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Original Research Article

Role of myeloperoxidase in the diagnosis and prognosis of patients with acute coronary syndrome without ST segment elevation

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Abstract

Inflammation and oxidative stress play an important role in destabilizing artherosclerotic plaque in patients with acute coronary syndrome. In the present study we tried to establish the role of myeloperoxidase, an inflammatory marker secretory of activated neutrophils, in the diagnosis and prognosis of patients with acute chest pain presenting to the emergency department. In our study, MPO (myeloperoxidase) was determined at three different times: T1 – at the admission; T2 – at 48 hours from the admission; T3 – at discharge. MPO can be a diagnostic marker for patients with NSTEACS because it has significantly higher values compared to the control group, from the moment of their presentation in the emergency department (1.7364±0.8356 U/ml, pT<0.0001), even in patients with normal troponin levels. Also, MPO can be considered as a prognostic factor of patients with acute coronary syndrome, presenting significantly increased values in patients with unfavorable evolution compared to those with favorable evolution, throughout the hospitalization (T1 – 2.400 U/ml versus 1.4641 U/ml, pT = 0.0002; T2 – 2.6625 U/ml versus 1.8333 U/ml, pT = 0.0102; T3 – 2.6813 U/ml versus 1.500 U/ml, pT = 0.0006).

Keywords: Acute coronary syndrome, Diagnosis, Myeloperoxidase, Neutrophils, Prognosis

Abbreviations

MPO – Myeloperoxidase; CCS - chronic coronary syndromes; ACS - acute coronary syndrome; NSTEACS - non-ST segment elevation ACS (acute coronary syndrome without ST segment elevation); STEMI – acute myocardial infarction with ST segment elevation; NSTEMI -– acute myocardial infarction without ST segment elevation; PMNs - polymorphonuclear neutrophils; LDL cholesterol - Low-density lipoprotein cholesterol; vs – versus.

INTRODUCTION

Cardiovascular diseases are the leading cause of death worldwide (Kolodziej, 2019). Acute coronary syndromes cover a broad spectrum of clinical conditions, ranging from unstable angina, to myocardial infarction without ST segment elevation (NSTEMI) and acute myocardial infarction with ST segment elevation (STEMI). Early

diagnosis is still difficult, and risk stratification remains a major objective in selecting optimal medical or interventional treatment regimens for patients with acute coronary syndrome (Cannon, 2002; Govindarajan, 2016; Sim, 2013). The extension of the cardiac lesions, the extension of the coronary disease and instability of the affection represent the three major determinants of the prognosis of acute coronary syndrome (Bugiardini, 2004).

Oxidative stress and inflammation play an important role in the pathogenesis of acute coronary syndrome (Loria, 2008). Now, there is evidence that myocyte damage is not daily related to platelet activation and aggregation in the coronary circulation, but is also preceded by the recruitment and activation of polymorphonuclear neutrophils (PMNs) (Gabay, 1999; Buffon, 2002), an event that is localized on the coronary circulation (Buffon, 2002; Takeshita, 1997; De Servi, 1995; Naruko, 2002). Activation of macrophages and neutrophils contributes to the transformation of stable coronary plaques into unstable lesions (Takahiko, 2002; Sugiyama, 2001; Kettle, 1997; Pek, 2019).

Therefore, there is an increased interest in the evaluation of myeloperoxidase (MPO), a pro-inflammatory enzyme that is found in large quantities in the broken plaque (Mullane, 1985) and can be determined in the peripheral blood.

One of the main secretory mediators through PMN activation is MPO, a hemoprotein traditionally considered as a microbicidal enzyme (Wang, 2007; Klebanoff, 1999).

Currently, there is evidence that MPO has a proaterogenic property: MPO has been linked to the development of lipid-laden soft plaque (Podrez, 1999, 2002), the production of cytotoxic and prothrombogenic oxidative lipids (Podrez, 2002; Schmitt, 1999) and the consumption of nitric oxide, which causes vasoconstriction (Eiserich, 2002; Wang, 2007). Also, it has been shown that MPO activates metalloproteinase and promotes destabilization and rupture of atherosclerotic plaque (Fu, 2001; Nicholls, 2005).

Increased MPO levels may be associated with the phenomenon of ventricular remodeling after myocardial infarction and associated changes, with the progression of evolution in the case of congestive heart failure (Askari, 2003). Persons with low serum MPO values, has been shown to be hereditary cardioprotected (Kutter, 2000).

In the present study, we evaluated the possibility that serum levels of myeloperoxidase may be a diagnostic and prognostic marker in patients presenting to the emergency department with acute chest pain.

MATERIAL AND METHOD

Acute chest pain of coronary origin is one of the most common causes of patients presenting in emergency department. The purpose of this paper was to analyze the prognostic value of plasma level of myeloperoxidase in patients with acute coronary syndrome without ST segment elevation. The determinations that are the object of the study were performed on a test group consisting of 55 patients diagnosed at the time of presentation in the emergency department of Constanta Emergency County Hospital with acute coronary syndrome without ST segment elevation (unstable angina and non-Q myocardial infarction), during 3 months. Patients included in the study were diagnosed with NSTEACS based on the clinical aspect of chest pain (acute chest pain lasting more than 20 minutes which has not ceased at rest nore on sublingual nitroglycerin administration) and electrocardiogram modifications (depression of ST segment over 1 mm or negative T wave). The average age of the 55 patients enrolled in the study was 62.22±10.30 years, the test group including 28 women (average age 62.18±9.99years) and 29 men (average age 62.26±10.81years).

The plasmatic level of MPO was also evaluated in patients from the study group who had associated risk factors: thus, 12 patients with NSTEACS and diabetes mellitus were identified (average age 58.17±9.40 years), 23 patients with dyslipidemia (average age 61.39±9.51 years) and 12 patients who were already known with chronic coronary syndrome (average age 60±10.72 years). Also, the variation in the plasma level of MPO was also analyzed according to sex (the test group being made from 28 women and 29 men).

In all patients in the study it was determined at the time of presentation to the emergency department troponin I and only patients diagnosed with NSTEACS and negative serum troponin values were included in the study.

The long-term and short-term prognosis of patients with acute coronary syndrome without ST elevation is still a clinical challenge. Despite the diagnostic and therapeutic advances, the occurance rate of adverse events is still relatively high, occurring at 6 months after the acute event, with a frequency of up to 16% (Van Domburg, 1998; Cohen, 2002; Keith, 2006). The patients enrolled in this study were supervised for 6 months, the supervision modalities being: questionnaires via phone, scheduled intermediate review, re-admission or any combination of these procedures. We accounted the deaths of cardiovascular causes and the presence of major cardiovascular events, defined as deaths by cardiovascular cause, re-admission for acute coronary syndrome or the need for revascularization.

Depending on the evolution of patients during the 6-month surveillance period, the study group was divided into two subgroups: group I – 16 patients with NSTEACS, aged 53-75 years (average age 64.94±8.57 years) who had an adverse evolution, presenting major cardiovascular events during the 6 months of surveillance; group II – 39 patients with symptoms with favorable evolution after discharge, aged 39-75 years

Table 1. Plasma level variation of MPO according to the evolution of patients with NSTEACS

MPO (U/ml)		Acute coronary syndrome without ST segment elevation		
		T1	T2	T3
	Control group (C)	Admission	48 hours	Discharge
Average	0.8444	1.7364	2.0745	1.8436
STDEV	0.3365	0.8356	0.9155	0.8952
pT (test group vs control)		*<0.0001*	*<0.0001*	*<0.0001*
pT (T2 and T3 vs T1)			*0.0455*	*0.5173*
pT (T3 vs T2)				*0.1839*

		NSTEACS with re-admission			***NSTEACS without re-admission***		
		T1	T2	T3	T1	T2	T3
	Control group (C)	Admission	48 hours	Discharge	Admission	48 hours	Discharge
Average	0.8444	2.4000	2.6625	2.6813	**1.4641**	**1.8333**	**1.5000**
STDEV	0.3365	0.7276	1.0788	1.0950	0.7224	0.7256	0.4989
pT (test group vs control)		*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*
pT (T2 and T3 vs T1)			*0.4261*	*0.3989*		*0.0272*	*0.7991*
pT (T3 vs T2)				*0.9614*			*0.0206*
pT (favorable vs re-admission)		*0.0002*	*0.0102*	*0.0006*			

(average age 61.10±10.84 years). The average duration of hospitalization was 9±4.02 days (higher in patients who subsequently developed major cardiovascular events compared to those with favorable evolution – 10.13±3.95 days versus 8.54±4.01 days).

Patients with acute infections, severe liver or kidney disease, malignancies, stroke, trauma or recent surgery history were excluded from the study.

The MPO level was determined in three predefined moments: T1 – upon admission, after confirming the diagnosis of ACS; T2 – 48 hours after admission; T3 – at the patient's discharge. Quantitative determination of MPO was performed from the serum, using the reagent kit AESKULISA MPO (catalog number REF 3303, provided by Diamedix). AESKULISA MPO is an immunological determination using highly purified native myeloperoxidase obtained from blood PMN, indicated for the qualitative and quantitative establishment of antibodies against MPO in human serum. Anti-MPO antibodies specifically recognize conformational epitopes for native MPO only.

In order to establish a reference system as valid as possible for the interpretation of the results obtained by investigating the test group, measuring the analyzed parameters was performed on a control group as well, consisting of 18 clinically healthy patients (9 women, 9 men), with ages between 40 – 55 years, who have participated voluntary to this study.

All participants (both those who constituted the study group and the patients who volunteered for the control group) were informed about their enrollment in this study and gave their written consent, signing the consent form.

Statistical analysis

For each mathematical quantifiable parameter the arithmetic mean was determined with standard deviation, the results appearing as mean ± standard deviation. In order to establish the significance of the changes between the values of some measurements of the different groups, the t-Student test was used considering statistically significant values of pT≤0.05.

RESULTS

NSTEACS patients have had significantly increased MPO (pT<0.05) level even in the admission point (Table 1); compared to the control group, the value of the MPO is increasing, so the highest values were reached at 48 hours after admission. Depending on the evolution of patients during the 6-month monitoring, it is found that in patients with NSTEACS who subsequently developed major cardiovascular events, the MPO value is significantly higher (pT<0.05) in all three moments of the study (T1, T2, T3) compared with the patients with favorable evolution after discharge (Figure 1). Also, in patients with unfavorable evolution the plasma value of MPO is increasing throughout the monitoring period (at discharge the plasma values being higher than both at

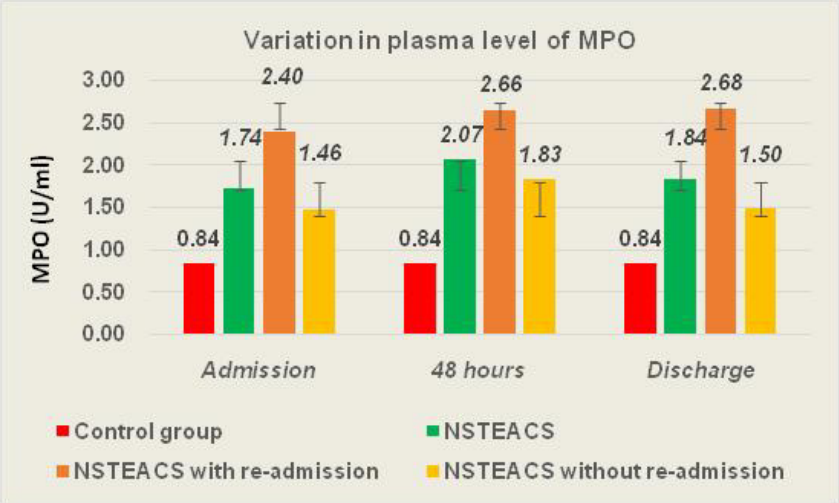

Figure 1. Variation in plasma level of MPO in patients in the study group

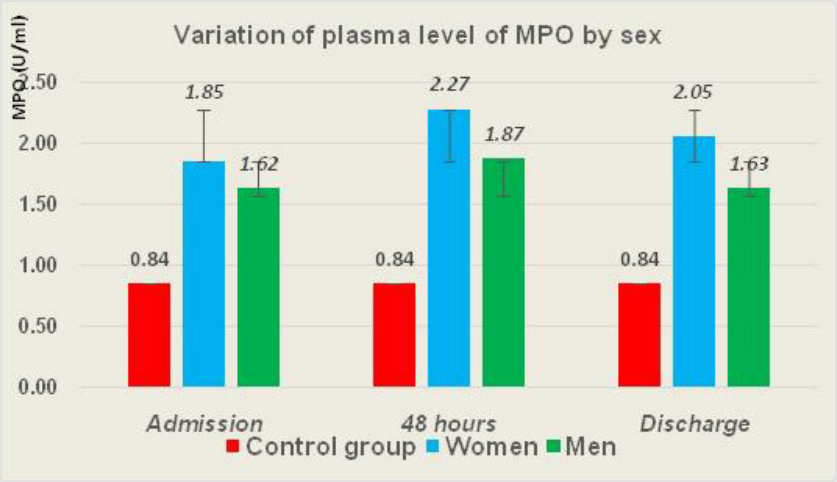

Figure 2. Variation of plasma level of MPO by sex

Table 2. Variation of plasma level of MPO by sex

MPO (U/ml)		Women (W)			Male (M)		
		T1	T2	T3	T1	T2	T3
	Control goup	Admission	48 hours	Discharge	Admission	48 hours	Discharge
Average	0.8444	*1.8464*	*2.2714*	*2.0536*	*1.6222*	*1.8704*	*1.6259*
STDEV	0.3365	0.8522	0.9794	1.0028	0.8182	0.8123	0.7236
pT (test group vs control)		*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*	*<0.0001*
pT (T2 and T3 vs T1)			*0.0889*	*0.4086*		*0.2686*	*0.9860*
pT (T3 vs T2)				*0.4144*			*0.2483*
pT (W vs M)		*0.3241*	*0.1039*	*0.0751*			

the time of admission and at the values determined at 48 hours), compared with the group with favorable evolution at which the plasma value of MPO begins to decrease after 48 hours.

Compared to the values of the control group, the plasmatic level of the MPO shows significantly increased values (pT <0.05) regardless of sex (Figure 2), but higher values are recorded in female patients compared to male

Table 3. The variation of plasma level of MPO (U/ml) according to the associated risk factors at the time of presentation in the emergency department

MPO (U/ml)		**Diabetes mellites**		
	Control group	***Admission***	***48 hours***	***Discharge***
Average	0.8444	1.7000	2.1583	1.8333
STDEV	0.3365	0.9789	0.9010	0.4755
pT (test control vs control)		*0.0123*	*0.0003*	*<0.0001*
pT (T2 and T3 vs T1)			*0.2454*	*0.6754*
pT (T3 vs T2)				*0.2810*
pT (NSTEACS vs diabetes mellites)		0.9065	0.7747	0.9554

MPO (U/ml)		**Dyslipidemia**		
	Control group	***Admission***	***48 hours***	***Discharge***
Average	0.8444	1.6826	2.0739	1.7000
STDEV	0.3365	0.8144	0.9031	0.7236
pT (test control vs control)		*<0.0001*	*<0.0001*	*<0.0001*
pT (T2 and T3 vs T1)			*0.1300*	*0.9393*
pT (T3 vs T2)				*0.1284*
pT (NSTEACS vs dyslipidemia)		0.7932	0.9978	0.4607

		Chronic coronary syndromes (CCS)		
MPO (U/ml)	**Control group**	***Admission***	***48 hours***	***Discharge***
Average	0.8444	1.7583	1.7250	1.6750
STDEV	0.3365	0.8404	0.6077	0.5848
pT (test group vs control)		*0.0032*	*0.0003*	*0.0004*
pT (T2 and T3 vs T1)			*0.9124*	*0.7806*
pT (T3 vs T2)				*0.8392*
pT (NSTEACS vs CCS)		0.9356	0.1166	0.4245

patients, without reaching statistical significance (pT>0.05), probably due to the small number of patients in the study (Table 2).

The same significantly increased values of MPO are also found in patients who were known to have dyslipidemia, diabetes mellitus or had a history of coronary heart disease compared to the values that were determined in the control group (pT<0.05) (Table 3).

DISCUSSION

Leukocytes play an important role in transforming a stable coronary plaque into an unstable atherosclerotic plaque (Kettle, 1997; Dinerman, 1990; Buffon, 2002).

Traditionally MPO has been considered to be a bactericidal agent (Klebanoff, 1984), but a number of recent studies emphasize the importance of MPO in the progression and evolution of acute coronary heart disease (Kolodziej, 2019; Pek, 2019). MPO, released mainly by activated neutrophils has important pro-oxidative and pro-inflammatory proprieties (Loria, 2008). Myeloperoxidase exerts pro-atherogenic effects and is implicated in recurrent coronary events (Kolodziej, 2019). MPO intervenes in the oxidation of LDL-cholesterol that becomes atherogenic (Podrez, 1999) and limits the bioavailability of nitric oxide, an endothelial derivative, which affects the dilatation of the coronary and secondary vessels aggravates cardiac ischemia (Eiserich, 2002). This harmful combination culminates in the concept that MPO can be an active mediator of the atherogenic process (Nicholls, 2005).

Studies evaluating the prognostic value of MPO in patients with acute coronary syndromes revealed discrepant results (Eggers, 2010; Kaya, 2012) and included a heterogeneous patient population. Also, the sample size was not large enough to provide solid conclusions (Kolodziej, 2019).

It is of interest that the determination of MPO allows the identification of patients with acute coronary syndrome who have negative troponin values (all patients in the study have normal troponin levels). At the same time, the high serum level of MPO highlights the patients with risk for the development of major cardiovascular events in the first 6 monts after an acute coronary event.

The results of our study are consistent with the data from the literature. There was a statistically significant increase of MPO throughout the entire hospitalization in patients with non-ST segment elevation ACS (NSTEACS) and unfavorable evolution after discharge compared to those who did not require re-admission during the 6-month monitoring period (T1 – 2.400 U/ml vs. 1.4641 U/ml, pT = 0.0002; T2 – 2.6625 U/ml vs. 1.8333 U/ml, pT = 0.0102; T3 – 2.6813 U/mlvs. 1.500 U/ml, pT = 0.0006). In patients with unfavorable evolution, a continuous increase of the plasma level of MPO is observed through-

out the study. Also, the serum level of MPO is significantly increased compared to the control group in patients with NSTEACS and associated risk factors: diabetes mellitus, dyslipidemia or chronic coronary syndromes.

Therefore, MPO can be considered as a marker of coronary atherosclerotic plaque instability and neutrophil activation, playing an important role in stratifying patients with normal troponin levels.

CONCLUSIONS

MPO highlights acute inflammatory state of coronary circulation indicating increased neutrophil activation, which ultimately precedes myocardial injury. The MPO level grows early, right from the moment of admission, allowing it's use as a diagnostic biomarker in patients with non-ST segment elevation ACS. The plasma level of MPO can identify patients with risk for major cardiac events (cardiovascular death, readmission for acute coronary syndrome or the need for revascularization)even in the absence of myocardial necrosis (normal values of troponin level), which makes the MPO dosage useful in stratifying the risk in patients with acute chest pain presenting in the emergency department. But further research and standardization of measurements are required to determine exactly the value of plasma MPO level assessment in cardiovascular disease.

Informed consent

The patient's informal approval has been obtained and recorded in the chart.

Author contributions

All the authors have equal contributions in this presentation.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

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