Original article

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Prognostic role of aldosterone in patients with acute coronary syndrome: short and medium term follow-up

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Aims **Different researches showed a correlation between aldosterone, atherosclerosis and ischemia in the last decade. Evidence exist about relationship between high levels of aldosterone and augmented risk of cardiovascular diseases, like hypertension, cardiac failure, coronary artery disease and stroke. The objective of this study was to determine the prognostic role of aldosterone in patients with myocardial infarction.**

Methods **Population of the study includes 96 consecutive patients admitted in our Department for ST-elevated and non-ST-elevated myocardial infarction from June 2009 to March 2012. Plasmatic aldosterone levels were dosed at admission in hospital in all patients. A 2 years prospective follow-up was performed and fatal events and nonfatal events like reinfarction, congestive heart failure and arrhythmias were recorded.**

Results **Aldosterone levels at admission were associated with incidence of congestive heart failure ($P = 0.02$), ventricular arrhythmias ($P = 0.01$) and all complications ($P = 0.003$) after 1-month follow-up. Moreover, high aldosterone levels gave important information at medium term (24 ± 6 months). Specifically, aldosterone was a predictive variable of reinfarction ($P < 0.0001$), congestive heart failure ($P < 0.0001$) and adverse events ($P = 0.0002$). The logistic regression analysis confirmed these results and showed that aldosterone may be predictive of adverse events at medium term follow-up [OR 1.1 (1.03–1.15); 95% confidence interval, $P = 0.02$].**

Conclusion **These data show a strong and significant correlation between aldosterone plasmatic levels at admission for myocardial infarction and fatal and nonfatal adverse events. Aldosterone appears a main marker of adverse clinical outcome according with literature. These data suggest necessity to identify if antialdosteronic drugs treatment, applied acutely in patients with aldosterone elevation, can influence favorably prognosis of patients with myocardial infarction.**

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Keywords: acute coronary syndrome, aldosterone, arrhythmias, failure, heart, myocardial infarction

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Introduction

The first study that clarified the role of aldosterone in myocardial infarction has been conducted by Beygui *et al.*[1] who analyzed the relationship between plasma aldosterone and outcome of patients with ST elevation myocardial infarction (STEMI) and without left ventricular dysfunction or heart failure.

The study enrolled 356 patients, undergoing Percutaneous Coronary Intervention (PCI) for STEMI, who were divided in four quartiles and monitored for 6 months. Results of the study showed that higher levels of aldosterone were associated with higher incidence of ventricular fibrillation ($P = 0.02$), heart failure ($P = 0.005$) and cardiovascular death ($P = 0.03$) during hospital stay. Moreover, patients of the highest quartile had worse outcome at 6 months than patients with lower levels of aldosterone independently from age, heart failure and successful reperfusion. Subsequently, the same group conducted a new study to determine the effect of spironolactone in patients with STEMI, showing that antialdosteronic drugs provide a lower incidence of arrhythmias and cardiac arrest.[2]

According to Beygui *et al.* data, Palmer *et al.*[3] reported that aldosterone levels correlate with long-term mortality of patients with AMI. The study recruited 546 patients with STEMI or non-STEMI and without postinfarction heart failure. Over 80% of patients had non-STEMI and follow-up was 5 years. These data, therefore, confirm results of Beygui *et al.* extending conclusions to the larger group of non-STEMI patients who were more than 80%

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of the total cohort. In addiction, levels of plasma aldosterone were elevated beyond the normal range in only a small percentage of patients suggesting that higher concentration of plasma aldosterone, within the normal range, may have an important impact on long-term survival.

Finally, the LURIC study, that considered a large cohort of normotensive and hypertensive patients with and without coronary artery disease, heart failure and acute coronary syndrome, demonstrated that higher levels of plasma aldosterone, although within the normal range, correlate with overall and cardiovascular mortality.[4]

A recent meta-analysis, which considered 19 randomized controlled trials and a total of 10 807 patients, confirmed the negative effect of aldosterone in patients with chronic heart failure and IMA, reporting a 20% reduction in all-cause mortality in patients treated with mineralocorticoid receptor antagonists.[5]

Primary objective of our study was to evaluate relation between plasmatic aldosterone levels at hospital admission and mortality (for cardiovascular disease or for all causes) and complications incidence (reinfarction, ventricular fibrillation, left ventricular insufficiency) at short term (less than 30 days after hospitalization) and at medium term (24 ± 6 months) in patients admitted for myocardial infarction in our Operative Unit of Cardiology of University Hospital 'Paolo Giaccone' of Palermo.

In addiction our study wanted evaluate efficacy of spironolactone on fatal and nonfatal adverse events reduction.

Materials and methods

The study included patients of every sex that were admitted for ST elevated and Non-ST-elevated myocardial infarction from June 2009 to March 2012 in our Operative Unit of Cardiology and that underwent to coronarography. Diagnosis of STEMI was made, according to the current guidelines, in those patients referred to our division for a typical chest pain lasting more than 20 min and with a persistent ST-elevation reflecting an acute and total occlusion of the artery responsible for the myocardial infarction.[6] A diagnosis of non-STEMI was made, always according to the current guidelines, in patients referred for typical chest pain but without a persistent ST elevation, when a positive value of troponin was found.[7] Exclusion criteria of the study were: potassium saver diuretics treatment before myocardial infarction, severe renal failure (creatinine >2.5 mg%), potassium levels more than 5 mmol/l, respiratory insufficiency, severe hepatic disease, malignant neoplasia or terminal cachexia, active infective diseases, mental disorders or linguistic barriers, that impeded adequate comprehension and collaboration.

All patients underwent to accurate medical history, objective clinical examination, standard ECG, echocardiography, samples for specific myocardial enzymes, blood glucose, total cholesterol, low density lipids (LDL), high density lipids (HDL), triglycerides, creatinine, BUN, serum electrolytes, AST levels, ALT levels, coagulation.

Left ventricular ejection fraction (LVEF), end-systolic volume, end-diastolic volume were evaluate with transthoracic echocardiography. Echocardiographic evaluation will performed with echocardiography 'Acuson Sequoia'. Chamber dimension, LVEF and systolic function, valve function and morphology, pattern Doppler and diastolic function were assessed with conventional echocardiography. LVEF was measured by modified biplane Simpson method.

Plasmatic aldosterone was dosed at admission in hospital in all patients by a commercial radioimmunoassay kit (ALDO-RIACT, Schering AG, Berlin, Germany). Considered normal range was 8–172 pg/ml.

Data about coronary anatomy, stent or bypass presence and about drugs that were administered during cardiac catheterization (heparin, aspirin, clopidogrel, abciximab) were recorded in every patient. TIMI flow grade was evaluated in patients that underwent to angioplasty. Observation period of our prospective study lasted 24 months and, for medium term follow-up, information about fatal and nonfatal adverse events were recorded contacting patients to conduct a clinical examination or, if it was not possible, contacting them, their relatives or their medical doctors with telephonic interviews. Recorded data were about cardiovascular and noncardiovascular death and further hospitalizations for cardiovascular reasons (reinfarction, congestive heart failure and arrhythmias).

Data management and statistical analysis

Statistical analysis was affected using Statview program (Abacus Concepts Inc.). Mean and SD were calculated for numeric variables and differences were obtained between groups by Student's t test. Prevalence of clinical and laboratory variables and difference between groups were calculated by χ^2 statistical test. Considered significant statistic level was $P < 0.05$.

Results

Three hundred and fifty-six patients were admitted in our intensive unit of cardiology with diagnosis of acute coronary syndrome from June 2009 to March 2012. Ninety-six patients with myocardial infarction that underwent to coronarography were recruited, 70 with ST-elevated myocardial infarction diagnosis and 26 with non-ST-elevated myocardial infarction diagnosis. All patients were informed at moment of enrollment about protocol and did consent to study participation. Median age of participants was 65 years, 57% was men and 57%

had familiar history for myocardial infarction. Regarding other principal cardiovascular risks, 69.7% presented hypertension before myocardial infarction, diabetes mellitus type 2 was present in 29.2%, dyslipidemia in 33.3%, obesity in 33.7% and smoke in 40.6%.

Basal characteristics of our population showed moderate-high risk patients with myocardial infarction, 31% with age at least 75 years, 23% with history of acute myocardial infarction, 42.7% with anterior or anterior-septal or anterior-lateral acute myocardial infarction. Median levels of aldosterone in our population was 71.3 pg/ml.

Mean ejection fraction of left ventricle at transthoracic echocardiography was 50%. In particular 40.5% of patients showed a normal ejection fraction (EF) and only 18.2% showed systolic dysfunction of left ventricle, defined to EF less than 40% presence. All patients underwent to coronary and ventricular catheterization that showed an involvement of one vessel in 51.6% of cases, an involvement of two vessels in 24.2% and a multivessel involvement in 24.2% of patients. Only in 2.5% of cases a full spontaneous reperfusion happened. Ninety percent of patients were treated with primary PCI and coronary stent application, with a successful reperfusion in 95% of patients. Remaining 5% of patients needed an aortic-coronary bypass. Patients that underwent to aortic-coronary bypass were 10.4% in all.

Global population was divided in three groups in accord with plasmatic aldosterone levels tertiles. Every tertile was defined by aldosterone levels 19.0 or less (I), from 19.1 to 66.0 (II), at least 66.1 pg/ml (III).

Patients treated with antialdosteronic drugs and standard therapy were 30 and they were distributed in plasmatic aldosterone levels tertiles: specifically nine in I tertile, 10 in II tertile and 11 in III tertile. Comparison between clinical characteristics of every tertile of patients is reported in Table 1.

Comparing recorded data during echocardiographic examination, there were not any statistically significant differences between tertiles, considering ejection fraction, end-systolic volume and end-diastolic volume.

At last, first and second tertiles were more frequently associated, but not significantly, with a less severe coronary disease, contrary to third tertile.

During hospital stay only two deaths occurred after ventricular. These complications occurred during hospital stay: cardiogenic shock in 2.1%, congestive heart failure in 11.46%, reinfarction in 3.1%, ventricular fibrillation in 4.2% and atrial fibrillation in 8.3% of patients.

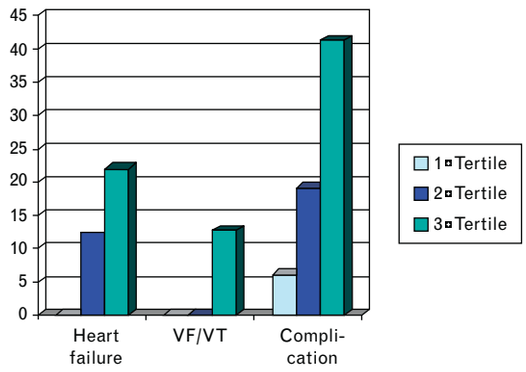
Cardiogenic shock, ventricular fibrillation and death occurred only in patients of the third tertile. Cardiac heart failure kept a higher frequency in the higher tertile (21.9%) than in the second tertile (12.5%); re-infarction occurred in 6.25% of cases of third tertile and in 3.1% of the second tertile, and minor arrhythmias (atrial fibrillation, supraventricular tachycardia and atrial tachycardia) occurred more frequent in the third and in the second tertile (9.4%, respectively) than in the first one (6.25%). The rates of in-hospital events in different groups, according to the baseline tertiles of plasma aldosterone levels, showed an almost stepwise increase in rates of

AQ8 **Table 1 Basal characteristics in agreement with plasmatic aldosterone levels tertiles**

Variables	Tertile 1	Tertile 2	Tertile 3	*P*
Age	62 ± 17	67 ± 14	64 ± 13	Ns[a]
Male sex (%)	56	41	75	0.02
Previous AMI[b] (%)	22	22	25	Ns
Hypertension (%)	62.5	87.5	59.4	0.02
Diabetes (%)	28	28	31	Ns
Smokers (%)	53	18.7	50	0008
Dyslipidemia (%)	28.1	40.6	31.5	Ns
BMI (kg/m^2), mean ± SD	26.4 ± 4.5	28.9 ± 5.4	27.4 ± 6.6	Ns
SBP (mmHg), mean ± SD	129 ± 20	144 ± 20	137 ± 26	Ns
DBP (mmHg), mean ± SD	77 ± 12	81 ± 13	80 ± 12	Ns
Ejection fraction (%), mean ± SD	50 ± 8	50 ± 10	48 ± 9	Ns
AMI location (%)				Ns
Anterior wall	37.5	43.75	50	
Inferior wall	53	34.4	34.4	
Lateral wall	9.4	25	15.6	
Angiographic characteristics,%				Ns
1 vessel	25	40.6	28	
2 vessels	34.4	9.3	28.1	
Multivessel	15.6	31.2	25	
Aldosterone (pg/ml), mean ± SD	11.8 ± 5.0	35.5 ± 12.4	167 ± 95	<0.0001
Troponine (ng/ml) mean ± SD	34.2 ± 33	21.3 ± 27	40.3 ± 69	Ns
C Reactive protein (pg/ml), mean ± SD	2.1 ± 2.9	2 ± 2.5	2.6 ± 3.5	Ns
Fibrinogen (mg/dl), mean ± SD	339 ± 122	381 ± 90	378 ± 89	Ns
Triglycerides (mg/dl), mean ± SD	136.8 ± 73	108.8 ± 40	143 ± 67	Ns
Total cholesterol (mg/dl), mean ± SD	176,3 ± 38	173.7 ± 39	189 ± 46	Ns
LDL[c] (mg/dl), mean ± SD	105.8 ± 36	103.6 ± 33	117 ± 43	Ns
HDL[d] (mg/dl), mean ± SD	41.4 ± 13	52.1 ± 20.7	43.8 ± 14	Ns

[a] Ns, NOT significant. [b] AMI, acute myocardial infarction. [c] LDL, low density lipids. [d] HDL, high density lipids.

Fig. 1



Intrahospital complications rate in relation to aldosterone tertiles during hospital stay with significantly difference between tertiles.

congestive heart failure ($P = 0.02$), VF/VT ($P = 0.01$) and all complications ($P = 0.003$) (Fig. 1).

So, higher levels of aldosterone at admission in patients with myocardial infarction were correlated with a worst short-term outcome.

Analyzing the group of 21 patients with fatal and nonfatal in-hospital events (re-infarction, congestive heart failure, ventricular fibrillation and cardiogenic shock), data showed that these patients presented a median aldosterone level of 132.4 versus 54.23 pg/ml ($P = 0.0002$) in patients without in-hospital complication or death.

Clinical baseline characteristics of patients are reported in Table 2 in two groups: one with adverse events during follow-up and one without events.

Events rate during medium term follow-up was 35.1% (26 patients); the following events occurred during the follow-up: four cardiovascular deaths, two cardiogenic shock, 15 cardiac heart failure and eight re-infarctions. Patients with adverse events did not show a higher statistically significant prevalence of principal negative prognostic factors like diabetes (23.1 versus 27.1%) or anterior infarction (50 versus 46%).

Higher aldosterone levels were associated with adverse events (re-infarction, congestive heart failure, ventricular fibrillation, cardiogenic shock) ($P = 0.0002$) and patients with these events showed a mean aldosterone level of 130.15 versus 60 pg/ml of patients without complications.

In addiction, analyzing percentage of affiliation to plasmatic aldosterone tertiles in the group of patients with events, 4.8% belongs to I tertile, 23.8% to II tertile and 71.4% to III tertile.

Other predictive variables of adverse events at univariate analysis were previous infarction ($P = 0.02$) and ejection fraction ($P = 0.0004$).

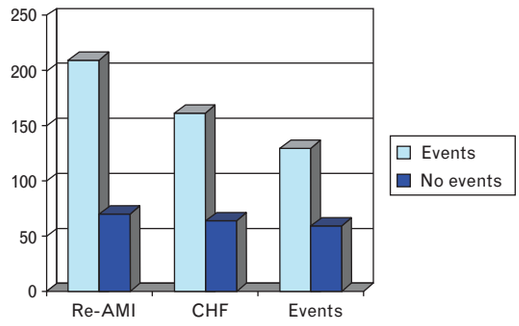
Analyzing specific events and their relations with aldosterone levels, higher levels of aldosterone were associated with higher incidence of re-infarction (210.25 ± 148.1 versus 69.5 ± 73.9; $P < 0.0001$) and congestive heart failure (162.3 ± 134 versus 64.9 ± 70.2; $P < 0.0001$) (Fig. 2).

Table 2 Basal characteristics of patients in relation to presence of absence of adverse events during follow-up

Variables	Events	No events	P
Age, mean ± SD	68 ± 15	65 ± 12	Ns[a]
Male gender (%)	65.4	65.12	Ns
Previous AMI[b] (%)	34.6	12.5	0.002
Hypertension (%)	76.9	64.6	Ns
Diabetes (%)	23.1	27.1	Ns
Smokers (%)	34.6	35.4	Ns
Dyslipidemia (%)	46.15	33.3	Ns
BMI (kg/m^2), mean ± SD	25 ± 8	28 ± 5	Ns
SBP (mmHg), mean ± SD	134 ± 26	140 ± 23	Ns
DBP (mmHg), mean ± SD	78 ± 12	81 ± 13	Ns
Ejection fraction (%), mean ± SD	45 ± 10	53 ± 8	0.0004
AMI location (%)			
Anterior wall	50	46	Ns
Inferior wall	19.2	40	Ns
Lateral wall	19.2	6.25	Ns
Angiographic characteristics (%)			
1 vessel	32	36.2	Ns
2 vessels	15.4	10.6	Ns
Multivessel	23.1	27.6	Ns
Aldosterone (pg/ml), mean ± SD (median)	130.15 ± 118	60 ± 68	0.001
Troponin, (ng/ml), media ± SD	26.8 ± 35	41.5 ± 59	Ns
C Reactive protein (pg/ml), mean ± SD	1.9 ± 1.6	3 ± 3.9	Ns
Fibrinogen (mg/dl), mean ± SD	389 ± 100	392 ± 100	Ns
Triglycerides (mg/dl), mean ± SD	123 ± 49	124 ± 56	Ns
Total cholesterol (mg/dl), mean ± SD	181 ± 46	178 ± 44	Ns
LDL[c] (mg/dl), mean ± SD	109 ± 40	111 ± 41	Ns
HDL[d] (mg/dl), mean ± SD	46 ± 14	45 ± 17	Ns

[a] Ns, Not significant. [b] AMI, Acute Myocardial Infarction. [c] LDL, Low Density Lipids. [d] HDL, High Density Lipids.

Fig. 2



Aldosterone levels in relation to incidence of reinfarction, heart failure and total fatal and nonfatal events.

Logistic regression analysis was applied to variables that were significant at univariate analysis: previous infarction, ejection fraction and aldosterone. Purpose of our study was to evaluate which variables were predictive of adverse events (Table 3); aldosterone and ejection fraction were the only predictive independent variables of adverse events [OR 1.1 (1.03–1.15), 95% confidence AQ6 interval (CI); $P = 0.02$ and OR 0.9 (0.85–0.98), 95% CI; $P = 0.009$].

In addiction, considering that 30 patients (10 in every tertile) were treated with spironolactone after hospital stay, relationship between administration of antialdosteronic drugs and outcome was analyzed in our study. Data of this analysis showed only a trend in reduction of adverse events in patients treated with spironolactone in comparison with patients that were not treated with antialdosteronic drugs (eight events versus 21 events; $P = 0.08$)

Discussion

The role of Aldosterone in cardiovascular pathophysiology was suggested for the first time by presence of mineralcorticoids receptors in vascular tissues, including heart. After that moment, different research confirmed the important pathophysiologic role of aldosterone in cardiovascular system.[8]

Indeed, mineralcorticoid receptors activation have proinflammatory, prothrombotic and profibrotic effects that contribute to development and progression of cardiovascular damaging effects that include: acute endothelial dysfunction, reduced nitric oxide bio-availability, augmented endothelial oxidative stress for increased ROS generation, augmented cardiovascular tone,[9] reduced coronary flow, inhibition of tissues catecholamine receptors, thrombogenesis, fast necrosis of vascular and myocardial smooth muscular cells, deposition of collagen in blood vessels, hypertrophy and myocardial fibrosis.

Table 3 Univariate and multivariate analysis for predictive variables of fatal and non fatal events during mean term follow up

Variables	Univarite analysis	Multivariate analysis OR (95% CI); *P*
Aldosterone (pg/ml)	$P = 0001$	1,1 (1,03–1,15); $P = 0.02$
EF[a] (%)	$P = 00004$	0,9 (0,85–0,98); $P = 0009$
Previous infarction	$P = 0,02$	2,5 (0,67–9,8); $P = 0.17$

[a] EF, ejection fraction.

Different studies suggest that infusion of aldosterone can acutely induces a reduced coronary perfusion in healthy volunteers.[10] The principal mechanism seems the augmented oxygen free radicals synthesis and the endothelial dysfunction due to NADPH-oxidase.[11] Prothrombotic action of aldosterone involves different adverse effects on endothelial cells, like reduction of NO release, stimulation of plasminogen activator inhibitor 1 synthesis and increase of ROS and NADPH oxidase enzyme expression.

Several potential mechanisms could contribute to elevation of plasmatic aldosterone levels after an acute myocardial infarction. Stimulation of renin-angiotensin-aldosterone after a myocardial infarction and high angiotensin II levels, are probably the most important factors that contribute to increase aldosterone secretion. Also activation of hypothalamus–pituitary–adrenal gland axis can contribute, considering that this axis is early stimulate after an acute myocardial infarction and that adrenocorticotropic hormone is a powerful short-term secretagogue of aldosterone.

Central pathophysiologic role of aldosterone in heart failure was confirmed and underlined in important clinical trials, like RALES[12] and EPHESUS.[13] These studies showed that spironolactone and eplerenone gives beneficial effects in patients with heart failure and reduced ventricular ejection fraction, expanding indication of antialdosterone drugs in heart failure.

Beygui *et al.*[1] analyzed correlation between plasmatic aldosterone and outcomes in STEMI. They showed that aldosterone plasmatic levels were associated with higher incidence of fatal and nonfatal events in patients with diagnosis of ST-elevated myocardial infarction that underwent to primary PCI.

Purpose of our study was to evaluate correlation between plasmatic aldosterone levels in patients with myocardial infarction and short-term outcome and its prognostic role at medium term (2 years).

Results of our work showed that elevated aldosterone plasmatic levels were associated with adverse outcome, finding higher percentage of adverse events in the third aldosterone tertile as proof of direct proportionality between neuroormonal activation grade and prognosis. Differences between tertiles were statistically significant for cardiac insufficiency ($P = 0.02$), VF/VT ($P = 0.01$) and

total complications ($P = 0.003$) during hospital stay, and for cardiac heart failure ($P < 0.0001$), reinfarction ($P < 0.0001$) and total complication ($P = 0.001$) during 2 years follow-up. Other predictive variables of worse outcome were ejection fraction ($P = 0.0004$) and previous infarction ($P = 0.002$) at univariate analysis. Extending literature data, our study also demonstrated that elevated aldosterone plasmatic levels are an independent predictive variable of adverse events like showed from multivariate analysis: aldosterone and ejection fraction maintained their statistical significance with a P value of 0.02 and 0.009, respectively (Table 3).

In conclusion, these data show a strong and significant correlation between aldosterone plasmatic levels at admission for myocardial infarction and fatal and nonfatal adverse events: higher versus lower aldosterone plasmatic levels are associated with medium and short-term adverse clinical events.

So aldosterone appears a main marker of adverse clinical outcome. These results extend Beygui *et al.*[1] data on prognostic significance of plasmatic aldosterone levels at short and medium term.

The study of Palmer *et al.*[3], that was performed on a larger cohort of patients, with a mean follow-up of 5 years, confirmed results of Beygui *et al.* study in patients with STEMI and in patients with non-STEMI that constituted 80% of the considered cohort.

Considering our results and data of literature about prognostic role of plasmatic aldosterone and considering that subgroup of patients treated with spironolactone showed a trend of lower rate of adverse events, there is necessity to identify if antialdosteronic drugs treatment, applied acutely in patients with aldosterone elevation, can influence favorably prognosis in a general setting of patients with myocardial infarction, expanding knowledge of historic RALES[12] and EPHESUS[13] trials.

In addition, whereas only 10.4% of the study population had levels of plasma aldosterone above normal values (8–172 pg/ml), it is possible to assume that beneficial effects on morbidity and mortality post-MI could be using antialdosteronic drugs in patients with myocardial infarction whose plasma levels of the hormone are not above the normal range. Data obtained from Pitt's *et al.* study are in agreement with this hypothesis and showed that aldosterone reduce left ventricular hypertrophy in hypertensive patients with low levels of aldosterone concentration.

Limitations of our study are: first, the small number of patients studied, due to important exclusion criteria like renal failure and active infective diseases; second, the effects of plasma aldosterone levels on long-term (5 years) clinical outcomes were not considered; third the serum levels of aldosterone were measured at admission; changes over time or their potential change due to various medications were not examined.

Finally, a limitation of this and all similar studies is the fact that circulating concentrations of aldosterone before the ischemic event remain unknown.

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