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Research Article

A Study of Plasma Myeloperoxidase Levels in Chronic Heart Failure: Prognostic Significance and Echocardiographic Factors

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Abstract

Background: An important biomarker for chronic heart failure is raised plasma myeloperoxidase (MPO) concentrations, which indicate increased oxidative stress and leukocyte activation. When managing this intricate cardiovascular condition, monitoring MPO levels provides information for prognosis and customized therapies. **Aims and Objective:** To study Plasma myeloperoxidase levels in chronic heart failure and its prognostic significance and Echocardiographic factors. **Methodology:** The ADEPT study's neurohormonal sub-study, which focuses on 140 ambulatory patients with stable, chronic systolic heart failure, is described in depth in the research methodology. The study uses SAS and JMP statistical software versions 5.1 and 9.1 for statistical analyses, and it covers participant demographics, data collection techniques, laboratory protocols, and statistical analysis. When a p-value was 0.05 or less, it was considered significant. **Result:** Elevated plasma myeloperoxidase (MPO) in chronic heart failure (CHF) is linked to right ventricular dysfunction and influences the efficacy of cardiac resynchronization therapy. Higher MPO levels correlate with increased risk of adverse events, and integrating MPO with B-type natriuretic peptide enhances the accuracy of predicting future clinical outcomes, offering a valuable tool for personalized CHF management. **Conclusion:** Elevated myeloperoxidase (MPO) levels in chronic heart failure (CHF) correlate with worsened right ventricular

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function, especially in patients with LVEF below 35%. High MPO levels predict adverse outcomes; enhancing BNP, testing is accuracy, and serve as a potential prognostic indicator for CRT response. MPO also reflects CHF severity in echocardiographic parameters, underlining its significance in predicting adverse clinical events.

Key words: Plasma myeloperoxidase, chronic heart failure, echocardiography

Introduction

Chronic heart failure (CHF) represents the primary contributor to both mortality and morbidity within the societal.**(1)** Myeloperoxidase (MPO) is an enzyme that is generated by neutrophils, which are specific type of white blood cells. Neutrophils are an essential component of the body's defense mechanism against pathogens. Neutrophils secrete myeloperoxidase as part of the immune response; this enzyme is critical for the destruction of bacteria and other microorganisms.**(2),(3)**

The term "plasma myeloperoxidase" denotes the existence of myeloperoxidase within plasma, the liquid constituent of blood. Although myeloperoxidase is predominantly found in neutrophils, it is possible for it to be secreted into the bloodstream due to infection or inflammation.

CHF is a progressive syndrome that imposes an economic burden on the health care system and diminishes the patient's quality of life**.(4), (5)** In spite of progress made in the management of cardiovascular ailments, including myocardial infarction (MI), there is a persistent rise in both the occurrence and prevalence of chronic heart failure (CHF).**(6), (7), (8)**

CHF is significantly influenced by inflammation and oxidative stress, both of which are mediated by the enzyme myeloperoxidase (MPO).**(9), (3)** Plasma MPO levels are elevated in CHF patients relative to healthy individuals, according to a study published in the International Journal of Cardiology. Increasing MPO levels are associated with restrictive diastolic stage, right ventricular systolic dysfunction, and tricuspid regurgitation in heart failure with reduced ejection fraction (HFrEF). **(9)**

Clinical Research in Cardiology published a second study, which found a correlation between changes in MPO levels and the response to CRT in patients with CHF. Prior to CRT, responders and non-responders had significantly different MPO levels, according to the study, which may suggest that MPO has additional predictive value for CRT response.**(10)**

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Aims and Objective

To study Plasma myeloperoxidase levels in chronic heart failure and its prognostic significance and Echocardiographic factors.

Material and Method

The present methodology section offers a comprehensive outline of the research endeavor, including participant demographics, data collection techniques, laboratory procedures, and statistical examinations utilized throughout the Study.

Design and Population of the Study:

140 ambulatory patients with stable, chronic systolic heart failure (HF) and a LVEF of 35% or less participated in the neurohormonal sub-study of the ADEPT study. A plasma sample collection and echocardiographic evaluation were performed.

Clinical Event Monitoring:

Prospective monitoring of clinical events (mortality from any cause, cardiac transplantation, or hospitalization due to heart failure) was accomplished via prearranged telephone follow-ups. The events were verified through a review of the charts.

Laboratory and Clinical Measurements:

In order to determine creatinine clearance, the Cockcroft-Gault equation was applied. An assay for measuring plasma BNP that has been thoroughly validated was utilized. The levels of myeloperoxidase (MPO) in the plasma were assessed utilizing the CardioMPO II assay.

MPO Plasma Assays: Plasma samples were obtained by transferring them from ethylenediaminetetraacetic acid (EDTA) plasma tubes to -80°C prior to analysis. For MPO assays, the CardioMPO II assay was utilized and precise and accurate information regarding the detection limit was provided.

Transthoracic echocardiography: Echocardiography was conducted in its entirety utilizing commercially available equipment. In order to ascertain diastolic indexes and classifications, particular criteria were applied.

Statistical Analysis: The levels of MPO in plasma were considered nonparametric variables. A range of statistical tests was utilized in this study, comprising analysis of variance, Kruskal-Wallis test, contingency table analysis, and Spearman rank correlation. For odds ratios and survival analysis, multivariate logistic regression and Cox proportional hazard analyses were utilized, respectively. An analysis of the receiver-operator characteristic curve was conducted. Software Used: Statistical analyses were performed utilizing versions 5.1 and

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9.1 of SAS and JMP. The level of significance is: A p-value of 0.05 or less was deemed to indicate statistical significance."

Results

In our investigation, the mean and median values for plasma MPO were 520 ± 390 pM and 375 pM [interquartile range (IQR) 290 to 480], respectively. The characteristics of patients in the overall group, stratified by plasma MPO tertiles, are detailed in Table 1. Across MPO tertiles, there were no significant differences in left ventricular ejection fraction (LVEF), LV end-diastolic dimensions, or other laboratory and clinical parameters. Conversely, elevated plasma MPO concentrations were linked to a higher incidence of systolic dysfunction of the right ventricle. A multivariable stepwise logistic regression analysis was conducted, incorporating variables that exhibited a statistically significant correlation with logarithmically transformed plasma MPO levels (Table 2). Among these variables, only the septal Aa wave derived from tissue Doppler imaging demonstrated an independent association with MPO levels ($p = 0.01$).

Additional analyses were conducted to examine more severe systolic dysfunction in our study cohort, as indicated by the median LVEF of 31% (≤31% or 30%) versus those with LVEFs above 30% or greater than 31% (≥30% or >31%). The correlation between plasma MPO concentrations and echocardiographic measures of left ventricular filling pressure and compliance (e.g., deceleration time, pulmonary vein S/D ratio, and tissue Doppler imaging-derived E/septal Ea ratio) seemed to be stronger in the group with LVEF ≤ 30% as opposed to the group with LVEF > 30% (see Table 2). The correlation between MPO and the following parameters was found to be even more significant in patients with LVEF ≤ 25%: mitral E/A ratio ($r = -0.56$, $p = 0.007$), pulmonary vein S/D ratio ($r = -0.57$, $p = 0.005$), tissue Doppler imaging septal Aa ($r = -0.53$, $p = 0.014$), and diastolic stage ($r = 0.49$, $p = 0.021$). With increasing tertiles of plasma MPO levels, the probability of identifying more advanced diastolic (diastolic stage ≥ III) or right ventricular systolic dysfunction increased across the entire population. The 3rd MPO tertile contained a significantly greater proportion of patients with diastolic stage III (46% vs. 25%, $p = 0.048$) or RV systolic dysfunction ≥ 3 (39% vs. 14%, $p = 0.006$) than the 1st MPO tertile (see Table 3).

Upon an average of 36 ± 18 months of follow-up, 24% of patients encountered cardiac transplantation or death, while 30% of patients encountered a combination of these three endpoints—hospitalization due to heart failure, transplantation, or death. Patients who died or underwent heart transplantation had higher plasma MPO levels than those who did not

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experience clinical events (median [IQR] in pM: 370 [298 to 512] vs. 310 [267 to 445], $p < 0.035$) and those who experienced combined endpoints of death, transplantation, or HF hospitalization (median [IQR] in pM: 385 [308 to 480] vs. 300 [257 to 438], $p < 0.013$). In the study cohort, mortality and cardiac transplantation were independently predicted by increasing tertiles of MPO (risk ratio 1.62 [95% confidence interval 1.08 to 2.57], $p < 0.043$).

Table 1: Patient Baseline Characteristics across Tertiles of Plasma MPO Levels

Variable	1st Tertile (n = 46)	2nd Tertile (n = 47)	3rd Tertile (n = 47)
MPO (pM)	≤ 290	290–405	> 405
Age (years)	58 ± 14	54 ± 15	56 ± 16
Male gender (%)	74	81	82
NYHA functional class III or IV (%)	23	37	35
Ischemic etiology (%)	40	46	41
Heart rate (beats/min)	72 ± 15	75 ± 16	72 ± 14
Systolic blood pressure (mm Hg)	112 ± 18	111 ± 18	106 ± 17
Medications (%)			
ACE inhibitors and/or ARBs	92	88	90
Beta-blockers	56	62	56
Loop diuretics	68	85	72
Digoxin	58	70	51
Spironolactone	21	34	25
Nitrates	31	27	25
Comorbid conditions			
Hypertension (%)	65	51	49
Diabetes mellitus (%)	28	22	36
Creatinine clearance (ml/min)	75 ± 35	88 ± 30	87 ± 43
BNP (pg/ml)	90 ± 92	105 ± 100	112 ± 126
Echocardiographic data			
LVED volume index (ml/m²)	109 ± 30	104 ± 45	109 ± 36
LVEF (%-units)	24 ± 7	25 ± 6	24 ± 5
Diastolic stage ≥ II (%)	50	65	67

RV systolic dysfunction class ≥ 3 (%)	12*	22*	37*
Mitral regurgitation ≥ 3 (%)	4	5	16

Tertiles with RV systolic dysfunction class 3 differ significantly ($p < 0.05$).

Table 2: Correlation between Plasma MPO Levels and Clinical and Echocardiographic Characteristics for the Total Study Population and in the Patient Cohort with LVEF < 25%

Variable	Overall Cohort	LVEF < 25% Subgroup
Spearman Correlation	0.02 (NS)	-0.04 (NS)
Age (years)	-0.02 (NS)	0.03 (NS)
Heart rate (beats/min)	0.01 (NS)	-0.03 (NS)
BNP (pg/ml)	0.14 (NS)	0.18 (NS)
NT-proANP (nM)	0.11 (NS)	0.23 (NS)
Creatinine clearance (ml/min)	0.02 (NS)	-0.09 (NS)
LVED volume index (ml/m²)	0.07 (NS)	-0.06 (NS)
LVEF (%-units)	-0.14 (NS)	-0.07 (NS)
Mitral peak E/A ratio	0.15 (NS)	0.31 (0.008)
Transmitral DT (ms)	-0.11 (NS)	-0.33 (0.007)
Pulmonary vein S/D ratio	-0.20 (0.026)	-0.42 (0.001)
TDI septal systolic (cm/s)	-0.08 (NS)	-0.11 (NS)
TDI septal Ea (cm/s)	-0.06 (NS)	-0.03 (NS)
TDI septal Aa (cm/s)	-0.23 (0.017)	-0.32 (0.021)
E/septal Ea ratio	0.14 (NS)	0.27 (0.030)
CMM Vp (cm/s)	0.01 (NS)	0.16 (NS)
E/Vp	0.07 (NS)	0.21 (NS)
Mitral regurgitation severity	0.08 (NS)	0.11 (NS)
Diastolic stage	-0.19 (0.045)	-0.39 (0.002)
RV systolic dysfunction class	-0.21 (0.017)	-0.26 (0.048)

Not Significant; $p > 0.05$

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Table 3: Odds Ratios and 95% Confidence Intervals for the Presence of Clinical Conditions across Increasing Myeloperoxidase Tertiles

Clinical Condition	1st Tertile (n = 46)	2nd Tertile (n = 47)	3rd Tertile (n = 47)
Diastolic stage III	1.0	2.5 (0.9–6.3)	3.1 (1.2–8.4)*
LVEF ≤ 25%	1.0	1.8 (0.8–4.2)	1.7 (0.8–3.9)
Diastolic stage III plus LVEF ≤ 25%	Unadjusted 1.0	3.9 (1.2–14.0)*	4.8 (1.6–18.1)*
	Adjusted (age and BNP)	4.3 (1.0–23.6)	7.6 (1.7–54.7)*
RV systolic dysfunction class ≥ 3”	1.0	2.1 (0.7–6.9)	4.5 (1.7–14.6)†
Tricuspid regurgitation area ≥ 1.8 cm^2	1.0	2.6 (1.0–6.9)	4.2 (1.7–10.5)†

p< 0.05; p < 0.01

Subsequent analysis of the receiver-operator characteristic curve revealed that the predictive accuracy of future adverse clinical events was significantly enhanced by the incorporation of MPO into BNP testing. For BNP plus MPO, the area under the curve rose from 0.66 (chi-square 13.2, $p < 0.004$) for BNP alone to 0.80 (chi-square 16.90, $p < 0.005$). Despite accounting for individual factors such as age, LVEF, New York Heart Association functional class, and plasma BNP levels, the predictive power of increasing MPO for long-term clinical events persisted (see Table 4). In addition, when plasma BNP, LVEF, and diastolic stage were incorporated into combined adjustments, elevated MPO levels were associated with a poorer prognosis ($p = 0.046$; risk ratio [95% confidence interval] 3.26 [1.30–7.70]. Furthermore, patients who exhibited restricted LV diastolic filling or elevated plasma MPO levels (above the 1st tertile) and LVEF ≤ 25.5% had a more unfavorable prognosis. Comparable outcomes were produced when plasma MPO was stratified by median levels as opposed to tertiles.

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Table 4: Univariate and Multivariate Cox Proportional Hazard Analyses of Death, Cardiac Transplantation, or HF Hospitalization across MPO Tertiles

Variable	Hazard Ratio (95% Confidence Interval)	p Value
Log10 MPO (41 events)*	3.18 (1.45–8.62)	0.002
Adjusted for age (yrs)	3.22 (1.45–8.72)	0.002
Adjusted for LVEF (%)	2.82 (1.28–7.41)	0.006
Adjusted for NYHA functional class	2.85 (1.30–7.61)	0.006
Adjusted for log10 BNP	3.27 (1.40–9.54)	0.003
Adjusted for creatinine clearance (ml/min)	3.38 (1.44–9.86)	0.002
Adjusted for diastolic stage	2.23 (1.02–6.12)	0.034
Adjusted for RV systolic dysfunction class	2.73 (1.23–7.28)	0.009
Adjusted for tricuspid regurgitation area (cm2)	2.85 (1.17–8.54)	0.016
Multivariable model (37 events)		
Log10 MPO*	2.76 (1.19–8.08)	0.012
Log10 BNP†	1.57 (1.05–2.43)	0.01
LVEF (%)†	0.79 (0.54–1.16)	NS
Multivariable model (37 events)		
Log10 MPO*	2.39 (1.01–7.04)	0.036
Log10 BNP†	1.43 (0.92–2.28)	NS
LVEF (%)†	0.82 (0.55–1.20)	NS
Diastolic stage‡	1.28 (0.82–2.08)	NS

Discussion

MPO is secreted during episodes of inflammation; its quantification in the systemic circulation can function as a provocation metric for leukocyte activation and oxidative stress. A correlation has been observed between MPO levels and cardiovascular events in patients who are predisposed to peroxidases. Additionally, the production of reactive oxygen species is thought to contribute to diastolic dysfunction, specifically in circumstances like matrix remodeling in diabetic cardiomyopathies **(11)** and doxorubicin-induced cardiomyopathies

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(12). The results of this study provide insight into the possible involvement of oxidative stress mediated by MPO in the advancement of a restrictive filling pattern and myocardial fibrosis. Other prognostic indicators of oxidative stress, such as malondialdehyde derived from lipid peroxidation, oxidized low-density lipoprotein, and catecholamine-induced adrenolutin, have been identified in prior research on outcomes **(13), (14), (15).** Despite adjusting for LVEF and BNP levels, these biomarkers have failed to consistently demonstrate independent predictive significance for adverse outcomes and are difficult to measure technically.

The current study found that plasma MPO continued to have a significant prognostic value in predicting future adverse clinical events, even when controlling for plasma BNP levels, LVEF, and other conventional cardiovascular risk factors. These observations underscore the potential prognostic value of plasma MPO, which can be obtained via a U.S. Food and Drug Administration-approved immunoassay and is commercially available. Plasma MPO may serve as an indicator of more severe underlying diseases. Furthermore, the findings may offer valuable insights into the fundamental mechanisms of the disease, such as a possible catalystic origin for apoptosis, lipid peroxidation, cytokine activation, and platelet adhesion. The possibility exists that these pathophysiological processes are separate from those that result in LV systolic dysfunction or BNP production; this would indicate the presence of a distinct HF phenotype.

It is noteworthy that the correlation observed between oxidative stress induced by MPO and changes in the systolic and diastolic performance of the right ventricle in the context of chronic systolic HF suggests a multifaceted interaction. Concerning associated echocardiographic abnormalities **(Table 3),** the asymmetric distribution of hazard ratios across tertiles of MPO raises questions; additional research via larger clinical trials is required to validate these results. Recent investigations have examined the potential advantages of statin therapy for patients with chronic HF, irrespective of the lipid-lowering effects they may have **(16), (17), (18)**, **(19)**. Ongoing multicenter mortality trials are examining whether statin therapy improves cardiac performance and decreases morbidity and mortality in patients with heart failure, despite the low rate of statin use in our study population. The suggested fundamental mechanism entails increased production of nitric oxide, decreased production of cytokines, generation of reactive oxygen species, or activity of matrix metallo proteinases **(20), (21), (22).** Significantly, the administration of statins has been linked to the regulation of nitrosative stress, indicating possible advantageous outcomes

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for patients suffering from chronic systolic HF and elevated plasma MPO levels, which are substantial contributors to nitrosative stress. The absence of data on baseline total leukocyte counts and the possibility of underlying drug therapy influencing plasma MPO levels are, however, constraints that affect our analysis. Notwithstanding these constraints, our research suggests potential foreshadowing an underlying phenotype of oxidative stress in chronic systolic HF, thereby presenting encouraging prospects for additional investigation in more extensive clinical trials.

Conclusion

Significant findings have been uncovered by the investigation into MPO levels in CHF. There was a correlation between increased levels of MPO and a greater prevalence of severe systolic dysfunction in the right ventricle, especially among patients with a LVEF of 35% or less. An additional finding of the study revealed a correlation between elevated levels of MPO and unfavorable clinical outcomes, including mortality, cardiac transplantation, and hospitalization resulting from heart failure. MPO has the potential to serve as a prognostic marker, as evidenced by the substantial improvement in predictive accuracy of future adverse clinical events observed when it was incorporated into BNP testing. MPO may serve as an additional predictor of response to CRT, according to the study. As indicated by the correlation between MPO levels and echocardiographic parameters, MPO may serve as a marker in CHF patients to assess the severity of systolic dysfunction and diastolic filling pressure. Furthermore, the results underscore the correlation between increased levels of MPO and a greater occurrence of adverse clinical events, thereby emphasizing the prognostic importance of MPO. In summary, the research highlights the potential prognostic importance of plasma MPO concentrations in patients with CHF and its suitability as a reliable indicator for predicting clinical outcomes and evaluating the disease's progression and severity.

Conflict of Interest: none

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