Adrenomedullin concentrations at two time points following myocardial infarction and prediction of mid-term outcomes

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Abstract

Introduction: Adrenomedullin (ADM) is a vasopeptide with multiple actions in the cardiovascular system and a potentially powerful tool in comparison to some of the well-established unimodal biomarkers of risk stratification in myocardial infarction (MI). Previous studies on ADM in acute MI were based on single assessment. Therefore the aim of the study was to examine the relation between ADM plasma concentrations assessed at different time points following MI and outcomes.
Material and methods: The study included 127 patients with acute MI treated with percutaneous coronary intervention and 60 healthy individuals as controls. Adrenomedullin concentration was assessed at baseline in all study subjects and 48 h after admission in patients with MI. The primary endpoint consisted of all-cause death, nonfatal myocardial infarction, stroke and the need of target vessel revascularization at 6-month follow-up.
Results: Mean ADM plasma concentration on admission was higher in patients with MI than in controls (30.3 ±14.3 pmol/l vs. 14.6 ±4.7 pmol/l, $p < 0.0001$). There was no significant difference between ADM concentration after 48 h (30.6 ±12.3 pmol/l) and on admission. The primary endpoint occurred in 9.4% of patients with MI. Multivariable analysis showed that ADM concentration at 48 h after admission (OR = 2.121, 95% CI 1.180-3.810 for every increase of 10 pmol/l, $p = 0.012$) was the only independent predictor of the primary endpoint.
Conclusions: In patients with acute MI adrenomedullin plasma concentration assessed at 48 h after admission, but not ADM concentration at baseline, is an independent predictor of major adverse cardiovascular events at mid-term follow-up.

Key words: myocardial infarction, percutaneous coronary intervention, adrenomedullin, outcomes.

Introduction

Despite invasive and medical treatment of myocardial infarction (MI) there is a persistent risk of recurrent cardiovascular events [1]. Identification of patients at risk of those incidents remains one of the most important targets of MI management. Various cardiac biomarkers assessed on admission or in the first days of hospitalization were proposed as useful

stratification measures including markers of inflammation, renal function, myonecrosis, vascular tone or platelet function [2-5].

Adrenomedullin (ADM) is a vasopeptide with multiple actions in the cardiovascular system. It was originally isolated from human pheochromocytoma, but subsequent studies discovered that endothelial cells are likely to be the major source of circulating ADM. It is a natriuretic and hypotensive peptide influencing many processes such as systemic haemodynamics, neurohormonal responses, inflammatory mediators, oxidative stress, and cellular proliferation or growth [6]. Multimodal ways of action make ADM a potentially powerful tool in comparison to some of the well-established unimodal biomarkers [2-5]. Moreover, ADM is not only a marker of cardiovascular status but exerts cytoprotective actions [7, 8].

Studies on plasma ADM concentrations in relation to mid- or long-term major adverse cardiovascular events in patients with acute MI are limited [9-15]. Most of them were based on single ADM assessment. There are no data about the relation between time of sampling of ADM during the first days of MI and outcomes.

Therefore, the aim of the study was to assess the relation between ADM plasma concentrations assessed at different time points after admission and outcomes in patients with acute MI.

Material and methods

Study group

The study included 127 consecutive patients with acute MI treated invasively (ST-elevation 75.6%, mean age 63.9 ±12.0, male sex 72.4%) and 60 healthy controls (mean age 40.5 ±7.7, male sex 71.7%) from the Warsaw region defined on the basis of their personal history (no risk factors of coronary artery disease), normal resting ECG and negative exercise stress testing on a treadmill.

Diagnosis of MI was made according to contemporary guidelines [16, 17]. Obtained information consisted of medical history, vital status, angiographic parameters and baseline laboratory parameters. Hypertension was defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg or current antihypertensive treatment. Diabetes mellitus type 2 was diagnosed according to WHO criteria or if a patient was on hypoglycaemic drugs [18]. Hyperlipidaemia was defined if the total cholesterol level was > 5.2 mmol/l or low-density lipoprotein (LDL) cholesterol level was > 3.4 mmol/l, or if the patient was treated with a lipid-lowering drug. Previous MI was classified on the basis of medical history records. Number of diseased coronary arteries was based on the presence of > 50% stenosis in any of the major coronary arteries. All patients with MI underwent resting echocardiography for the assessment of left ventricular ejection fraction (LVEF) during the first 24 h after admission for MI (after the invasive treatment) using a Hewlett-Packard Sonos 2500 (Hewlett-Packard, Andover, MA).

The Local Ethics Committee of the Institute of Cardiology, Warsaw, Poland approved the study protocol and all patients provided written informed consent.

Adrenomedullin assay

Adrenomedullin concentration in plasma was assessed by means of immunoradiometric assay (Shionogi, Osaka, Japan) [19]. Blood was drawn from the antecubital vein on admission (in all patients with MI and controls) and after 48 h (in all MI patients). The detection limit was 0.5 pmol/l, and the working range was 1-300 pmol/l (coefficient of variability < 15%).

Primary endpoint

Primary endpoint consisted of all-cause death, nonfatal MI, stroke and the need of target vessel revascularization at 6 months follow-up.

Statistical analysis

Baseline characteristics of study patients were summarized in terms of frequencies and percentages for categorical variables and by means and standard deviations (SD) for continuous variables with normal distribution. Categorical variables were compared by either Fisher's exact or χ^2 test and continuous variables by Student's *t*-test or Mann-Whitney *U* test for unpaired samples, when appropriate. Correlations were assessed by means of Pearson's r-test or Spearman's rho-test, when appropriate. Multivariable analysis was performed with the use of stepwise logistic regression. All significant variables from the univariable analysis entered the multivariable stage. A *p*-value (two-tailed) of < 0.05 was considered statistically significant and confidence intervals (CI) were 95%. All data analyses were performed using SPSS version 15.0 software (SPSS Polska Sp. Z o.o., Cracow, Poland).

Results

Adrenomedullin concentrations in patients with MI and controls

Adrenomedullin concentration on admission was higher in patients with MI than in controls (30.3 ±14.3 pmol/l vs. 14.6 ±4.7 pmol/l, $p < 0.0001$) (Figure 1). In the MI group vasopeptide concentrations did not change significantly in the first 48 h from admission. The absolute and relative changes

of ADM concentration after 48 h in comparison to baseline in patients with MI were –0.3 ±13.2 pmol/l and 9.5 ±49.4% (in both cases p = NS).

ADM concentrations and MI patients' characteristics on admission

Baseline clinical, angiographic and laboratory characteristics of MI patients in relation to plasma ADM concentration on admission and after 48 h are presented in Table I. Adrenomedullin plasma concentration 48 h after admission correlated significantly with the largest number of assessed parameters including age, heart rate on admission, LVEF, as well as high-sensitivity C-reactive protein (hs-CRP) and glucose level on admission. In comparison, adrenomedullin plasma concentration on admission correlated significantly with LVEF as well as creatinine, hs-CRP and glucose level on admission.

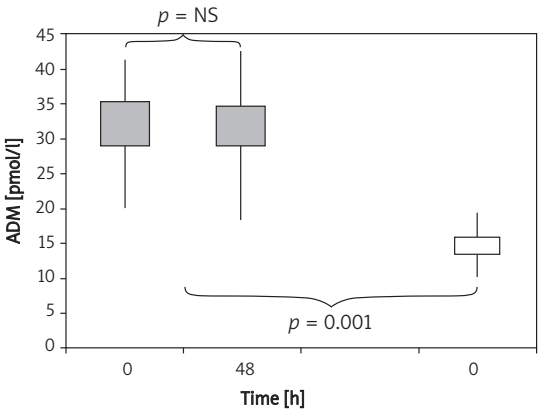

Figure 1. Plasma concentration of ADM at different time points (admission, 48 h) in patients with myocardial infarction (grey bars) and controls (white bars). Bars show 95% confidence interval for mean and whiskers present standard deviation of the mean

Predictors of outcome in patients with MI

The primary endpoint occurred in 12 patients during follow-up (9.4%). There were 6 deaths (4.7%), 3 nonfatal myocardial infarctions (2.35%) and 3 target vessel revascularizations (2.35%). Patients with the primary endpoint were older, more likely to have

Table I. Relation between ADM plasma concentration on admission/after 48 h and baseline characteristics

Parameter	ADM on admission	Value of p	ADM at 48 h	Value of p
	[pmol/l (SD)]		[pmol/l (SD)]	
Male/female sex	30.7 (14.5)/29.2 (14.0)	NS	30.1 (12.1)/31.7 (12.7)	NS
History – no/yes				
Hypertension	32.3 (14.4)/29.0 (14.0)	0.09	32.2 (12.5)/29.0 (12.0)	NS
Diabetes	29.7 (13.3)/34.3 (19.8)	NS	29.9 (12.3)/35.5 (11.9)	NS
Hyperlipidaemia	32.6 (15.4)/27.8 (12.8)	0.06	31.4 (13.7)/29.7 (10.6)	NS
MI	30.7 (14.7)/27.1 (10.7)	NS	30.3 (11.7)/34.0 (18.0)	NS
Current cigarette Smoker – no/yes	28.2 (13.4)/29.3 (15.4)	NS	28.7 (12.8)/28.4 (7.6)	NS
	Corr. coeff.		Corr. coeff.	
Age [years]	0.14	NS	0.22	0.03
HR on admission [beats/s]	0.06	NS	0.23	0.02
Systolic BP on admission [mmHg]	–0.13	NS	–0.16	NS
Diastolic BP on admission [mmHg]	–0.10	NS	–0.08	NS
Number of diseased coronary arteries – no.	–0.09	NS	0.11	NS
LVEF [%]	–0.29	0.002	–0.39	< 0.001
Troponin I [ng/ml]	–0.13	NS	–0.17	NS
Creatinine [µmol/l]	0.30	0.001	0.18	0.08
hsCRP [mg/dl]	0.38	< 0.001	0.38	< 0.001
Glucose [mmol/l]	0.32	0.001	0.23	0.03
Total cholesterol [mmol/l]	–0.18	0.05	–0.19	0.06
LDL cholesterol [mmol/l]	–0.07	NS	–0.05	NS

ADM – adrenomedullin, BP – blood pressure, HR – heart rate, hsCRP – high sensitivity C-reactive protein, LDL – low density lipoprotein, LVEF – left ventricular ejection fraction, MI – myocardial infarction, SD – standard deviation

Table II. Baseline characteristics of MI patients with and without the primary endpoint

Parameter	With primary endpoint (n = 12)	Without primary endpoint (n = 115)	Value of p
Age [years] (SD)	66.1 (11.0)	63.7 (12.1)	NS
Male sex, n (%)	12 (100)	80 (69.6)	0.04
History, n (%)			
Hypertension	5 (41.7)	57 (49.6)	NS
Diabetes	0	17 (14.8)	NS
Hyperlipidaemia	3 (25.0)	60 (52.2)	0.05
MI	5 (41.7)	7 (6.1)	0.004
Current cigarette smoker, n (%)	1 (8.3)	12 (10.4)	NS
HR on admission [beats/s] (SD)	78.1 (12.5)	73.8 (9.0)	NS
Systolic BP on admission [mmHg] (SD)	151.1 (34.2)	137.4 (21.1)	NS
Diastolic BP on admission [mmHg] (SD)	90.8 (26.8)	78.2 (10.9)	NS
Number of diseased coronary arteries, n (SD)	1.83 (0.94)	1.51 (0.83)	NS
LVEF [%] (SD)	44.3 (17.6)	51.2 (9.4)	NS
ADM on admission [pmol/l] (SD)	33.2 (15.5)	30.0 (14.2)	NS
ADM at 48 h [pmol/l] (SD)	44.3 (19.8)	29.7 (11.3)	0.004
Troponin I [ng/ml] (SD)	9.8 (26)	5.3 (11.8)	NS
Creatinine [µmol/l] (SD)	91.2 (36.9)	77.7 (25.7)	NS
hsCRP [mg/dl] (SD)	1.3 (2.4)	0.7 (1.8)	NS
Glucose [mmol/l] (SD)	8.6 (3.2)	7.2 (2.8)	NS
Total cholesterol [mmol/l] (SD)	5.2 (0.6)	5.1 (1.2)	NS
LDL cholesterol [mmol/l] (SD)	3.6 (0.9)	3.7 (2.6)	NS

ADM – adrenomedullin, BP – blood pressure, HR – heart rate, hsCRP – high sensitivity C-reactive protein, LDL – low density lipoprotein, LVEF – left ventricular ejection fraction, MI – myocardial infarction, SD – standard deviation

a history of MI and less likely to have hyperlipidaemia than those without the primary endpoint (Table II). They had a higher concentration of ADM at 48 h, but not on admission in comparison to patients without the events (Figure 2). There was a significant increase of ADM concentration over time in patients with the events (p = 0.01), but not in those without the events.

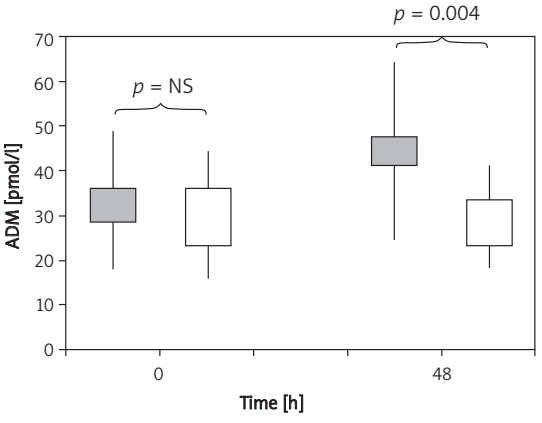

Figure 2. Plasma concentration of ADM at different time points (admission, 48 h) in patients with (grey bars) and without (white bars) the primary endpoint. Bars show 95% confidence interval for mean and whiskers present standard deviation of the mean

The multivariable analysis model including age, history of MI, hyperlipidaemia and ADM concentration at 48 h showed that ADM concentration at 48 h after admission was the only independent predictor of the primary endpoint (OR = 2.121, 95% CI 1.180-3.810 for every increase of 10 pmol/l, p = 0.012).

Discussion

We demonstrate that plasma ADM measured at 48 h after admission can be an independent predictor of mid-term major adverse cardiovascular events. Although we cannot directly explain the pathomechanism of that relation, we show that ADM plasma concentration 48 h after admission correlates with the largest number of baseline clinical and laboratory parameters. Those parameters included markers of inflammation (hs-CRP on admission), cardiac dysfunction (LVEF) and haemodynamic status (heart rate on admission),

which suggests the vasopeptide's multimodal way of action and makes it a good candidate for a marker of future adverse events.

Previous studies on the relation between ADM plasma concentration and events during follow-up were based on a single sampling performed during the hospitalization, but not on admission for MI. In the study by Nagaya *et al.*, plasma ADM on day 2 was the only non-invasive variable to independently predict mortality at 25 months follow-up after MI [9]. Similar findings come from the small study of Katayama *et al.*, where plasma ADM concentration obtained at 24 h after the onset of MI was the strongest predictor of 1-year mortality in multivariate analysis [10]. In contrast, in the Richards *et al.* study, adrenomedullin assessed at day 2 to 4 after MI discriminated patients in relation to death in univariate analysis, but in contrast to N-terminal pro-brain natriuretic peptide it did not provide independent predictive information on death and left ventricular failure at 24 months follow-up [11]. According to the authors, the results might have been influenced by the fact that ADM levels in heart failure presumably reflect a more systemic or peripheral response to cardiac impairment instead of the ventricular response itself (such as for natriuretic peptides). However, in two recent studies it was demonstrated that a mid regional pro-ADM (MR-proADM) assessed after 3 to 5 days in patients with ST-elevation myocardial infarction or within 36 h in patients with non-ST-elevation myocardial infarction is a powerful predictor of adverse outcome and adds further prognostic information over NT-proBNP and commonly used risk scores [14, 15]. It is worth noting that in the latter study MR-proADM concentrations assessed within 36 h from the onset of symptoms were a better predictor of outcome than the marker levels at discharge [15]. Earlier sampling of ADM (up to 48 h after the onset of symptoms) may be more justified than late assessment (after day 3) as most of the initial studies reported peak ADM concentrations in plasma to occur in the acute phase of MI [20, 21].

Our results confirm the previous findings that ADM concentration assessed in the first days after admission is an independent predictor of clinical outcome. We have also discovered that biomarker levels on admission were of no predictive value for outcomes in the studied group. At the same time thre was no significant rise in ADM concentration in plasma at 48 h after admission in patients with MI in comparison to baseline. However, despite a similar mean level of ADM concentration over time in the whole studied group, there was an increase in mean plasma ADM concentration in time in MI patients who suffered from the major adverse cardiovascular event during follow-up in comparison to patients without the event, whose mean ADM concentration remained unchanged during the first 48 h after admission.

The first limitation of our study is the fact that despite being the largest study to date we were unable to analyse the relation between ADM concentration and individual components of the primary endpoint. Secondly, although differences in patients' age between the study group and controls may be potentially considered as a confounding factor, previous studies showed no significant variations of ADM plasma concentration with respect to sex and age [22].

We believe that ADM concentration at 48 h after admission or its increase during the first days of acute MI may be a good predictor of future outcome beyond markers included in most of the currently used risk scores such as ejection fraction or other biomarker levels.

In conclusion, our study indicates that in patients with acute MI, adrenomedullin plasma concentration assessed at 48 h from admission, but not at baseline, is an independent predictor of major adverse cardiovascular events at mid-term follow-up.

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