 (95% CI: 0.55-0.69, p=0.001). The logistic model combining the 2 markers yielded an AUC of 0.76 (95% CI: 0.69-0.82, p<0.001) which exceeded that of either peptide alone (figure 6). Discharge MPO and NT-BNP was better at predicting death or non-fatal MI than admission measurements (discharge AUC for MPO 0.62, p=0.05, for NT-BNP 0.66, p=0.013 vs. admission AUC for MPO 0.56, p>0.05, for NT-BNP 0.69, p<0.001).

**Secondary endpoints: MPO and NT-BNP as predictors of death**

Plasma median MPO was raised in patients experiencing death compared to survivors (median [range] ng/ml, 43.4[8.1-132.1] vs. 34.5[6.6-400.2], p=0.011). This was also true for median NT-BNP (median [range] fmol/ml, 5755.1[10.3-10552.8] vs. 1099.2[2.43-9570.6], p=0.0001). On the Cox proportional hazards model the only independent predictor of death was log median NT-BNP (HR 2.993, 95% CI: 1.171-7.655, p=0.022).

The Kaplan-Meier survival curve revealed a significantly better clinical outcome in patients with median NT-BNP below the median compared with those with median NT-BNP above the median (log rank 11.47, p=0.0007, graph not shown). A positive MPO and NT-BNP was associated with a significantly higher rate of the death than having one raised peptide level or two low levels of peptide (log rank 22.63, p <0.00001).

**Secondary endpoints: MPO and NT-BNP as predictors of non-fatal MI**

Plasma median MPO was no different in patients experiencing non-fatal MI compared to survivors (median [range] ng/ml, 44.7[8.1-105.6] vs. 34.5[6.6-400.2], p=0.091).
This was also true for median NT-BNP (median [range] fmol/ml, 2219.7[2.6-9316.3] vs. 1180.0[2.43-10552.8], p=0.119). Multivariate statistics did not reveal any significant differences; however the Kaplan-Meier curve showed that a positive MPO and NT-BNP was associated with a significantly higher rate of non-fatal MI than having one raised peptide level or two low levels of peptide (log rank 7.46, p =0.006).

**Secondary endpoints: MPO and NT-BNP as predictor of heart failure**

Plasma median MPO was no different in patients who were readmitted with heart failure compared to survivors who were not admitted (median [range] ng/ml, 46.6[6.8-84.7] vs. 35.1[6.6-400.2], p=0.244). Plasma median NT-BNP was significantly higher in those readmitted with heart failure compared to survivors who were not admitted (median [range] fmol/ml, 3622.4[2.4-9053.1] vs. 1180.0[2.6-10552.8], p=0.002). In a Cox proportional hazards model however only age (HR 1.04, p=0.09), Killip class (HR 2.39, p=0.08) and past history of MI (HR 3.37, p=0.007), were found to be independent predictors of heart failure.

**Discussion**

The aim of this study was to assess the utility of MPO and NT-BNP in determining the prognosis of AMI patients. The results of this study confirm the independent prognostic value of MPO and NT-BNP in determining death or non-fatal MI in patients who have an acute ST-segment elevation MI. The predictive value of MPO provides risk prediction independent of NT-BNP and other known clinical predictors of death or non-fatal MI. Our study showed only weak correlation between MPO and peak troponin I and no correlation between MPO and LVWMI, reiterating the fact that MPO is not a marker of myocardial necrosis. Recruitment and degranulation of
the neutrophil leading to the release of MPO is seen as a key step in AMI.\textsuperscript{16} Both MPO and NT-BNP are raised after an AMI and their secretion patterns differ over the 5 days following an AMI with significant differences noted for both peptides. It is clear that MPO is raised very early after an AMI with levels falling rapidly after the first 24 hours suggesting that neutrophil activation plays a role very early in AMI and may even precede the onset of AMI.

Reperfusion therapy has improved mortality post MI, however the outcome of patients despite this is still poor;\textsuperscript{17} for this reason risk stratification remains important and may be useful to select treatment regimes in the future.

We used MPO, an inflammatory marker from the leucocyte and NT-BNP which is a more stable by-product in the production of BNP.\textsuperscript{18} We have clearly shown the benefit of using each peptide alone at predicting death or MI. In addition MPO had predictive power even in the patients with NT-BNP levels above the median, suggesting that further risk stratification of this high-risk group is possible. Furthermore a positive MPO and NT-BNP was associated with a significantly higher rate of the primary endpoint than having one raised peptide level or two low levels of peptides. Using a combination of MPO and NT-BNP in a multi-marker risk stratification approach in STEMI patients gives an increased area under the ROC curve and more predictive power. The utility of MPO as a prognostic marker has been borne out previously in patients with acute coronary syndromes\textsuperscript{19} where it was found to be an independent predictor of death or non-fatal MI in this population group. In another study the usefulness of MPO in patients presenting to the emergency room with chest pain was examined.\textsuperscript{9} Here it was found to be useful as an independent predictor of early MI and major adverse cardiac events in the ensuing 30 days and at 6 months. Brennan et al study recruited all patients presenting with chest
pain and the study included 23.5% of patients with a final diagnosis of AMI; in comparison our study has examined only patients with a diagnosis of STEMI, a relatively high-risk group.

In univariate analysis both MPO and NT-BNP were significantly raised in patients who subsequently died compared to survivors. However on multivariate analysis NT-BNP retained independent prognostic information but not MPO. This concurs with previous studies on the utility of NT-BNP in predicting death.\textsuperscript{20,21} However neither peptide marker had utility in predicting non-fatal MI in univariate or multivariate analysis. One of the limitations of this study and the reason why the secondary endpoints of death and MI did not achieve statistical significance may well have been due to the number of patients recruited. A larger study may be appropriate to detect the utility of this combination of markers in predicting death and MI individually. The re-infarction rate is also high and this may be due in part to the fact that reperfusion was obtained with thrombolysis. Care must be taken to extrapolate these findings in patients undergoing mechanical reperfusion.

Previous multimarker strategies have used combinations of markers including, inflammatory markers, myocardial necrosis markers and markers of left ventricular systolic dysfunction\textsuperscript{22} in formulating a risk assessment profile in Non-STEMI patients. This is the first study however reporting the utility of MPO in combination with NT-BNP in patients with STEMI.

In conclusion, the present study reveals that MPO is a predictor of death or non-fatal MI in patients with STEMI. This study confirms previous findings that MPO is involved during an AMI and it may be useful in a multimarker approach with NT-BNP for risk stratification in STEMI patients. MPO and NT-BNP may be useful tools
for risk stratification of all acute coronary syndromes, including higher risk STEMI patients.

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Conflicts of Interest

Nil
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Legends

Figure 1 Time dependent changes in MPO (mean ± SD) after onset of AMI

Figure 2 Time dependent changes in NT-BNP (mean ± SD) after onset of AMI

Figure 3 Kaplan-Meier Curve: Time to Primary Outcome related to median serum MPO

Figure 4 Kaplan-Meier Curve: Time to Primary Outcome related to median serum NT-BNP

Figure 5 Kaplan-Meier Curve: Time to Primary Outcome related to low or high median serum MPO and NT-BNP levels. 1) Low MPO and NT-BNP, 2) Low MPO and high NT-BNP 3) High MPO and Low NT-BNP 4) High MPO and NT-BNP

Figure 6 Combined Receiver Operating Curve comparing median NT-BNP, median MPO and the combined predicted probabilities of Primary Outcome
### Table 1
Characteristics of 384 Patients in the study separated by MPO quartiles.

Values are means (SD) or numbers (percentage)

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<tr>
<td>NT-BNP (pmol/L)</td>
<td>665.2±868.6</td>
<td>926.6±718.0</td>
<td>1220.0±1292.8</td>
<td>1372.1±981.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Male Sex</td>
<td>79 (20.5)</td>
<td>71 (18.5)</td>
<td>75 (19.5)</td>
<td>58 (15.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>LVWMI</td>
<td>1.50±0.36</td>
<td>1.58±0.35</td>
<td>1.58±0.39</td>
<td>1.61±0.41</td>
<td>0.211</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>5.5±2.9</td>
<td>4.7±1.9</td>
<td>4.5±2.1</td>
<td>4.5±2.4</td>
<td>0.244</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130.3±25.9</td>
<td>134.1±21.5</td>
<td>129.5±24.0</td>
<td>131.2±22.8</td>
<td>0.560</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77.0±16.0</td>
<td>78.7±15.1</td>
<td>77.6±17.7</td>
<td>77.0±13.3</td>
<td>0.865</td>
</tr>
</tbody>
</table>
Table 2 Multivariate Cox Proportional-Hazards Regression model of Predictors of Death and Nonfatal Myocardial Infarction (age, sex, serum creatinine, Killip class, territory of AMI, LVWMI, whether the patient received thrombolysis or not, NT-BNP, troponin I and MPO)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazards Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Median MPO</td>
<td>6.91</td>
<td>(1.79-26.73)</td>
<td>0.005</td>
</tr>
<tr>
<td>Log Median NT-BNP</td>
<td>4.21</td>
<td>(1.53-11.58)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Figure 2
Figure 3
Figure 4
Figure 5

Log rank 30.73,
p = 0.00001
Figure 6