

Beneficial neurohumoral profile in left ventricular systolic dysfunction following acute myocardial infarction

Research Article

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Abstract: Objectives. The goal of our study was to determine the effects of combined renin-angiotensin-aldosterone system (RAAS) blocking therapy, including a selective aldosterone inhibitor eplerenone, on neurohumoral profile in patients with left ventricular (LV) systolic dysfunction following an acute myocardial infarction (MI). We also assessed the effect of multiple neuroendocrine inhibitors therapy on renal function and explored the interaction between changes in renal function and heart failure markers.

Methods. Our study incorporated 74 patients aged between 39 and 86 (mean 64.5 +/- 11.4) with established acute MI and reduced left ventricular ejection fraction (EF ≤ 40%). The additive effect of eplerenone (25-50 mg/d) on top of the standard heart failure regimen on plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-proBNP), renin and aldosterone were assessed at study entry and at six months. Renal function was determined by creatinine and estimated glomerular filtration rate (eGFR), calculated using the Cockcroft-Gault formula. The changes in LV volumes and systolic function were assessed by a transthoracic echocardiography at baseline and at the end of follow-up.

Results. Following 6 months of combined RAAS blocking therapy, incorporating aldosterone inhibitor eplerenone, plasma levels of NT-proBNP (-77.7%, p= 0.001) and renin (-52.2%, p= 0.083) decreased. As expected, an increase in aldosterone levels was observed (+36.8%, p= 0.758). A mild decline in eGFR (-2,0 ml/min, p= 0.028) was observed, with potassium levels increasing slightly, but remaining within the normal range (4.28 vs. 4.48 mmol/L, p= 0.028). We found that baseline creatinine correlated with measures characterising myocardial function (NT-proBNP, LVEF). The highest correlation was with NT-proBNP at baseline (r = 0.537, p < 0.001). Logistic regression models for prediction of significant left ventricular ejection fraction improvement (LVEF after 6 months-LVEF at baseline ≥ 5%) did not demonstrate that renal function measurements are suitable for this purpose.

Conclusions. A combined heart failure regimen, including aldosterone inhibitor eplerenone, in patients with left ventricular systolic dysfunction following acute MI decreases circulating levels of natriuretic peptides and renin and increases levels of aldosterone. The reduction in NT-proBNP is related to improvement of left ventricular systolic function and possibly to improved LV compliance and reduction of LV-filling pressures, whereas the increase in aldosterone levels could reflect activated feedback mechanisms of RAAS. A mild reduction in eGFR can be expected in the course of HF therapy in post-MI patients with normal baseline renal function. A severe hyperkalemia can be prevented by close monitoring of renal function and potassium levels. Our findings suggest, that there is a direct linear relationship between renal function and markers of myocardial function early post-MI, which is no longer present after six months. Cardio-renal correlation is best reflected by raw values of creatinine.

Keywords: Heart failure • Left ventricular systolic dysfunction • Renin-angiotensin-aldosterone system • NT-proBNP • Eplerenone

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1. Introduction

Heart failure (HF) is accompanied by the progressive activation of several neurohormonal systems and the release of biologic effectors into the bloodstream. Increased levels of norepinephrine, natriuretic peptides, such as atrial natriuretic peptide and brain natriuretic peptide (BNP), as well as activation of the renin-angiotensin-aldosterone system, have been described and associated with poor prognosis [1]. Angiotensin converting enzyme (ACE) inhibitors and beta blockers are recognized as the standard of care in patients with systolic left ventricular dysfunction associated with either chronic heart failure due to an ischemic or non-ischemic etiology as well as for the therapy of systolic LV dysfunction in patients post-acute myocardial infarction. Despite treatment with ACE-Is, patients with HF may demonstrate elevated aldosterone levels [2]. Evidence supporting the additional use of the aldosterone receptor blockers, spironolactone and eplerenone in heart failure has been growing. The RALES (Randomized Aldactone Evaluation Study) trial demonstrated that addition of spironolactone in patients with systolic HF and severe symptoms (NYHA classes III–IV) reduced all-cause mortality, cardiovascular mortality, as well as morbidity related readmissions [3]. The mechanism of action and neurohormonal impact of this therapy was further clarified by Rousseau et al. [4] in a neurohormonal substudy of RALES, where Spironolactone administration in patients with congestive HF reduced circulating levels of natriuretic peptides and increased levels of aldosterone. Both spironolactone and eplerenone are effective aldosterone blocking agents, but because of its greater selectivity, eplerenone has a lesser incidence of side effects [5]. The beneficial effects of eplerenone on top of standard medical therapy in patients with acute MI and left ventricular systolic dysfunction was showed in EPHEsus trial (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study [6], demonstrating improved survival and reductions in cardiovascular death, sudden death, and hospitalization for HF in eplerenone group. The most recent, EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) [7] trial extended the benefits of eplerenone to patients in chronic systolic HF and mild symptoms (NYHA class II), expanding indications for mineralocorticoid receptor antagonists in current HF treatment guidelines [8]. However neurohormonal analysis in this patient group was not carried out.

The present study was conducted to evaluate the effects of eplerenone 6 months administration in addition to standard HF therapy in post-acute MI patients on neurohumoral markers of heart failure severity — namely,

NT-pro BNP, renin and aldosterone. We hypothesized, that with coronary revascularization and a full standard HF therapy, left ventricular contractility should improve, followed by a positive shift in the neurohormonal profile.

Association between renal dysfunction and heart failure is well established. In recent studies, up to 30% of patients with heart failure had abnormal renal function which was associated with longer hospital stay, higher hospital costs, higher in-hospital mortality rates and more readmissions [9]. Renal dysfunction is a major independent risk factor for mortality in patients with post-MI left ventricular dysfunction and HF, as shown in the SAVE and Valsartan in Acute Myocardial Infarction (VALIANT) trials [10,11]. Most pharmacological treatments that improve the prognosis of patients with HF cause a decline in renal function. A nearly 20% increase in serum creatinine is expected with the use of ACE inhibitors, angiotensin receptor blockers (ARBs), and aldosterone antagonists. A reduction in eGFR was observed in moderate to severe heart failure patients with addition of angiotensin receptor blocker to ACE inhibitor in the Valsartan in Heart Failure Trial (Val-HeFT) [12]. Thus in our study we aimed to assess the effect of multiple neuroendocrine inhibitors therapy on renal function in patients with mild to moderate HF and normal baseline renal function as well as to explore the relationship between renal function and heart failure markers.

2. Materials and methods

2.1 Study population

From all patients hospitalized with acute MI to our institution between September 2007 and August 2008 we randomly selected a group of 90 patients with LV systolic dysfunction (LVEF \leq 40%) and mild to moderate heart failure symptoms (NYHA class II-III).

In order to minimize the risk of hyperkalemia, patients with severe renal dysfunction (creatinine \geq 150 μ mol/L) or potassium levels higher than \geq 5.2 mmol/L were not eligible for enrollment. All patients underwent coronary angiography within 24 hours from hospital admission and majority of them, 71 (78.9%) underwent percutaneous coronary intervention (PCI). Among the remaining 19 patients, 11 were planned for surgical revascularization, in 6 coronary lesions were judged to be unsuitable for intervention, 1 patient was successfully thrombolized and 1 patient was found to have normal coronary angiogram. Eplerenone 25 mg/d was commenced within 3 days after hospitalization and was uptitrated to 50 mg/d three weeks later in the absence of hyperkalemia. Treatment with eplerenone was given in addition to standard medical therapy, which could include ACE inhibitors,

angiotensin receptor blocker (ARB), if ACE-Is were not tolerated, beta-blockers, diuretics, digoxin, antiplatelets and statins. The mean follow-up period was 6 months. Out of 90 patients selected initially, 11 were excluded from the follow-up as they underwent coronary artery bypass grafting, one excluded due to sudden cardiac death and 4 patients were lost to follow-up. Thus, data on 74 patients was available for final analysis. Study population baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics of study population.

	Total population (n= 74)
Age, yrs	64.5 ± 11.4
Male gender, n (%)	57 (77)
Hypertension, n (%)	58 (78)
Diabetes mellitus, n (%)	10 (14)
History of MI, n (%)	9 (12)
Heart rate, bpm	87.65 ± 20.20
Blood pressure, mmHg	
Systolic	132.07 ± 27.63
Diastolic	81.19 ± 16.76
NYHA functional class, n (%)	
II	53 (72)
III	21 (28)
IV	0
LV ejection fraction,%	36.28 ± 7.38
Angiography findings, n (%)	
Normal coronary arteries	1 (1.35)
Single vessel disease	17 (23)
Double- vessel disease	20 (27)
Triple-vessel disease	36 (49)
PCI, n (%)	66 (89)
Heart failure therapy, n (%)	
Beta-blockers	72 (97)
ACEI/ARB	67 (91)
Loop diuretics	54 (73)
Digitalis	5 (7)
Renal function	
Creatinine, μmol/L	100.42 ± 41.73
Potassium, mmol/L	4.28 ± 0.57
Sodium, mmol/L	141.55 ± 3.89
CG-GFR, ml/min	82.40 ± 29.24
Neurohormones	
N-terminal pro-BNP, pg/ml	3333.14 ± 4281.70
Renin mU/ml	3.54 ± 9.17
Aldosterone pg/ml	191.89 ± 187.73

MI: myocardial infarction; LV: left ventricular; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; ACEI: ngiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; GFR: glomerular filtration rate; N-terminal portion brain natriuretic peptide

2.2 Measurements of neurohormonal markers

For the establishment of the baseline neurohormonal profile blood analysis was performed within the first week following acute MI. Plasma renin, aldosterone and

NT-proBNP levels were determined. The second laboratory measurements were taken after 6 months of HF treatment during ambulatory follow-up.

2.3 Measurements of renal function

Renal function tests - creatinine, potassium and sodium levels were measured at baseline, and were monitored closely throughout the study at regular follow-up visits. Glomerular filtration rate, as the standard indicator of renal function, was estimated for each patient using the Cockcroft Gault equation. This formula has been validated in several studies of HF and renal dysfunction.

2.4 Echocardiographic measurements

All patients underwent 2D transthoracic examination using a GE scanner (Vivid-7 Dimension). First echocardiographic examination performed within the first week after the myocardial infarction and second study done at the end of ambulatory follow-up 6 months later. LV end-diastolic and end-systolic volumes (LVEDV, LVESV) were obtained using a modified biplane Simpson's method from apical four and two-chamber views and the LV ejection fraction was calculated by the following formula: $([LVEDV - LVESV] / LVEDV) \times 100$ (%). The LV mass was calculated using Devereux's formula: $([interventricular\ septal\ thickness + LV\ end\ diastolic\ diameter + posterior\ wall\ thickness]^3 - LV\ end\ diastolic\ diameter^3) \times 1.05\ g/cm^3$ and LV mass index expressed in g/m^2 was calculated.

3. Statistical analysis

Descriptives are presented as mean +/- standard deviation. Comparing measures at baseline with measures after six months, paired samples t-test or Wilcoxon test was applied. In order to investigate linear relationships between measures of renal function and myocardial function parameters, Pearson or Spearman correlations were calculated. Finally, ability of prediction of improvement of LV ejection fraction was explored using logistic regression. Level of significance was set to 0.05.

4. Results

In total, 74 patients, 57 (77.0%) men and 17 (23.0%) women, aged from 39 to 86 (mean 64.5 +/- 11.4) were analysed. The mean LV ejection fraction at baseline was $36.28 \pm 7.38\%$ with majority of patients (72%) being in NYHA functional class II. 89% of patients underwent PCI and majority received a standard heart failure therapy regimen with beta blockers (97%), ACEI/ARB (91%) and

loop diuretics (73%). A significant reduction in heart rate at 6 months was observed (87 vs. 69 bpm, $p=0.001$), attributed to blockade of sympathetic nervous system with beta-blockers used in vast majority of our patients. Patients systolic blood pressure at six months increased slightly (132 vs. 145 mmHg, $p=0.052$), with no significant changes in diastolic blood pressure (81 vs. 87 mmHg, $p=0.287$). Serum creatinine levels remained within normal range, whilst mild, but statistically significant reduction in eGFR was observed (82 vs. 80 ml/min, $p=0.028$). The decrease in eGFR did not have an adverse effect on serum potassium levels, which increased slightly, but remained within normal range (4.28 vs. 4.48 mmol/L, $p=0.028$). Dynamics of patients characteristics as well as renal parameters are presented in Table 2.

Table 2. Patients characteristics and measures of renal function at baseline and at 6 months.

	Baseline	6 months	P value
Cardiovascular parameters			
Heart rate, bpm	87.65 ± 20.20	69.64 ± 13.47	0.001
Arterial blood pressure, mmHg			
Systolic	132.07 ± 27.63	145.77 ± 22.83	0.052
Diastolic	81.19 ± 16.76	87.83 ± 16.88	0.287
Renal function parameters			
Serum creatinine, $\mu\text{mol/L}$	100.42 ± 41.73	100.58 ± 19.25	0.139
Serum potassium, mmol/L	4.28 ± 0.57	4.48 ± 0.50	0.002
Serum sodium, mmol/L	141.55 ± 3.89	140.38 ± 2.69	0.348
eGFR, ml/min	82.40 ± 29.24	80.492 ± 4.44	0.028

4.1 Neurohormonal measurements

Changes in serum neurohormonal levels from baseline to 6 months are showed in Table 3.

Table 3. Changes in serum neurohormonal levels from baseline to 6 months. Additionally to mean values, neurohormonal levels in two groups with different degree of left ventricular systolic dysfunction severity are presented (group-1 incorporating patients with LVEF $\leq 35\%$, group-2 - patients with LVEF 36-40%).

	Baseline	6 months	P value
NT-proBNP, pg/m			
Mean	3333.14 ± 4,281.70	742.70 ± 782.07	0.001
group-1	3927,54 ± 4202,593	873,61 ± 883,130	0,011
group-2	2241,14 ± 3145,555	644,00 ± 725,574	0,018
Renin, mU/ml			
Mean	3.54 ± 9.17	1,69 ± 2.13	0.083
group-1	3,93 ± 11,737	1,92 ± 2,532	0,465
group-2	2,81 ± 7,405	1,50 ± 1,761	0,414
Aldosterone, pg/ml			
Mean	191.89 ± 187.73	303.91 ± 741.17	0.758
group-1	191,04 ± 184,388	156,31 ± 84,810	0,799
group-2	231,06 ± 225,237	779,86 ± 1447,791	0,398

The severity of left ventricular systolic dysfunction is demonstrated by high baseline NT-proBNP levels. As expected, we observed a significant reduction in mean

NT-proBNP concentration at six month (3333 vs. 742, $p=0.001$), which corresponds to significant increase in LV ejection fraction. As shown in Figure 1, mean NT-proBNP plasma concentration decreased by 77.7%.

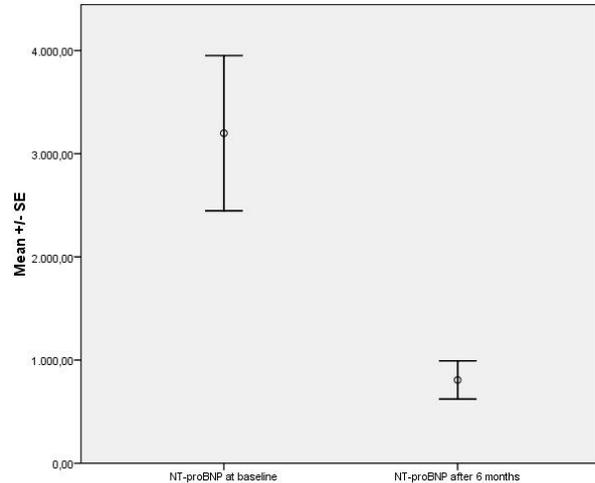


Figure 1. Dynamics of NT-proBNP levels.

For further analysis we subdivided our study population into two groups based on their baseline left ventricular ejection fraction, group 1 incorporating patients with LVEF $\leq 35\%$, and group 2 with LVEF between 36-40%. Higher degree of LV systolic dysfunction in group 1 corresponded to higher baseline NT-proBNP levels, compared to group 2 (3927.54 vs. 2241.14, $p=0.039$). As shown in Figure 2, following coronary revascularization and in the course of HF therapy, NT-proBNP decreased significantly in both groups (3928 vs. 874, $p=0.011$ and 2241 vs. 644, $p=0.018$, respectively at baseline and 6 months), without a significant difference between the groups at six months.

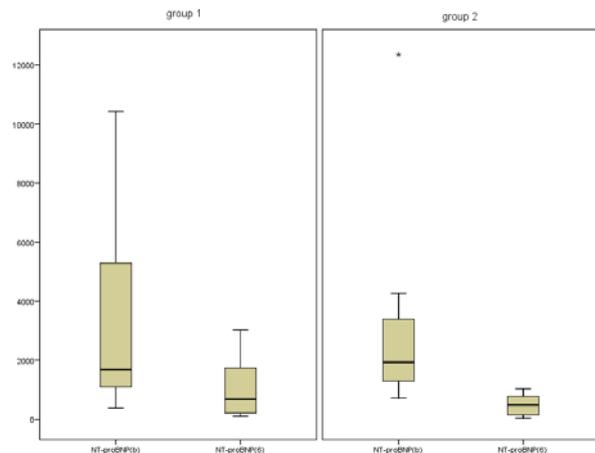


Figure 2. Changes in serum NT-proBNP levels from baseline to 6 months compared between two groups with different severity of LV systolic dysfunction: group 1 with LVEF $\leq 35\%$ and group 2 with LVEF 36-40%. Significant NT-proBNP reduction observed in both groups.

Elevated plasma renin concentration observed at baseline reflects activation of RAAS cascade in patients with heart failure. In the course of RAAS blocking therapy, we observed a 52.3% reduction in renin concentration (3.54 vs. 1.69, $p=0.083$) (Figure 3). Although the difference in renin concentration between the groups with different degree of LV dysfunction severity is statistically insignificant, the group with lower LV ejection fraction had higher renin levels (3.93 vs. 2.81, $p=0.746$).

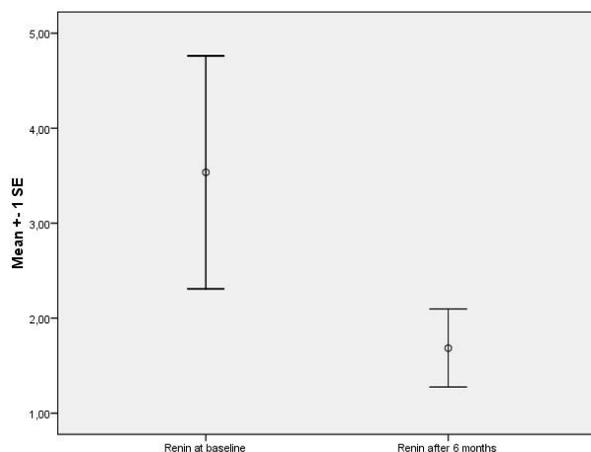


Figure 3. Dynamics of renin levels.

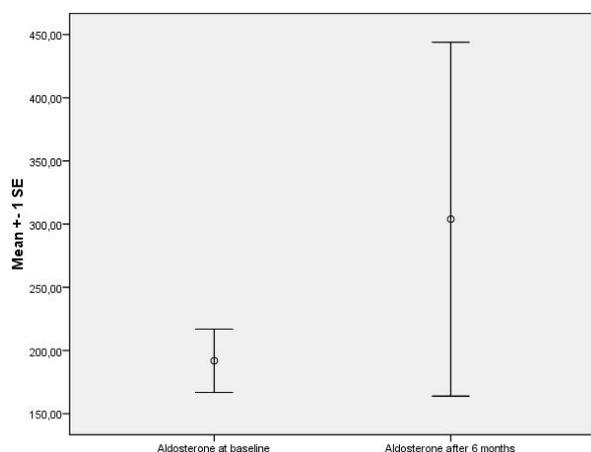


Figure 4. Dynamics of aldosterone levels.

Although changes are not statistically significant, we observed an increase in plasma aldosterone levels at six months (191 vs. 303, $p=0.758$) (Figure 4). No sig-

nificant difference in aldosterone levels was observed between the two groups.

4.2 Echocardiographic measurements

Echocardiographic measurements at baseline and at six months are presented in Table 4. The severity of LV systolic dysfunction is demonstrated by low baseline LV ejection fraction, which improved significantly following revascularization and 6 months of combined HF therapy (36% vs. 40%, $p=0.001$). Although echocardiographic measurements of LV volumes are statistically insignificant, one can notice a modest improvement in parameters characterizing LV contractility, namely a reduction of LV end-systolic volume, an increase in LV stroke volume and improved cardiac output.

Table 4. Dynamics of echocardiographic and hemodynamic parameters.

	Baseline	6 months	P value
LV EF, %	36.28 ± 7.38	40.76 ± 8.07	0.001
LVEDV, ml	145.63 ± 46.39	148.11 ± 53.38	0.864
LVESV, ml	93.92 ± 36.35	89.89 ± 38.66	0.415
LV stroke volume, ml	51.91 ± 15.70	58.21 ± 20.44	0.326
Cardiac output, l/min	3.59 ± 1.07	3.78 ± 1.24	0.851
Myocardial mass index g/m ²	125.48 ± 36.07	120.71 ± 26.02	0.955

LV EF- left ventricular ejection fraction, LVEDV- left ventricular end-diastolic volume, LVESV- left ventricular end-systolic volume

4.3 Relationship between measures of renal and myocardial function

To explore the relationship between measures of renal and myocardial function we calculated correlation coefficients and compared baseline values with values at 6 months. Results of this analysis are presented in Table 5. One can observe, that raw creatinine at baseline significantly correlated with different parameters of myocardial function measured at baseline: NT-proBNP ($p < 0.001$), LV ejection fraction ($p = 0.003$) and LV myocardial mass index ($p = 0.005$). However, this correlation is no longer present after 6 months. In addition to the analysis carried out, we have built several logistic regression models. These were intended to answer the question wheth-

Table 5. Correlation between measures of renal function and measures of myocardial function*.

	NT-proBNP(B)	LVEF (B)	LVMMI (B)	NT-proBNP (6)	LVEF (6)	LVMMI (6)
creatinine(B)	0.537 (<0.001)	0.350 (0.003)	0.376 (0.005)	-0.092 (0.604)	-0.351 (0.045)	0.108 (0.548)
eGFR(B)	-0.358 (0.011)	-0.101 (0.422)	-0.189 (0.168)	-0.317 (0.088)	0.067 (0.724)	0.033 (0.864)
creatinine(6)	-0.107 (0.618)	0.333 (0.044)	0.177 (0.366)	-0.095 (0.603)	-0.162 (0.367)	0.063 (0.726)
eGFR(6)	-0.203 (0.364)	-0.228 (0.203)	0.277 (0.154)	-0.349 (0.069)	-0.061 (0.747)	0.035 (0.845)

* correlation coefficient and p value are reported: r(p); letter B stands for baseline measurement, number 6 – for measurement after 6 months

er one can predict significant improvement of LV ejection fraction (improvement $\geq 5\%$) using measures of renal function. In this analysis we have also included levels of aldosterone, renin and NT-proBNP. The pattern applied was as follows. First of all, we have built 6 univariate models. In each of the models, a binary variable indicating LVEF improvement acted as a dependent variable, whereas one of six previously mentioned baseline measurements (creatinine, eGFR, aldosterone, renin, NT-proBNP) acted as an independent one. Since none of the variables appeared to be significant in univariate models, a final multivariate model was not built. Results of this analysis are presented in Table 6. One can observe that although creatinine was not a significant independent variable, it seems to be the most prominent for prediction of left ventricular EF improvement.

Table 6. Logistic regression models for prediction of LV ejection fraction improvement.

	Regression coef. (SE)	P value	OR (95% CI)
eGFR	0,005 (0,018)	0,788	1,005 (0,970;1,040)
Creatinine	-0,047 (0,026)	0,072	0,954 (0,907;1,004)
NT-proBNP	0,000 (0,000)	0,582	1,000 (1,000;1,000)
Renin	0,041 (0,055)	0,455	1,042 (0,936;1,160)
Aldosterone	-0,002 (0,003)	0,509	0,998 (0,993;1,004)

5. Discussion

5.1 Neurohumoral activation in heart failure

We evaluated the effect of combined RAAS inhibition, including aldosterone receptor blocker eplerenone, in patients with HF following acute myocardial infarction. Heart failure results in the activation of the sympathetic nervous and the renin-angiotensin-aldosterone systems by arterial underfilling, and by hemodynamic and hormonally mediated effects on the kidney [13]. Direct adrenergic and hemodynamic effects on kidneys result in augmented plasma renin activity and the subsequent production of angiotensin-II (AII). Being a potent vasoconstrictor, AII reduces renal perfusion, stimulates release of arginine vasopressin, pro-inflammatory cytokines, and aldosterone [14]. While protective during an acute stress response, chronic stimulation of RAAS has detrimental effects including vasoconstriction, vascular smooth muscle proliferation, endothelial dysfunction, inflammation, fibrosis, and thrombosis [15]. RAAS blockers (along with beta-blockers) have become the cornerstone of pharmacological therapy for systolic heart failure. The three main classes of RAAS inhibitors currently used in clinical practice are ACE-Is, angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists with a fourth class of agents

– the direct renin inhibitors (DRIs) – under active investigation.

Our study demonstrated, that following revascularization and in the course of HF therapy, incorporating an aldosterone receptor antagonist, significant reduction of plasma levels of NT-proBNP and, to a lesser extent renin concentration was observed, whereas an increase in aldosterone levels was noted. As expected, patients with more pronounced LV systolic dysfunction (LVEF $\leq 35\%$) had higher baseline NT-proBNP levels, compared to those with LVEF 36-40%. It is established, that circulating plasma levels of cardiac natriuretic peptides are inversely related to the severity of left ventricular dysfunction and have been found to be a prognostic predictors [16,17]. More specifically, the plasma NT-proBNP level is directly correlated to change in ventricular wall stress. Natriuretic peptides have several biologic functions, including vasodilatation, increased compliance in large vessels, enhanced baroreceptor sensitivity, and renal effects, particularly sodium excretion [18]. Our results are consistent with the data of Tsutamato et al. [19], who after four months of spironolactone therapy showed a significant decrease in BNP and pro-atrial natriuretic factor levels in a group of patients with mild to moderate non-ischemic cardiomyopathy. The observed reduction in NT-proBNP levels could be related not only to an improvement in left ventricular contractility, but also to an improvement in left ventricular diastolic properties and reduced LV-filling pressures. It is known, that aldosterone has several deleterious effects on the failing heart, primarily sodium and fluid retention, but also endothelial dysfunction, left ventricular hypertrophy, and myocardial fibrosis, resulting in increased myocardial stiffness and increased left ventricular mass [20,21]. Anti-aldosterone therapy can influence the progression of left ventricular remodeling by a reduction in interstitial fibrosis and reorganization of the collagen matrix [22,23]. Although the myocardial mass reduction observed in our study was statistically insignificant, it could have played a beneficial role in LV diastolic performance.

An increase in aldosterone levels observed during 6 months of HF therapy probably reflects an activated feedback mechanism of RAAS, a phenomenon known as “aldosterone escape”. For many years, it was believed that ACE-Is suppressed aldosterone levels sufficiently. Nevertheless elevated aldosterone levels have been noted in up to 38% of patients on chronic ACE inhibitor therapy [24,25]. It is established, that following an acute fall of aldosterone in response to administration of ACE inhibitor, the level rises again and returns to baseline in some patients. Interestingly, patients progress toward aldosterone escape regardless

of whether the ACE inhibitor dose is low or high [26]. Pitt et al. [3] in the Randomized ALdactone Evaluation Study (RALES) tested the hypothesis, that addition of aldosterone inhibitor to HF therapy, will overcome this phenomenon and allow a complete blockade of RAAS, however neurohormonal impact of this therapy remained unclear. The mechanism of action and neurohormonal impact of antialdosterone therapy was clarified by Rousseau et al [4] in a neurohormonal substudy of RALES, where in a subgroup of 107 patients (NYHA functional class III to IV) spironolactone administration in patients with congestive HF reduced circulating levels of natriuretic peptides and increased levels of aldosterone. Elevated aldosterone levels correlate with the risk of cardiovascular events, as shown in the neurohormonal substudy of the SAVE trial [27], where patients with lower aldosterone levels had a better prognosis and remained free of cardiovascular events for 2 years. The extent to which aldosterone escape occurs is highly variable. The underlying mechanisms for the described variety in individual responses to medical HF therapy remains uncertain, but they have been related to differences in race, ethnicity, comorbid conditions, concomitant use of other medications, and certain genetic predispositions [28,29].

Activation of RAAS in our study population is demonstrated by raised baseline renin levels. Elevated plasma renin activity has been found to be a marker of poor prognosis in heart failure patients. It is also a marker for subsequent adverse events in HF. The physiological pathways regulating renin release can be influenced by a number of pharmacologic agents currently used to treat HF. While beta-adrenergic receptor blockers directly inhibit secretion of renin, ACE inhibitors raise renin levels and downstream components of the RAAS cascade. Loop diuretics, commonly used to relieve congestion in HF patients are also known to activate neurohumoral axis. Bayliss et al. [30] demonstrated that addition of loop diuretic in heart failure patients resulted in significant increase in plasma renin activity and aldosterone levels. The main mechanism for renin release is thought to be diuretic-induced volume contraction. The higher renin levels observed in a group with worse LV systolic function could be attributed not only to the more pronounced RAAS activation, but also to higher doses of loop diuretics used. Atrial natriuretic peptides inhibit renin release, resulting in reciprocal relationship in healthy subjects with normal ventricular function, although this regulation may be disturbed by LV dysfunction. This explains the inverse relationship between BNP and renin levels observed in our study. There are, however, very little data on the relationship between BNP and plasma renin activity in chronic HF.

5.2 The effects of HF therapy on renal function

Impaired renal function is a major adverse prognostic factor in acute and chronic heart failure. Data from the Second Prospective Randomized Study of Ibopamine on Mortality and Efficacy (PRIME-II) showed that GFR decline was a stronger predictor of mortality than ejection fraction in patients with advanced and severe chronic HF [31]. Contrary to the general view, renal impairment in heart failure may be evident in any stage of the disease. Although worsening renal function in patients with decompensated HF is more common, patients with mild heart failure and even those with asymptomatic left ventricular systolic dysfunction exhibit such abnormalities, which confer to an adverse prognosis. We observed a mild decline in eGFR (-2.0 ml/min) in our patients. Whether such a small observed decline in eGFR may be clinically relevant is questionable. Our findings correlate with the results of Rossinol et al. [32], who analysed effects of eplerenone on renal function in EPHEBUS study population. In a group of patients with heart failure and left ventricular systolic dysfunction after an acute myocardial infarction, investigators observed a gradual decline in eGFR (-4.6 ± 0.9 ml/min/ 1.73m^2) with an adjusted mean difference of -1.4 ± 0.3 ml/min in eplerenone group compared with placebo. The difference in eGFR appeared as early as the first month and persisted throughout the study. The important message of this post hoc analysis was that the effects of eplerenone on kidney function did not reduce the survival benefits of eplerenone. It was suggested, that eplerenone should not be stopped if a modest decline in eGFR occurs. The decline in eGFR in our study was of smaller magnitude compared to that observed in EPHEBUS study population. One of the possible explanations could be the difference in baseline renal function. The mean baseline eGFR in EPHEBUS study population was lower (70 ± 21 ml/min/ 1.73m^2), with one third of patients having baseline renal dysfunction (eGFR <60 ml/min/ 1.73m^2). The second possible explanation could be the difference in the extent of the follow-up, 24 vs. 6 months, as it is known that HF patients tend to have a declining renal function in the long term. The reduction in eGFR observed in our patients could be attributed not only to the use of eplerenone. ACE inhibitors and ARBs have also been associated with a decline in eGFR, primarily mediated through the reduced effects of angiotensin II. A majority of our patients were also treated with loop diuretics and their long-term use per se may activate the RAA and sympathetic nervous systems, as well as induce a decrease in eGFR [33].

The issue of multiple RAAS inhibitors safety has been widely debated. When multiple neuroendocrine inhibitors are combined, they have increased propensity to raise

serum potassium levels. In RALES and EPHEBUS [3,6], the average increase in serum potassium levels in the treatment groups was 0.3 mmol/L and the increased incidence of serious hyperkalemia (>6.0 mmol/L) with the aldosterone blocker, although not statistically significant in RALES, was significant in the EPHEBUS study. In our study population with normal baseline renal function we observed a smaller, 0.2 mmol/L increase in serum potassium levels, with none of the patients developing severe hyperkalemia. The safety of eplerenone was also addressed in an EMPHASIS-HF trial [7], investigating effects of eplerenone vs. placebo in post-MI patients with mild heart failure. There was an increased incidence of hyperkalemia (potassium levels exceeding 5.5 mmol) in eplerenone group compared to those in placebo group, 11.8% vs. 7.2%. Patients with a baseline serum potassium level above 5.0 mmol/L and a baseline eGFR below 30 ml/min/1.73 m² were excluded from the study, thus aldosterone antagonists should be avoided in these patients. Nevertheless it was suggested, that eplerenone is safe and beneficial when given to patients without renal dysfunction. Taken together, it can be concluded, that in a selected group of patients, with a careful dosage titration and close monitoring of renal function, multiple RAAS blocking therapy, including aldosterone inhibitor, can be safe. In contrast, in congested HF patients requiring a large doses of loop diuretics, eplerenone administration reduces the risk of hypokalemia. This is important, because a serum potassium level below 4.0 mmol per liter has been associated with an increased risk of death from any cause among patients with systolic heart failure [34].

5.3 Relationship between cardiac dysfunction and renal function

Interactions between the heart and kidney in the setting of heart failure are complex and have a substantial impact on patient care and outcomes. The interdependence of cardiocirculatory aberrations and renal dysfunction is known as cardiorenal syndrome. Clearly, the cardiac and renal systems are significantly intertwined and disease in one organ often results in the other. The pathways leading to these impairments involve not only hemodynamic deterioration, but also neurohormonal, inflammatory and intrinsic renal mechanisms that produce this syndrome [34]. Although worsening renal function in patients with decompensated heart failure is more common, patients with mild heart failure and even those with asymptomatic left ventricular dysfunction exhibit such abnormalities, which confer an adverse prognosis. With respect to the kidneys, activation of RAAS is not only a response to preserve systemic circulatory volume, but it

is also a primary response to preserve glomerular filtration, which decreases with decreased renal blood flow and decline in perfusion pressures. The significance of neurohormonal pathways in development of renal dysfunction in patients with heart failure is showed by Weinfeld et al [35]. In a study of 48 heart failure patients, authors find no correlation between renal dysfunction and cardiac output, filling pressures, or systemic vascular resistance. Investigators concluded, that renal perfusion is effected by endogenous vascular factors, including endothelin, nitric oxide, prostaglandin, natriuretic peptides, independent of central hemodynamics. In our study population we observed a significant correlation of renal function tests with markers of cardiac function, namely NT-proBNP and LV ejection fraction, at baseline. Interestingly, this correlation is no longer present after 6 months. The correlation at baseline could possibly be explained by a strong influence of acutely failing heart on hemodynamics and renal perfusion pressures early after coronary event, when LV systolic function is at its worst, as well as influence of marked RAAS activation. However with interventional and pharmacological treatment strategies and subsequent improvement in LV systolic function, as well as suppression of RAAS activation, this cardiac-renal relation at 6 months is no longer present.

6. Conclusions

Combined RAAS blocking therapy, incorporating aldosterone receptor inhibitor eplerenone, in patients with left ventricular systolic dysfunction following acute MI, decreases circulating levels of natriuretic peptides and renin and increases levels of aldosterone. The marked reduction in NT-pro BNP levels is related to significant improvement in LV systolic function and possibly improvement in LV compliance and reduction of LV-filling pressures. Whereas the increase in aldosterone levels could reflect activated feedback mechanisms of RAAS. A mild reduction in eGFR in the course of HF therapy can be expected in post-MI patients with normal baseline renal function. A severe hyperkalemia can be prevented by close monitoring of renal function and potassium levels. Our findings suggest that there is a direct linear relationship between renal function and markers of myocardial function early post-MI, which is no longer present after 6 months. Cardio-renal correlation is best reflected by raw values of creatinine.

Conflict of interest

None declared.

References

- [1] Omland T., Aakvaag A., Bonarjee V.S., et al. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction: comparison with plasma atrial natriuretic peptide and N-terminal proatrial natriuretic peptide. *Circulation* 1996;93:1963-1969
- [2] Struthers A.D. Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. *J Card Fail* 1996;2:47-54
- [3] Pitt B., Zannad F., Remme W.J., et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med.* 1999; 341(10):709-717
- [4] Rousseau M.F., Gurne O., Duprez D., Mieghem W., Robert A., Ahn S., Galanti .L, Ketelslegers J.M. Beneficial neurohormonal profile of spironolactone in severe congestive heart failure. *J Am Coll Cardiol* 2002; Vol 40
- [5] Delyani, J.A., 2000. Mineralocorticoid receptor antagonists: the evolution of utility and pharmacology. *Kidney Int.* 57, 1408–1411
- [6] Pitt B., Remme W., Zannad F., et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003;348(14):1309-1321. [Ephesus]
- [7] Zannad F., McMurray J.J.V., Drexler H., Krum H., Van Veldhusein J.D., Swedberg K., Shi H., Vincent J., Pitt B. Rationale and design of the Eplerenone in mild patients hospitalization and survival study in heart failure (Emphasis-HF). *Eur J Heart Fail* 2010; 12 (6): 617-622
- [8] ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. McMurray JJ., Adamopoulos S., Anker SD, Auricchio A., Böhm M., Dickstein K., Falk V., Filippatos G., Fonseca C., ESC Committee for Practice Guidelines. *Eur J Heart Fail.* 2012 Aug;14(8):803-869
- [9] Forman D.E., Butler J., Wang Y., Abraham W.T., O'Connor C.M. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004; 43: 61-67
- [10] Jose P., Skali H., Anavekar N., Tomson C., Krumholz H.M., Rouleau J.L., Moya L., Pfeffer M.A., Solomon S.D. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. *J Am Soc Nephrol.* 2006;17:2886 -2891
- [11] Anavekar N.S., McMurray J.J., Velazquez E.J., Solomon S.D., Kober L., Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med.* 2004;351:1285–1295
- [12] Anand I.S., Bishu K., Rector T.S., Ishani A., Kuskowski M.A., Cohn J.N. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation.* 2009; 120:1577–1584
- [13] Francis G.S., Tang W.H. Pathophysiology of congestive heart failure. *Rev Cardiovasc Med.* 2003;4 (Suppl 2):S14-S20
- [14] Weber K.T. Aldosterone in congestive heart failure. *N Engl J Med.* 2001;345(23):1689-1697
- [15] Gradman A.H. Evolving understanding of the renin–angiotensin–aldosterone system: pathophysiology and targets for therapeutic intervention. *Am Heart J* 2009;157:S1-6
- [16] Rouleau J.L., Packer M., Moya L., et al. Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: effect of captopril. *J Am Coll Cardiol* 1994;24:583–591
- [17] Hall C., Rouleau J.L., Moya L., et al. N-terminal proatrial natriuretic factor: an independent predictor of long-term prognosis after myocardial infarction. *Circulation* 1994;89:1934–42
- [18] Levin E.R., Gardner D.G., Samson W.K. Natriuretic peptides. *N Engl J Med* 1998;339:321–328
- [19] Tsutamoto T., Wada A., Maeda K., et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. *J Am Coll Cardiol* 2001;37:1228–1233
- [20] Struthers A.D., MacDonald T.M. Review of aldosterone- and angiotensin II-induced target organ damage and prevention. *Cardiovasc Res* 2004; 61:663–670
- [21] Edelmann .F, Schmidt A.G., Gelbrich G., et al. Rationale and design of the “aldosterone receptor blockade in diastolic heart failure” trial: a double-blind, randomized, placebo-controlled, parallel group study to determine the effects of spironolactone on exercise capacity and diastolic function in patients with symptomatic diastolic heart failure

- (Aldo-DHF). *Eur J Heart Fail* 2010; 12:874–882.
- [22] Weber K.T., Brilla C.G.. Pathological hypertrophy and cardiac interstitium: fibrosis and renin-angiotensin-aldosterone system. *Circulation* 1991;83:1849-1865
- [23] Silvestre J.S., Heymes C., Oubenaissa A., Robert V., Aupetit-Faisant B., Carayon A., Swynghedauw B., Delcayre C. Activation of cardiac aldosterone production in rat myocardial infarction: effect of angiotensin II receptor blockade and role in cardiac fibrosis. *Circulation* 1999; 99: 2694-2701
- [24] MacFadyen R.J., Lee A.F., Morton J.J., Pringle S.D., Struthers A.D. How often are angiotensin II and aldosterone concentrations raised during chronic ACE inhibitor treatment in cardiac failure? *Heart* 1999; 82:57–61
- [25] Struthers A.D. The clinical implications of aldosterone escape in congestive heart failure. *Eur J heart Fail* 2004; 6: 539-545
- [26] Tang W.H., Vagelos R.H., Yee Y.G., et al. Neurohormonal and clinical responses to high-versus low-dose enalapril therapy in chronic heart failure. *J Am Coll Cardiol* 2002; 39:70–78
- [27] Vantrimpont P., Rouleau J.L., Ciampi A., Harel F., De Champlaine J., Bichet D., Moya JA. Two-year time course and significance of neurohumoral activation in the Survival and Ventricular enlargement (SAVE) study. *Eur Heart J* 1998; 19: 1552-1563
- [28] Shirani J., Dilsizian V. Imaging left ventricular remodeling: targeting the neurohumoral axis. *Nat Clin Pract Cardiovasc Med* 2008;5 Suppl 2:S57-62
- [29] Yancy C.W., Lee D.C. Personalized medicine in heart failure: are we there yet? *J Am Coll Cardio* 2012;5:419-421
- [30] Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Heart J* 1987;57:17–22
- [31] Hillege H.L., Girbes A.R., de Kam P.J., Boomsma F., de Zeeuw D., Charlesworth A., Hampton J.R., van Veldhuisen D.J. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation*. 2000;102:203–210.
- [32] Rossignol P., Cleland J.G., Bhandari S., Tala S., Gustafsson F., Fay R., Lamiral Z., Dobre D., Pitt B., Zannad F. Determinants and Consequences of Renal Function Variations With Aldosterone Blocker Therapy in Heart Failure Patients After Myocardial Infarction Insights From the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study *Circulation*. 2012 Jan 17;125(2):271-9. Epub 2011 Nov 29.
- [33] Gupta S., Neyses L. Diuretic usage in heart failure: a continuing conundrum in 2005. *Eur Heart J*. 2005;26:644–649
- [34] Ahmed A., Zannad F., Love T.E., et al. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. *Eur Heart J* 2007;28:1334-1343
- [35] Brown J.R., Uber P.A., Mehra M.R. The progressive cardiorenal syndrome in heart failure: mechanism and therapeutic insights. *Curr Treat Options Cardiovasc Med* 2008; 10: 342-348
- [36] Weinfeld M.S., Chertow G.M., Stevenson L.W. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J*. 1999; 138: 285-290