ORIGINAL PAPER

doi: 10.5455/medarh.2018.72.406-409
MED ARCH. 2018 DEC; 72(6): 406-409
RECEIVED: OCT 08, 2018 | ACCEPTED: NOV 28, 2018

Serum Aldosterone as Predictor of Progression of Coronary Heart Disease in Patients Without Signs of Heart Failure After Acute Myocardial Infarction

Nerma Resic[1], Azra Durak-Nalbantic[2], Alen Dzubur[2], Alden Begic[3], Edin Begic[4]

[1]Intensive Care Unit, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

[2]Department of Cardiology, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

[3]Department of Angiology, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

[4]Department of Cardiology, General Hospital «Prim. dr. Abdulah Nakas», Sarajevo, Bosnia and Herzegovina,

Corresponding author: Nerma Resic, MD, PhD, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina. ORCID ID: https://www.orcid.org: 0000-0002-8499-457X. E-mail: resicnerma@yahoo.com.

ABSTRACT

Introduction: In patients with acute myocardial infarction (AMI) early risk assessment of development of complications is of great importance. It is proven that aldosterone level has a major role in progression of cardiovascular pathology. **Aim:** Determination of influence of aldosterone plasma level in the progression of heart disease in patients without signs of heart failure after AMI. **Material and Methods:** Research included 207 patients, hospitalized in the acute phase of myocardial infarction, and who were divided into two groups: 127 patients with no clinical signs of heart failure and 60 patients with heart failure. **Results:** The serum aldosterone concentration was 73.4% higher in the group of decompensated patients, 128 pg/mL (75.4-236 pg/mL) in decompensated and 73.7 pg/mL (42.7 -115.25 pg/mL) in compensated. In the group of compensated patients, changes in aldosterone levels showed a statistically significant effect on the incidence of post-infarction angina (p=0.0001) as well as reinfarction (p=0.009). There is a connection between changes in aldosterone plasma level and positive stress test (p=0.012). **Conclusion:** In patients with AMI, elevated serum aldosterone level can be prognostic factor of the progression of coronary heart disease, development of heart failure, as well of development of post-infarction angina, myocardial reinfarction and pathological finding on the stress test.

Keywords: Aldosterone, Myocardial Infarction, Heart failure.

1. INTRODUCTION

Immediately after the onset of acute myocardial infarction (AMI), and in response to infarction-induced hemodynamic changes, there is an increase in neurohumoral activity, including the activation of the *renin–angiotensin–aldosterone (RAAS) system*, the sympathetic nervous system and the growth of natriuretic peptide production (1, 2). Neurohumoral activation in post-infarction period shows crucial role of aldosterone in the genesis of myocardial and vascular tissue damage (3). Aldosterone has number of proven adverse effects on the cardiovascular system, where the mechanisms by which some of these effects are achieved are still incompletely explained. It has been considered that aldosterone increases sympathetic activity by decreasing the intake of noradrenaline in the heart muscle, decreases parasympathetic activity and also induces an inflammatory response (4-8). It is associated with left ventricular hypertrophy, myocardial and renal fibrosis, leads to failure of baroreceptor, to direct damage to the blood vessels, induces endothelial dysfunction, weakens the elasticity of the arteries and increases vascular tone (4-8). More recent studies emphasize the harmful effects of aldosterone on endothelial function through mechanisms that involve the formation of oxidative stress. Aldosterone induces an increase in oxidative stress in the smooth muscle cells of the blood vessels, which can play a role in endothelial dysfunction through mechanisms involving the reduction of the bioavailability of nitric oxide (9-11). Several studies have shown increased production of aldosterone in a pathologically changed heart (8). Patients with primary aldosteronism have an increased risk of cardiovascular events, including coronary artery disease, myocardial infarction, heart failure, stroke and atrial fibrillation (12-14). Hyperaldosteronism is associated with dys-

function of pancreatic beta cells, reduced sensitivity of skeletal muscle insulin cells and increased inflammatory adipokine synthesis. In this way, systemic subclinical inflammation, glucose intolerance, and accelerated atherogenesis are induced (15). Recent data suggest that the cardiovascular system and smooth muscle blood vessels have the ability to respond directly to exogenous aldosterone, at the same time they can produce aldosterone locally in response to angiotensin II (7, 8). De Rita and associates studied the effect of aldosterone in plasma on the progression of carotid plaque surface by multiple linear regression, with variables that were previously shown to maximally explain variations in the total plaque surface (age, sex, total cholesterol, systolic blood pressure and its therapy, diabetes, smoking, and statins) (16, 17). Aldosterone-induced endothelial dysfunction in the early morning period could potentially contribute to the cardiovascular events that occur more frequently at this time of day. It has been shown that morning peak levels of aldosterone have a major acute effect on the autonomic nervous system (4).

2. AIM

Aim of article was to determinate the influence of aldosterone plasma level in the progression of heart failure in patients with AMI.

3. PATIENTS AND METHODS

Research included 207 patients (157 male and 50 female) hospitalized in the acute phase of myocardial infarction on the Intensive Care Unit, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Center University of Sarajevo (CCUS), Sarajevo (ethical approval obtained from Ethical Committee, CCUS). Patients were divided into two groups: 127 patients with no clinical signs of heart abnormalities (without clinical signs of cardiac decompensation) and 60 patients with heart failure (with cardiac decompensation). When admitted to the clinic, for each patient, anamnestic data, an objective physical examination, an ECG (electrocardiogram), and blood samples for laboratory analysis were taken. Based on anamnestic data, ECG findings and, where appropriate, troponin findings, a diagnosis of myocardial infarction was established. Based on the physical examination, the level of BNP and X-ray imaging, the diagnosis of cardiac decompensation was established. Blood samples for the analysis of aldosterone levels were taken 24 hours after admission to the clinic with basic laboratory findings routinely taken in acute myocardial infarction. Blood samples were taken before a meal, before the ACE inhibitor or aldosterone antagonist was included in the therapy. The level of aldosterone in the blood was determined at the Institute of Nuclear Medicine of CCUS, through radioimmunoassay (RIA) method on the Wizard 1470 apparatus. The reference values of aldosterone are 8.00-172 pg/mL at rest, or 30.0-355 pg/mL after physical activity. Reference values at rest were used, considering that all of the patients were hospitalized due to an acute infarction and that the samples were taken in a hospital bed.

Patients underwent stress test (ergometer) during follow-up. The test was considered to be positive if the ECG recording recorded ST depression more than 1 mm (0.1 mV) for a minimum duration of 0.08 s in at least three consecutive leads.

Patients were monitored for one year after being discharged from the hospital through regular ambulatory check-ups. The first examination was done a month after hospitalization, and then the examinations were done every 3-4 months, with the registration of occurrence of subjective and objective signs of heart failure.

For the statistical analysis of the obtained data, the SPSS software package for Windows (version 19.0, SPSS Inc., Chicago, Illinois, USA) was used. Since the distribution of continuous variables was asymmetrical, we used the median and interquartile range to represent the mean and the scattering measure, and for their comparison nonparametric tests (Mann-Whitney U test, Kruskal-Wallis test). For the connection and the direction of the relationship between the variables, we used correlation tests, depending on the type of variable (Spearman, Pearson). By univariate logistic regression, we examined the effect of aldosterone on the prediction of variables with two outcomes. ROC curve was used to test whether aldosterone may be the marker of cardiac decompensation.

4. RESULTS

Out of total number, 157 (75,8%) patients were males. The serum aldosterone concentration was 73.4% higher in the group of decompensated patients, 128 pg/mL (75.4-236 pg/mL) in decompensated and 73.7 pg/mL (42.7-115.25 pg/mL) in compensated (Figure 1). The difference in aldosterone values among the groups was statistically significant (p=0.0001, U=2632.0).

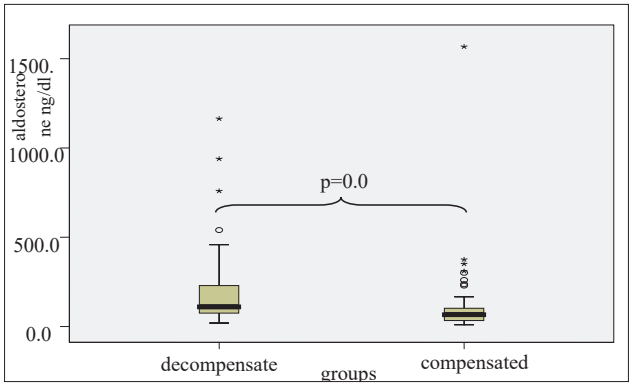

Figure 1. Level of aldosterone in serum according to groups compensated/decompensated (* are marked patients with atypically high levels of aldosterone, above average-median).

In the group of decompensated patients, changes in aldosterone levels did not show a statistically significant effect on the incidence of angina p=0.853, while in the compensated group they showed a statistically significant effect with p=0.0001. Regression analysis showed that elevation of aldosterone levels by 10 ng/dL in the group of compensated patients increases the chances of developing angina by 20.5% in our sample, or from 8.9% to 33% in the population of cardiac compensated pa-

tients. In the group of decompensated patients, changes in aldosterone levels did not show a statistically significant effect on the occurrence of reinfarction (p=0.335), while in the compensated group they showed a statistically significant effect (p=0.009). Regression analysis showed that elevation of aldosterone levels by 10 ng/dL, in the group of cardiac-compensated patients, increases the chance of re-infarction by 5.4% in our sample, i.e. from 1.3% to 9.7% in the population of cardiac compensated patients. In the group of patients with stress test (49 patients, 23,7% of total number of patients), changes in aldosterone levels showed a statistically significant effect on the emergence of a positive finding (p=0.012). Regression analysis showed that elevation of aldosterone levels by 10 ng/dL increases the chances of developing a positive finding by 25.5% in our sample, i.e. from 5.1% to 49.8% in the population of such respondents.

5. DISCUSSION

Assessment of the complications following AMI is complex and in everyday clinical practice the weaknesses and shortcomings of the available methods and previous recommendations are recognized. There are ideas about the possible role of aldosterone as an indicator of persistent coronary insufficiency, so two recent studies have speculated on the importance of aldosterone in the pathophysiology of coronary disease. The OPERA study linked the elevated level of aldosterone not only with heart failure and total mortality, but also with the onset of myocardial reinfarction (2, 18).

Until now no studies have been conducted that would connect the occurrence of post-infarct angina with the values of aldosterone. Catena et al. suggest that high aldosterone levels could induce myocardial (interaction between aldosterone and the cardiovascular system has been expanded beyond systolic heart failure, diastolic heart failure, arrhythmia, primary hypertension, and primary aldosteronism) (19).

In our study, in the group of compensated patients, changes in aldosterone levels showed statistical significance for post-infarction angina pectoris. We did not find this connection in a group of decompensated patients. The obtained results confirm that elevated levels of aldosterone potentiate the growth of oxidative stress, vascular inflammation, smooth muscle cell proliferation, and endothelial dysfunction, which represent important links in the development and maintenance of atherosclerotic processes. It has already been noted that patients with primary aldosteronism have an increased risk of cardiovascular events, including coronary artery disease and AMI (17, 18).

Ivanes et al. find association of aldosterone with the later occurrence of cardiac deaths and acute coronary events (20). This is also one of the few studies in which the comparable level of aldosterone with progression of coronary disease and mortality in a patient who had no specific circumstances such as myocardial infarction and cardiac decompensation. The level of aldosterone was strongly and independently correlated with the occurrence of coronary incidence and cardiac death in a patient with stable coronary disease (18).

Hillaert et al. showed a link between aldosterone levels in plasma with total atherosclerotic loading in these patients and the occurrence of myocardial infarction, cerebrovascular accident and cardiovascular mortality (18).

In the group of compensated patients, changes in aldosterone values showed a statistically significant effect on the occurrence of reinfarction p=0.009, which is in line with the aforementioned OPERA study in which the elevated level of aldosterone was associated with the occurrence of myocardial reinfarction. The obtained result can be related to the previously contemplated stimulation of expression of MMP and PAI-1 by RAAS, leading to destabilization of atherosclerotic plaque and fibrinolytic balance changes (6).

This finding is not found in the group of patients with cardiac decompensation, which suggests that in our study, in patients with acute myocardial infarction, the occurrence of reinfarction is also independent of the development of cardiac decompensation.

Stress test at least three weeks after AMI is a common strategy for monitoring patients with a AMI without complications and present method for detection of post-infarction latent coronary insufficiency.

Garnier et al. in its mouse model demonstrated the specific effect of aldosterone on coronary vascular functions as it has not been described by aldosterone provocation models, so these results also suggest that the coronary artery may be aldosterone's target. The results obtained are consistent with previous studies by De Rite and associates which suggest that aldosterone levels are associated with the progression of atherosclerotic processes (16). On the other hand, the level of aldosterone in the blood did not show a positive correlation with the degree of tolerance of body load after infarction, i.e. no significant relationship was found between the levels of aldosterone and the duration of stress test. Tomaschitz et al. suggested that plasma aldosterone levels are associated with increased cardiovascular mortality (22). Palmer al al. proved that plasma aldosterone levels after AMI are independent predictors of survival and hospitalization for heart failure during five year-follow-up period (23). Yuyun et al. suggested that is plasma aldosterone levels predicts major adverse cardiovascular events in patients with acute myocardial infarction (8). Our research supports the results of these research and although the sample is quite small, it can be the basis for future research, where stratification of patients will be made in relation to the localization of infarction in order to follow the effects of aldosterone. The fact is that aldosterone should be established as part of routine laboratory tests, which would be used in the admission of patients with AMI.

6. CONCLUSION

In patients with AMI, elevated serum aldosterone level can be prognostic factor of the progression of coronary heart disease, development of heart failure, as well of development of post-infarction angina, myocardial reinfarction and pathological finding on the stress test.

- **Author's Contribution:** N.R. and A.D.N. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work, N.R., A.Dz., A.B and E.B. had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they are agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflicts of interest:** There are no conflicts of interest.
- **Financial support and sponsorship:** None.

REFERENCES

1. Koid SS, Campbell DJ. Evolving concepts of the renin-angiotenzin-aldosteron system. Journal of Renin-Angiotenzin-Aldosteron System. 2013; 14(1): 93-96.
2. Udell JA, Morrow DA, Braunwald E, et al. Inhibition of Renin-Angiotensin System Reduces the Rise in Serum Aldosterone in Acute Coronary Syndrome Patients with Preserved Left Ventricular Function: Observation from the AVANT GARDE TIMI 43 Trial. Clin Chem. 2013; 59(6): 959-967.
3. Beygui F, Vicaut E, Ecollan P, et al. Rationale for an early aldosteron blocade in acute myocardial infarction and design of the ALBATROSS trial. Am Heart J. 2010; 160(4): 642-648.
4. Murin J. Cardiovascular effects of aldosterone Bratisl Lek Listy. 2005; 106(1): 3-19.
5. Sata M, Fukuda D. Crucial role of renin angiotensin system in the pathogenesis of atherosclerosis. J Med Invest. 2010 Feb; 57(1-2): 12-25.
6. Hansson GK, Hermansson A. The immune system in atherosclerosis. Nat Immunol. 2011 Mar; 12(3): 204-212.
7. Young MJ, Lam EY, Rickard AJ. Mineralocorticoid receptor activation and cardiac fibrosis. Clin Sci. 2007; 112(9): 467-475.
8. Yuyun MF, Jutla SK, Qiunn PA, et al. Aldosterone predicts major adverse cardiovascular events in patients with acute myocardial infarction. Heart Asia. 2012; 4: 102-107 doi:10.1136.
9. Mentz RJ, Bakris GL, Waeber B, et al. The past, present and future of renin–angiotensin aldosterone system inhibition Int J Cardiol. 2013 Sep 1; 167(5): 1677-1687.
10. Verma A, Bulwer B, Dhawan I, et al. Aldosterone Receptor Antagonist and Heart Failure Following Acute Myocardial Infarction Acta Cardiol Sin. 2010; 26: 203-215.
11. Sun Y, Zhang J, Lu L, et al. Aldosterone-induced inflammation in the rat heart : role of oxidative stress Am J Pathol. 2002 Nov; 161(5): 1773-1781.
12. Catena C, Colussi G, Brosolo G, et al. Aldosterone and aldosterone antagonists in cardiac disease: what is known, what is new. Am J Cardiovasc Dis. 2012; 2(1): 50-57.
13. Guichard JL, Clark D, Calhoun DA, et al. Aldosterone receptor antagonists: current perspectives and therapies Vasc Health Risk Manag. 2013; 9: 321-331.
14. Desai AS, Lewis EF, Li. R. et al. Rationale and desing of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial: A Randomized, controlled study of spironolactone in patiens with symptomatic heart Failure and preserved ejection fraction Am Heart J. 2011; 162(6): 966-972.
15. Milliez P, Girerd X, Plouin PF. et al. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism J Am Coll Cardiol. 2005 Apr 19;45(8):1243-8.
16. De Rita O, Hackam DG, Spence JD. Effects of aldosterone on human atherosclerosis: plasma aldosterone and progression of carotid plaque. Can J Cardiol. 2012 Nov-Dec; 28(6): 706-711. doi: 10.1016/j.cjca.2012.04.014.
17. Beygui F, Motalescot J, Vicant E. et al. Aldosteron and long-term outcome after myocardial infarction; A substudy of the french nation wide Observatoire sur le Prise en charge hospitaliere, l,Evolution a un an et les caracteristiques de patients presentant un infarctus du myocarde avec on sans onde Q (OPERA) study. Am Heart J. 2009; 157(4): 680-687.
18. Hillaert AM, Lentjes EG, Kemperman H. et al. Aldosterone, atherosclerosis and vascular events in patients with stable coronary artery disease. 2013; 167(5) :1929-1935.
19. Catena C, Colussi G, Nait F. et al. Aldosterone and the heart: still an unresolved issue?. Front Endocrinol (Lausanne). 2014; 5: 168.
20. Ivanes F, Susen S, Mouquet F. et al. Aldosterone, mortality, and acute ischaemic events in coronary artery disease patients outside the setting of acute myocardial infarction or heart failure. Eur Heart J. 2012 Jan; 33(2): 191-202.
21. Garnier A, Bendall JK, Fuchs S. et al. Cardiac specific increase in aldosterone production induces coronary dysfunction in aldosterone synthase-transgenic mice. Circulation. 2004; 110: 1819-1825.
22. Tomaschitz A, Pilz S, Ritz E. et al. Plasma aldosterone levels are associated with increased cardiovascular mortality: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Eur Heart J. 2010 May; 31(10): 1237-1247.
23. Palmer BR, Pilbrow AP, Frampton CM. et al. Plasma aldosterone levels during hospitalization are predictive of survival post-myocardial infarction. Eur Heart J. 2008 Oct; 29(20): 2489-2496.