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High-dose spironolactone changes renin and aldosterone levels in acutely decompensated heart failure

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SOUHRN

Kontext: U pacientů s akutně dekompenzovaným srdečním selháním (ADHF) korelují vyšší koncentrace aldosteronu s horším výsledkem léčby po propuštění; nabízí se tedy představa, že další ovlivnění hodnot mineralokortikoidů během hospitalizace nebo bezprostředně po ní by mohlo zlepšit výsledný stav pacientů.
Metody a výsledky: Předkládáme výsledky naší observační, retrospektivní sekundární analýzy údajů ze studie se 100 pacienty s ADHF. V této studii bylo 50 pacientů zařazeno do podskupiny s podáváním spironolactonu (50–100 mg/den). Ve skupině s hodnotami reninu > 16,5 pg/ml a aldosteronu > 100 ng/dl byl zjištěn vyšší podíl pacientů v podskupině s podáváním spironolactonu (44,7 % vs. 66,7 %, resp. 56 % vs. 64,7; obojí $p < 0,05$). V podskupině pacientů léčených spironolactonem a s koncentracemi reninu a aldosteronu nad mezní hodnotou došlo mezi vstupním vyšetřením a třetím dnem k jejich významnému zvýšení (z 24 % na 32 %, resp. z 16 % na 44 %; obojí $p < 0,05$). Logaritmus koncentrace reninu a aldosteronu byl vyšší u pacientů s vyššími než mezními hodnotami reninu i aldosteronu (obojí $p < 0,05$).
Závěry: Spironolacton ve vysokých dávkách přidávaný ke standardní léčbě ADHF vede k dalšímu zvýšení koncentrací reninu a aldosteronu. Je třeba dále zkoumat, zda zvýšené hodnoty reninu a aldosteronu v důsledku odpovědi na úplnou blokádu receptorů pro mineralokortikoidy stále ještě mají prognostickou hodnotu.

Keywords:
Acute heart failure
Aldosterone
Mineralocorticoid receptor antagonism
Renin

ABSTRACT

Background: In acutely decompensated heart failure (ADHF) patients higher aldosterone levels correlate with worse post-discharge outcomes, suggesting that further modulation of the mineralocorticoid system during or immediately after hospitalization might favourably improve outcomes.
Methods and results: This was an observational, retrospective secondary analysis of a study including 100 patients with ADHF. In that study 50 patients were submitted to spironolactone treatment (50–100 mg/day). A higher proportion of patients with renin levels above 16.5 pg/mL and aldosterone levels above 100 ng/dL was observed in subjects submitted to spironolactone treatment (44.7% vs. 66.7% and 56% vs. 64.7%, respectively, both $p < 0.05$). In the group of patients submitted to spironolactone treatment the proportion of patients with renin and aldosterone levels above the cutoff had a significant increase from baseline to day 3 (24% to 32% and 16% to 44%, respectively, both $p < 0.05$). Log renin and aldosterone were higher in patients with renin and aldosterone levels above the cutoff point (both $p < 0.05$).
Conclusions: High-dose spironolactone added to standard ADHF therapy induces an additional increase in renin and aldosterone levels. Whether higher levels of renin and aldosterone due to the reactive response to full MRA still have prognostic value requires further investigation.

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Introduction

The use of mineralocorticoid receptor antagonists (MRAs) has demonstrated to improve outcomes and reduce mortality in chronic heart failure (HF) and post-myocardial infarction [1–3]. The benefit observed with MRAs is probably due to excessive neurohormonal activation blockade.

Particularly, aldosterone is probably essential for the progression of HF. Higher aldosterone levels were found in patients with chronic HF when compared with controls, and were found to be associated with poor outcome [4–7]. A rise in aldosterone levels was also observed in the acute myocardial infarction setting [8,9], and likewise associated with worse outcomes in this setting [10].

In acutely decompensated heart failure (ADHF) patients with ejection fraction (EF) < 40%, higher aldosterone levels correlate with worse post-discharge outcomes [11], suggesting that further modulation of the mineralocorticoid system during or immediately after hospitalization might favourably improve outcomes. Regarding this matter, high dose spironolactone as add-on therapy in the acutely decompensated heart failure (ADHF) setting has demonstrated to be safe and likely to provide greater symptomatic relief translated into a more pronounced decrease in natriuretic peptides [12].

We used an ADHF model to study the influence of the MRA spironolactone on renin and aldosterone. The aim of this study is to demonstrate the renin and aldosterone associations and changes before and after spironolactone introduction.

Methods

Study design

This study is based on analysed data from a previous prospective, interventional, clinical trial that we performed [12]. In that study we enrolled 100 consecutive patients who presented in a Portuguese tertiary hospital with ADHF, between February 2012 and February 2013. They were non-randomly assigned in a sequential 1 : 1 ratio to spironolactone plus standard ADHF therapy or standard ADHF therapy alone, 50 patients within each arm (i.e. patients were alternatively assigned to spironolactone arm or standard ADHF therapy arm in a sequential manner – the first patient to one arm and the next to the other arm. This sequence was repeated until we reach 100 patients, 50 patients within spironolactone group and 50 patients within control group). Patients were blinded to the allocation, and the clinicians were not blinded to the allocation. The recommended spironolactone dose was 100 mg/day, however the assistant physician could decrease the spironolactone dose to 50 mg/day after 48 h upon admission. After 72 h the study was open label. Furosemide dose and form of administration was performed according to the treating physician.

Patients were eligible for enrollment if they presented with decompensation of chronic HF with symptoms leading to hospitalization. All patients presented at the emergency department severely symptomatic in NYHA class IV. ADHF was diagnosed on the basis of the presence of history of chronic HF, at least one symptom (dyspnea, orthopnea, or edema), one sign (rales, peripheral edema, ascites, or pulmonary vascular congestion on chest radiography) and elevated natriuretic peptides. Exclusion criteria were: chronic use of MRAs, cardiac surgery within 60 days of enrollment, cardiac mechanical support, cardiac resynchronization-therapy within the last 60 days, comorbid conditions with an expected survival of less than 6 months, acute MI at time of hospitalization, hemodynamically significant uncorrected primary cardiac valvular disease, patients requiring intravenous vasodilators or inotropic agents, supine systolic arterial blood pressure < 90 mmHg, plasma creatinine (pCr) level >1.5 mg/dL, serum potassium level > 5.0 mmol/L, hemoglobin (HgB) level < 9 g/dL, and sepsis.

Institutional review board or ethics committee approval was obtained. All patients provided written informed consent to participate in the study.

Study assessments

Patient's clinical status including physical examination was prospectively recorded by the same assistant physician at day 1 and day 3.

Medications and respective dosages were prospectively recorded by the investigators according to the assistant physician prescriptions.

Blood and spot urine samples were collected in the first 24 hours (h) after admission (day 1) of the patient to the hospital. The first dose of spironolactone was only administered after the first sample was collected. Fifty patients had daily oral spironolactone according to the study protocol described above. The day 3 samples were collected between 72 and 96 h of hospitalization. All samples were collected in the morning with the patient in supine position, and first-morning spot urine was used. All patients had low-salt, low-calorie hospital diet. Extra fruit and vegetables administration was not allowed. An assessment of biomarkers (including pCr, plasma urea [pUr], electrolytes, N-terminal pro-brain natriuretic peptide [NTproBNP], high-sensitivity troponin T [hsTnT] and proteinuria) was performed at a central core laboratory at day 1 and day 3. Clinical assessment and routine analyses were performed daily during hospital stay. A transthoracic echocardiography was performed on all the patients within 72 h upon admission. Left ventricle ejection fraction (LVEF) was calculated according to biplane Simpson method.

Aldosterone was measured using radioimmunoassay (RIA) Coat-a-Count® (Siemens) and renin with RIA (DiaSource®).

Variable definitions

We defined high renin levels when values were above the 16.5 pg/mL cutoff, and high aldosterone levels when values were above the 100 ng/dL cutoff. The manufacturer suggested a cutoff of 16.5 pg/mL for renin and a cutoff of 160 ng/dL for aldosterone. We lowered aldosterone cutoff to 100 ng/dL to increase test sensitivity, although levels above 160 ng/dL are more specific, we might miss important information, since for example in the EVEREST trial only 33.2% of patients had aldosterone levels above 160 ng/dL [11], and increased mortality was also observed in lower aldosterone quartiles.

We studied aldosterone (ng/dL) and renin (pg/mL) regarding the following covariates: age; sex; diabetes mellitus (DM); ischemic HF; EF (%); atrial fibrillation (AF); systolic blood pressure (SBP); intravenous (IV) furosemide dose; proportion of patients with IV furosemide at day 3; proportion of patients on angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers (BB), and spironolactone; pCr (mg/dL), pUr (mg/dL), NTproBNP (pg/mL), hsTnT (ng/mL), sodium (mmol/L), potassium (mmol/L), uNa/K ratio, proteinuria (g/g), red-cell distribution width (RDW), HgB (g/dL), and length of stay.

Statistical analysis

Normally distributed continuous variables are expressed as mean ± standard deviation (SD), and skewed distributions are presented as median (inter-quartile range, IQR).

Because of the positively skewed distributions of aldosterone, renin, pCr, proteinuria, RDW, NTproBNP, hsTnT and uNa/K ratio, these variables were log transformed for analysis.

Categorical variables are expressed in proportions (%).

Comparison between groups was performed using parametric, non-parametric tests, or chi-square tests, as appropriate. Significant association was defined by a probability (p) value ≤ 0.05.

Table 1 – Population characteristics, laboratory results and spironolactone dose at admission day (day 1) and day 3.

Age (years)	76.0 ± 10.88		
Male sex (%)	39		
DM (%)	45		
Ischemic HF (%)	50		
EF < 40 (%)	32		
AF (%)	59		
RDW (%)	15.20 [14.40–16.0]		
Hemoglobin (g/dL)	12.43 ± 2.07		
Length of stay (days)	8.86 ± 3.36		
	Day 1	**Day 3**	***p* value**
Spironolactone (%)	50	50	1[b]
Spironolactone dose (mg)	94.50 ± 23.31	62.74 ± 24.33	**< 0.001**
ACEi/ARB (%)	44	61	0.069[b]
ACEi/ARB dose (mg)	4.79 ± 3.01	3.79 ± 2.63	**0.034**
Beta-blocker (%)	37	57	0.143[b]
Beta-blocker dose (mg)	4.06 ± 1.77	3.19 ± 1.54	**0.026**
Furosemide IV dose (mg)	81.08 ± 22.08	67.57 ± 25.54	**0.001**
Oral furosemide (%)	0	63	**< 0.001**[b]
Oral furosemide dose (mg)	0	74.60 ± 28.10	**< 0.001**
SBP (mmHg)	139.79 ± 25.86	121.97 ± 16.20	**< 0.001**
Sodium (mmol/L)	140.54 ± 4.38	140.68 ± 3.95	0.718
Potassium (mmol/L)	4.03 ± 0.51	4.04 ± 0.54	0.950
Plasma creatinine (mg/dL)	1.04 [0.89–1.31]	1.06 [0.85–1.40]	0.082[a]
Plasma urea (mg/dL)	55.21 ± 20.84	62.3 ± 25.47	**0.001**
Proteinuria (g/g)	0.289 [0.188–0.629]	0.299 [0.160–0.097]	**0.045**[a]
NTproBNP (pg/mL)	2 750 [1 672–6 032]	1 835 [902–3 837]	**< 0.001**[a]
uNa/K ratio	3.04 [1.52–5.76]	2.80 [1.50–4.78]	0.341[a]
Renin (pg/mL)	4.35 [2.30–10.78]	5.34 [3.14–16.30]	**0.011**[a]
Aldosterone (ng/dL)	35.0 [12.0–92.5]	67.0 [21.3–125.0]	**0.002**[a]
hsTnT (ng/mL)	0.033 [0.193–0.050]	0.030 [0.018–0.051]	**0.039**[a]

Continuous variables are presented as mean value ± standard deviation [SD], p value or median [inter-quartile range, IQR], p value.
Categorical variables are presented as absolute number (%), p value.
Note: Day 1 analysis was collected before spironolactone administration.
ACEi/ARB – angiotensin converting enzyme inhibitors/angiotensin receptor blockers; AF – atrial fibrillation; DM – diabetes mellitus; EF – left ventricular ejection fraction; HF – heart failure; hsTnT – high sensitivity troponin T; NTproBNP – N-terminal pro brain natriuretic peptide; RDW – red cell distribution width; SBP – systolic blood pressure; uNa/K – urinary sodium to potassium.
[a] Non-parametric paired sample test.
[b] Chi-square test.
Bold means p value < 0.05

Statistical analysis was performed using SPSS software (version 19, Chicago, IL, USA).

Results

Baseline characteristics, medications and lab results

Mean ± SD age of the 100 patients admitted due to ADHF was 76.0 ± 10.9 years. Thirty-nine patients were male; 50 patients had documented ischemic heart disease (IHD); 45 had DM; 59 had AF; 32 patients had EF < 40%.

Furosemide dose, SBP, proteinuria, NTproBNP, renin, aldosterone and hsTnT decreased from admission to day 3 (all, p < 0.05). The proportion of patients taking ACEi/ARB and BB did not differ between admission and day 3.

Patient characteristics, lab results at admission day and hospital length of stay are shown in Table 1.

Comparison between normal and high renin values at admission

A higher proportion of patients with renin levels > 16.5 pg/mL had AF (52.5% vs. 85%, $p = 0.008$). Log RDW, log renin, and hospital length of stay were higher in patients with renin levels above the cutoff (1.18 ± 0.03 vs. 1.21 ± 0.06, $p = 0.004$ and 8.36 ± 3.21 vs. 10.85 ± 3.25, $p = 0.006$, respectively) – Table 2. On the other hand, uNa/K ratio was lower in patients with higher renin levels (0.50 ± 0.38 vs. 0.22 ± 0.31, $p = 0.003$) (Table 2 and Fig. 1).

Comparison between normal and high aldosterone values at admission

Patients with lower aldosterone levels were more often male (45.5% vs. 17,4%, $p = 0.015$). Higher levels of serum potassium, log proteinuria, log RDW, log NTproBNP, log aldosterone, and plasma urea were observed in patients with aldosterone levels above the 100 ng/dL cutoff (all $p < 0.05$) (Table 2). Similarly to renin findings, a lower uNa/K ratio was observed in patients with higher aldosterone levels (0.49 ± 0.37 vs. 0.29 ± 0.37, $p = 0.026$) (Table 2 and Fig. 1).

Comparison between normal and high renin values at day 3

A higher proportion of patients with renin levels > 16.5 pg/mL was observed in subjects submitted to spironolac-

Table 2 – Comparison between normal and high renin and aldosterone values at admission.

	Renin < 16.5 (n = 80)	Renin ≥ 16.5 (n = 20)	*p* value	Aldosterone < 100 (n = 77)	Aldosterone ≥ 100 (n = 23)	*p* value
Age	75.99 ± 10.33	76.05 ± 13.13	0.982	74.91 ± 10.70	76.65 ± 10.88	0.066
Male sex – no. (%)	30 (37.5)	9 (45)	0.539	35 (45.5)	4 (17.4)	**0.015**
DM – no. (%)	38 (47.5)	7 (35)	0.315	34 (44.2)	11 (47.8)	0.756
EF < 40% – no. (%)	26 (32.5)	5 (25)	0.517	25 (32.5)	6 (26.1)	0.562
Ischemic HF – no. (%)	37 (46.3)	13 (65)	0.134	37 (48.1)	13 (58.5)	0.476
AF – no. (%)	42 (52.5)	17 (85)	**0.008**	44 (57.1)	15 (65.2)	0.490
SBP	140.93 ± 26.08	135.25 ± 25.11	0.383	140.84 ± 26.72	136.26 ± 22.94	0.459
Beta-blocker – no. (%)	31 (38.8)	5 (25)	0.252	27 (35.1)	9 (39.1)	0.722
ACEi/ARB – no. (%)	34 (42.5)	8 (40)	0.839	32 (41.6)	10 (43.5)	0.870
Sodium	140.75 ± 4.41	139.70 ± 4.26	0.340	140.84 ± 4.54	139.52 ± 3.69	0.205
Potassium	4.05 ± 0.50	3.98 ± 0.55	0.586	3.97 ± 0.47	4.24 ± 0.57	**0.023**
Log creatinine	0.02 ± 0.11	0.02 ± 0.14	0.888	0.02 ± 0.12	0.04 ± 0.11	0.495
Log proteinuria	–0.44 ± 0.40	–0.45 ± 0.47	0.962	–0.51 ± 0.39	–0.23 ± 0.42	**0.008**
Log RDW	1.18 ± 0.03	1.21 ± 0.06	**0.004**	1.18 ± 0.04	1.20 ± 0.04	**0.047**
Log NTproBNP	3.49 ± 0.45	3.41 ± 0.35	0.444	3.42 ± 0.41	3.67 ± 0.47	**0.014**
Log uNa/K ratio	0.50 ± 0.38	0.22 ± 0.31	**0.003**	0.49 ± 0.37	0.29 ± 0.37	**0.026**
Log aldosterone	1.53 ± 0.43	1.70 ± 0.49	0.135	1.39 ± 0.34	2.15 ± 0.12	**< 0.001**
Log renin	0.52 ± 0.33	1.46 ± 0.22	**< 0.001**	0.69 ± 0.48	0.78 ± 0.50	0.402
Log hsTnT	–1.47 ± 0.39	–1.47 ± 0.33	0.995	–1.47 ± 0.39	–1.47 ± 0.34	0.988
Urea	53.78 ± 19.68	60.95 ± 24.68	0.170	52.44 ± 20.52	64.48 ± 19.60	**0.014**
Hemoglobin	12.50 ± 1.98	12.16 ± 2.44	0.512	12.39 ± 2.06	12.59 ± 2.17	0.689
Log length of stay	0.89 ± 0.17	1.01 ± 0.15	**0.003**	0.91 ± 0.16	0.91 ± 0.19	0.958

ACEi/ARB – angiotensin converting enzyme inhibitors/angiotensin receptor blockers; AF – atrial fibrillation; DM – diabetes mellitus; EF – left ventricular ejection fraction; HF – heart failure; hsTnT – high sensitivity troponin T; NTproBNP – N-terminal pro brain natriuretic peptide; RDW – red cell distribution width; SBP – systolic blood pressure; uNa/K – urinary sodium to potassium.
Bold means *p* value < 0.05

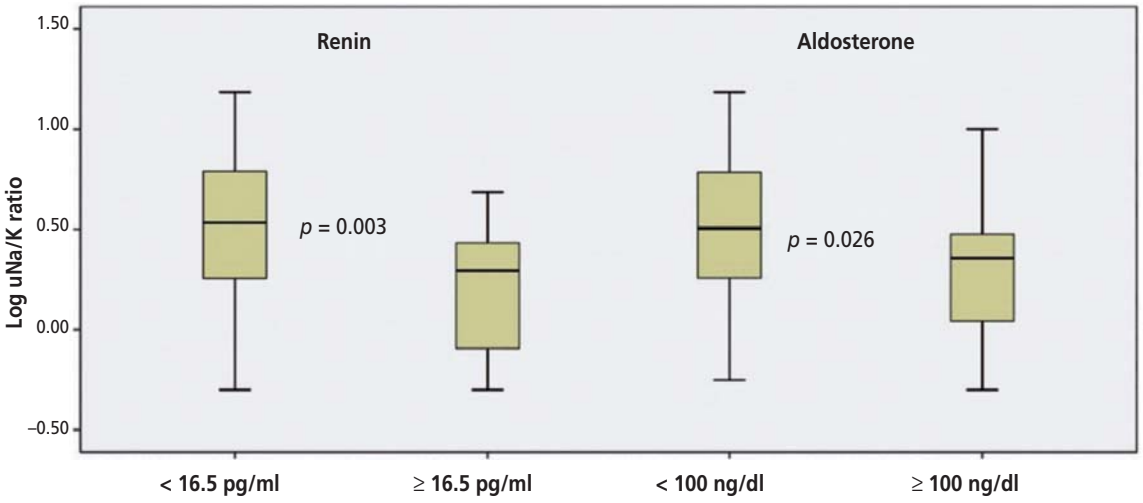

Fig. 1 – Comparison of urinary sodium to potassium ratio according to renin and aldosterone levels at admission.
Renin = log renin; aldosterone = log aldosterone; uNa/K = urinary sodium to potassium. Patients with higher renin and aldosterone levels at admission had lower urinary sodium to potassium ratios.

Table 3 – Comparison between normal and high renin and aldosterone values at day 3.

	Renin < 16.5 (n = 76)	Renin ≥ 16.5 (n = 24)	*p* value	Aldosterone < 100 (n = 66)	Aldosterone ≥ 100 (n = 34)	*p* value
Age	76.58 ± 9.61	74.17 ± 14.25	0.346	78.02 ± 9.28	72.09 ± 12.70	**0.009**
Male sex – no. (%)	28 (36.8)	11 (45.8)	0.431	25 (37.9)	14 (41.2)	0.749
DM – no. (%)	37 (48.7)	8 (33.3)	0.188	29 (43.9)	16 (47.1)	0.766
EF < 40% – no. (%)	22 (28.9)	9 (37.5)	0.430	18 (27.3)	13 (38.2)	0.262
Ischemic HF – no. (%)	36 (47.4)	14 (58.3)	0.241	30 (45.5)	20 (68.8)	0.205
AF – no. (%)	43 (56.6)	16 (66.7)	0.264	42 (63.6)	17 (50)	0.189
SBP	123.55 ± 16.73	116.96 ± 13.52	0.082	122.55 ± 15.76	120.85 ± 17.20	0.623
Beta-blocker – no. (%)	46 (60.5)	11 (45.8)	0.205	38 (57.6)	19 (55.9)	0.871
ACEi/ARB – no. (%)	48 (63.2)	13 (54.2)	0.431	41 (62.1)	20 (58.8)	0.749
IV furosemide – no. (%)	27 (35.5)	10 (41.7)	0.587	25 (37.9)	12 (35.4)	0.800
Spironolactone – no. (%)	34 (44.7)	16 (66.7)	**0.050**	28 (56)	22 (64.7)	**0.035**
Spironolactone dose	63.89 ± 24.96	60.29 ± 23.48	0.620	60.00 ± 23.31	66.30 ± 25.68	0.355
Sodium	141.11 ± 3.85	139.33 ± 4.05	0.055	141.12 ± 4.33	139.82 ± 2.96	0.121
Potassium	4.01 ± 0.56	4.14 ± 0.49	0.299	4.00 ± 0.50	4.10 ± 0.61	0.402
Log creatinine	0.03 ± 0.14	0.05 ± 0.16	0.675	0.02 ± 0.14	0.07 ± 0.14	0.058
Log proteinuria	–0.46 ± 0.38	–0.59 ± 0.31	0.132	–0.49 ± 0.35	–0.49 ± 0.41	0.955
Log RDW	1.18 ± 0.03	1.21 ± 0.06	**0.007**	1.19 ± 0.04	1.18 ± 0.04	0.658
Log NTproBNP	3.27 ± 0.50	3.29 ± 0.51	0.881	3.28 ± 0.49	3.24 ± 0.52	0.679
Log uNa/K ratio	0.42 ± 0.40	0.34 ± 0.37	0.378	0.44 ± 0.38	0.31 ± 0.40	0.120
Log aldosterone	1.64 ± 0.45	1.94 ± 0.51	**0.007**	1.47 ± 0.38	2.21 ± 0.19	**< 0.001**
Log renin	0.59 ± 0.34	1.52 ± 0.25	**< 0.001**	0.69 ± 0.45	1.07 ± 0.54	**< 0.001**
Log hsTnT	–1.51 ± 0.33	–1.52 ± 0.42	0.838	–1.51 ± 0.33	–1.51 ± 0.39	0.942
Urea	60.86 ± 25.20	66.92 ± 26.32	0.312	60.70 ± 26.83	65.44 ± 22.64	0.380
Hemoglobin	12.52 ± 2.11	12.16 ± 1.96	0.465	12.38 ± 2.11	12.53 ± 2.03	0.728
Log length of stay	0.89 ± 0.17	0.99 ± 0.13	**0.008**	0.89 ± 0.18	0.96 ± 0.13	**0.043**

ACEi/ARB – angiotensin converting enzyme inhibitors/angiotensin receptor blockers; AF – atrial fibrillation; DM – diabetes mellitus; EF – left ventricular ejection fraction; HF – heart failure; hsTnT – high sensitivity troponin T; NTproBNP – N-terminal pro brain natriuretic peptide; RDW – red cell distribution width; SBP – systolic blood pressure; uNa/K – urinary sodium to potassium.
Bold means *p* value < 0.05

tone treatment (44.7% vs. 66.7%, $p = 0.050$). Log renin and aldosterone levels were higher in patients with renin levels above the cutoff point (both, $p < 0.05$). Contrary to the findings at admission, uNa/K ratio did not differ between groups (Table 3).

Comparison between normal and high aldosterone values at day 3

Patients with lower aldosterone levels were older (78.02 ± 9.28 vs. 72.09 ± 12.70, $p = 0.009$). Similarly to the findings described for renin at day 3, a higher proportion of patients with aldosterone levels above 100 ng/dL was observed in subjects submitted to spironolactone treatment (56% vs. 64.7%, $p = 0.035$). Log renin and aldosterone were also higher in this group of patients (both, $p < 0.05$), and uNa/K ratio did not differ between groups (Table 3).

Spironolactone influence in renin and aldosterone levels

After three days of spironolactone administration the proportion of patients with renin and aldosterone levels above the cutoff had a significant increase (from 24% to 32%, $p = 0.003$, and from 16% to 44%, $p < 0.001$, respectively) (Table 4 and Fig. 2).

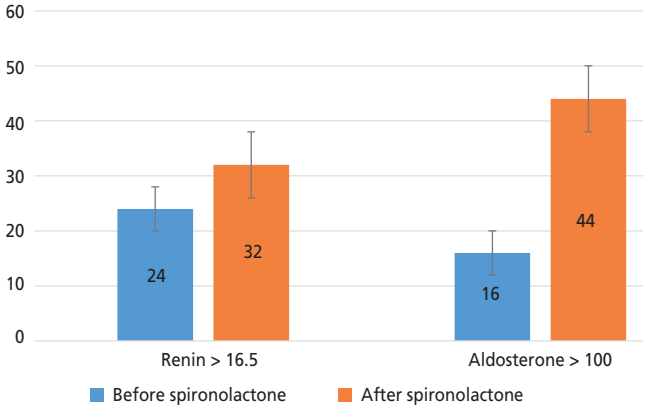

Fig. 2 – Comparison of renin and aldosterone levels before and after spironolactone treatment. Results are presented in percentage (%) of total. Renin is expressed in pg/mL and aldosterone in ng/dL. The proportion of patients with increased levels of renin and aldosterone is significantly higher in patients submitted to spironolactone treatment. The proportion of patients with renin levels above 16.5 pg/mL increases from 24% before spironolactone administration on to 32% after spironolactone administration, *p* value = 0.003. The proportion of patients with aldosterone levels above 100 ng/dL increases from 16% before spironolactone administration to 44% after spironolactone administration, *p* value < 0.001.

Discussion

The main results of our pilot study suggest that in patients submitted to spironolactone treatment the levels of renin and aldosterone increase. Higher levels of renin and aldosterone were not observed with the use of drugs other than spironolactone (p.e. ACEi/ARBs, BB or loop diuretics).

At admission higher renin and aldosterone levels were associated with lower urinary Na/K ratio levels, these findings were not reproduced when patients were submitted to MRA. In addition, higher levels of renin and aldosterone at admission were associated with higher RDW. Higher renin was associated with longer length of stay, and higher aldosterone with higher NTproBNP.

Baseline aldosterone blood levels measured in chronic HF patients with LVEF < 40% during the first days after admission for AHF were significantly correlated with higher mortality and re-hospitalization for HF [11]. Aldosterone levels were found to increase substantially during hospitalization and remain elevated after discharge, despite excellent background RAAS inhibitor therapy. The association between higher aldosterone levels and worse outcome remains positive, although weaker, when considering discharge aldosterone measurement [11]. Based on these findings the authors of this trial suggest that further neurohormonal modulation may be required in order to improve outcomes. In our interventional trial [12] we demonstrated that additional MR blockade during the acute decompensation is not associated with electrolyte disorders or kidney dysfunction and probably portends greater congestion relief, translated into a steep natriuretic peptide decrease. In this secondary analysis we demonstrated that renin and aldosterone levels are increased by spironolactone and not by ACEi/ARB, beta blockers or diuretics, as shown by the significant higher proportion of patients with levels of renin and aldosterone above the cutoff within spironolactone group, and not in patients under ACEi/ARB, beta blockers or diuretics. Furthermore, blood pressure and electrolytes are not likely to influence the observed variation in these hormones. These findings are concordant with previous reports in which the physiological elevation in plasma renin activity (PRA) and aldosterone were demonstrated in response to eplerenone and spironolactone treatment [13–17]. A previous study reported an increase in both PRA and aldosterone after eplerenone treatment for 10 days in dogs [18]. Similarly, in humans, eplerenone resulted in elevations in serum aldosterone and PRA when administered for 8 weeks in addition to a fixed-dose of an ACEi in mildly hypertensive patients [16]. A larger study, reported an increase in serum aldosterone with eplerenone

Table 4 – Comparison of renin and aldosterone levels at admission and day 3 within spironolactone and control groups.

	Day 1			Day 3		
	Spironolactone	Control	p value	Spironolactone	Control	*p* value
Renin > 16.5 – no. (%)	12 (24)	8 (16)	0.317	16 (32)	8 (16)	**0.050**
Aldosterone > 100 – no. (%)	8 (16)	15 (30)	0.096	22 (44)	12 (24)	**0.035**

Note: Day 1 analysis were performed before spironolactone administration
Bold means *p* value < 0.05

treatment that was dose-responsive [19]. Furthermore, in patients with resistant hypertension an inverse correlation between blood pressure and serum aldosterone was demonstrated after treatment with eplerenone for 12 weeks [20], and another study demonstrated a time-dependent aldosterone increased in response to eplerenone [13]. The most robust explanation to this finding results from the demonstration that the main physiologic regulators of aldosterone synthase are angiotensin II and potassium [21]. Thus, increases in serum potassium and angiotensin II resulting from a decreased sodium and increased potassium reabsorption in the proximal tubules, would lead to an up-regulation of aldosterone synthase, consequently increasing aldosterone levels. Another potential explanation for the increase in aldosterone is a direct regulation of aldosterone synthase by mineralocorticoid receptor [13]. Our results can be very interesting and innovative, since MRA can probably improve outcomes in ADHF and also can increase renin and aldosterone levels, therefore higher levels of aldosterone may not held place for prognostic purposes when full MRA is provided. However, further studies are warranted to fully understand the mechanisms underlying the rise in aldosterone following MRA and the prognostic significance of MR blockade in the decompensated HF setting.

The median aldosterone levels at admission appear higher than the median values found in previous reports of patients with acute and chronic heart failure after the widespread use of ACEi/ARB [4–7,11]. This finding may be explained by the lower proportion (only 44%) of the patients on baseline ACEi/ARB, potentially leading to higher levels of renin and aldosterone[7,22], similar to the levels found before the widespread use of the RAAS inhibitors [6,23].

In the present study, higher levels of renin and aldosterone at admission were associated with higher RDW and lower urinary Na/K ratio levels. Additionally, higher aldosterone levels alone were associated with higher NT-proBNP and higher levels of renin alone were associated with longer length of stay. Despite these side findings do not compose the bulk of our study, we think they deserve a brief discussion.

Higher levels of renin and aldosterone at admission were associated with higher RDW. RDW is a percentual measure of the variability in the size of circulating erythrocytes [24]. Disorders related to ineffective erythropoiesis or increased destruction cause greater heterogeneity in size and a higher RDW [25]. In patients with ADHF higher RDW has been associated with slower diuretic response [26] and increased long-term mortality [27]. The relationship between elevated hormone levels and poor outcome can reflect the possibility that hormonal activation is not only serving as a marker for the severity of the disease, but is also contributing to progression of HF [5].

Higher aldosterone levels were associated with higher NTproBNP. To the best of our knowledge this is the first study to demonstrate a significant association between increased aldosterone levels and increased natriuretic peptides. However, previous studies demonstrated that aldosterone receptor antagonism with spironolactone induces a more noticeable decreases in plasma BNP levels than placebo or no spironolactone [12,28], suggesting that aldosterone may have an important role in the process of left ventricular remodeling [28].

As described above, increased neurohormonal activation is associated is worse outcome [11]. Our study was underpowered to detect major events, but length of stay could serve as a potential indirect severity measure. However length of stay may be affected by co-morbidities other than HF and in-hospital complications. Despite the association of higher levels of renin at admission and longer length of stay may appear to be an attractive result, the lack of correspondence in aldosterone and the bias inherent to length of stay, make this result less appealing and with dubious external validity.

Activation of the RAAS causes reabsorption of Na^+ and the excretion of K^+ in various epithelia such as the distal nephron [29]. Higher renin and aldosterone levels at admission were also associated with lower urinary Na/K ratio levels, these findings were not reproduced when patients were submitted to MRA. These observations are consistent with the RAAS effects on distal nephron, i.e. higher levels of renin and aldosterone lead to higher Na^+ reabsorption and K^+ excretion, decreasing uNa/K ratio. On the other hand, in the group of patients submitted to spironolactone treatment, uNa/K ratio increased probably reflecting the MRA effect. These dynamic changes suggest that uNa/K ratio can serve as a potential biomarker for MRA [13].

Our study has several limitations that should be noticed. First, it was a single-centre of a small sample size study. Second, no randomization or concealed allocation was performed, therefore we cannot exclude a selection bias potentially affecting the external validity of our results, particularly on outcome results such as length of stay, however we included internal control variables like renin, aldosterone and NTproBNP that are less likely to be affected by bias and appear to be consistent with previous reports. Third, this study was performed post-hoc, therefore it is subject to the potential biases inherent to analyses of observational data. Fourth, baseline blood samples were collected in the first 24 h after admission and before spironolactone administration, but most patients had already received diuretics and/or vasodilators, as a consequence renin and aldosterone admission levels may not reflect the real decompensation values. Fifth, high aldosterone cutoff was lowered to 100 ng/dL to increase test sensitivity, despite losing specificity we were able to detect a higher proportion of patients with aldosterone increments. Finally, our inclusion criteria by restricting the enrolment of patients with hyperkalemia, impaired renal function, and severe valvular disease may be responsible for the good treatment response of our population and therefore limit the external validity of our conclusions.

Conclusion

Higher levels of aldosterone are associated with higher mortality risk in ADHF patients. High-dose spironolactone added to standard ADHF therapy induces an additional increase in renin and aldosterone levels. Whether higher levels of renin and aldosterone due to the reactive response to full MRA still have prognostic value requires further investigation.

Conflict of interest
The authors have no conflicts of interest to disclose.

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Ethical statement
The research was done according to local ethical standards.

Informed consent
The patients agreed to participate in the study and signed an informed consent.

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