Hyperkalemia During Spironolactone Use in Patients with Decompensated Heart Failure

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Summary

Background: The incidence of hyperkalemia related to spironolactone use is low in stable heart failure; however, it has not been studied during decompensation.

Objective: To evaluate the influence of spironolactone on serum potassium in decompensated heart failure (HF).

Methods: In a cohort study, patients that had been hospitalized due to decompensated HF, with left ventricular ejection fraction (LVEF) < 0.45 and serum potassium between 3.5 and 5.5 mEq/l were selected. The patients were divided according to spironolactone use (Group S) or no use (Group C). The outcome was potassium increase (> 6.0 mEq/l) and the use of calcium polystyrene. A multivariate analysis through logistic regression was carried out and values of p < 0.05 were considered significant.

Results: A total of 186 patients (group S: 56; group C: 130) were studied; LVEF of 0.25, aged 55.5 years and 65.2% of them males. The incidence of hyperkalemia was 10.7% in group S and 5.4% in group C (p = 0.862). The multivariate analysis showed that serum urea > 60.5 mg/dl during the hospitalization presents a relative risk of 9.6 (95%CI 8.03 – 11.20; p = 0.005) for the occurrence of hyperkalemia.

Conclusion: The incidence of hyperkalemia was two-fold higher with spironolactone use, but it was not statistically significant. The increase in urea levels was associated to the hyperkalemia. Randomized studies are necessary to clarify this issue. (Arq Bras Cardiol 2008;91(3):177-182)

Key words: Heart failure, congestive; hyperkalemia; spirolactone; kidney / drug effects

Introduction

Due to the increased number of spironolactone prescriptions for heart failure (HF) verified after the RALES[1] study demonstrated a reduction of 30% in mortality, there was an increase in the hospitalizations due to hyperkalemia[2,3].

In the present study, the renal function worsening was more prevalent in the group treated with spironolactone, despite the low incidence of hyperkalemia (2%)[3]. Although it is expected an increase in the incidence of hyperkalemia with the current treatment of HF due to the use of angiotensin-converting enzyme inhibitor (ACEI) and spironolactone, its actual frequency is not well known and can vary according to the disease severity and presentation. The literature has shown that patients treated with ACEI and spironolactone have a higher tendency to develop hyperkalemia[3-7].

It is possible, however, that hyperkalemia occurs at a higher frequency in the decompensated phase, related to the worsening in the renal function due to low cardiac output or the effect of medications.

At the decompensated phase, the patients that benefit from the neurohormonal blockade are the same who present an increased risk of renal function worsening and hyperkalemia.

The ACEI, the angiotensin II receptor blockers (ARB) and spironolactone decrease the elimination of potassium in the renal tubules and increase the probability of hyperkalemia development at the decompensated phase[8,9]. The betablockers contribute to the increase of serum potassium through the inhibition of the sympathetic nervous system, due to the inhibition of the production and release of plasma renin[10,11].

Oral vasodilators are important in the treatment of decompensation, but are many times difficult to be maintained. When there is hyperkalemia, ACEI, ARB and spironolactone

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are withdrawn until serum potassium is normalized, interrupting the patient's compensation process.

The importance of spironolactone in the treatment of HF has been well established. In contrast, there are no data evaluating its role during cardiac decompensation; when added to other medications, it can promote hyperkalemia and influence the withdrawal of vasodilators.

The present study aims at evaluating the influence of spironolactone and its association with the increase in serum potassium in patients with decompensated heart failure.

Methods

A cohort study was carried out, which included patients with a diagnosis of decompensated heart failure from the Emergency Room of Instituto do Coracao (The Heart Institute) – INCOR-HCFMUSP, admitted at Hospital Auxiliar de Cotoxo (HCFMUSP) between February 22, 2005 and November 22, 2006.

The routine approach for the decompensated HF includes the definition of Stevenson's clinical hemodynamic profile, identification of comorbidities and complementary examinations (serum measurements of urea, creatinine, sodium, potassium, complete blood count, brain natriuretic peptide (BNP) and electrocardiogram). As a rule, for patients with a cold and wet profile or cold and dry, dobutamine was chosen to improve cardiac output, which is the medication of choice at our service.

In cases of chronic use of betablockers, milrinone or levosimendan were chosen. To control pulmonary and peripheral congestion, furosemide IV was preferentially used, associated or not with hydrochlorothiazide. The use of IV vasodilators was reserved for patients with systolic arterial pressure > 90 mmHg at the moment of admission; however, they were rarely used by the assistants due to the need for invasive monitoring. The oral vasodilators available at our Service and used for the patients' compensation were: captopril or enalapril maleate, losartan potassium and hydralazine plus isosorbide, isolated or associated, at the highest tolerated dose. The use of digoxin was allowed according to the decision made by the patient's physician.

The following criteria were considered for the patients' inclusion: age older than 18 years; left ventricle ejection fraction (LVEF) ≤ 0.45 by the Teicholz or Simpson method and serum potassium between 3.5 and 5.5 mEq/l.

The exclusion criteria were: serum creatinine ≥ 2.5 mg/dl or urea = 100 mg/dl.

To define the etiology of the ventricular dysfunction, the following criteria were used:

- Ischemic: area inactive at the electrocardiogram, history of myocardial revascularization or coronary obstruction demonstrated by coronary angiography.
- Chagasic: reagent serology by ELISA or indirect immunofluorescence.
- Hypertensive: history of systemic arterial hypertension, ruling out other causes for myocardiopathy.
- Others.

As routinely done in our service, the measurements of urea, creatinine, sodium and potassium were carried out three times a week, until the control of the low cardiac output, pulmonary and peripheral congestion had been attained; however, they were monitored up to hospital discharge according to the clinical evolution. With the data at the moment of hospitalization, the glomerular filtration rate (GFR) was calculated through the Crockoft-Gault method.

The patients that met the inclusion criteria were divided in two groups, according to the use and maintenance (group S) or not (group C) of spironolactone during the hospital stay, maintained by the Emergency Room (ER) physicians before the transference to the Hospital Auxiliar de Cotoxó. The researchers did not interfere with the patients' prescription at any time during the follow-up.

In group C, 34.5% of the patients had previously used spironolactone, which was withdrawn at the moment of hospital admission by the ER physicians. All patients that were treated at our Service and used spironolactone (group S) had previously used the medication. Therefore, spironolactone was withdrawn in approximately 21.6% of the patients that joined the study at the moment they arrived at the ER.

During the hospital stay, the substitution or maintenance of medications that could elevate serum potassium in the presence of hyperkalemia was carried out following the medical criterion, as well as the choice of treatment with calcium polystyrene (Sorcal®). At our Service, the hypokalemic diet is part of the treatment to correct the hyperkalemia, being prescribed by the doctor when necessary.

The primary outcome was the incidence of potassium increase ($K^+ > 6.0$ mEq/l) and use of calcium polystyrene.

Statistical analysis

The categorical variables were expressed as proportion and percentages, and the continuous variables, as means and standard deviations.

The statistical analysis was carried out using the *t* test, Fisher's test and Chi-square test. For the comparisons, differences with $p < 0.05$ were considered statistically significant.

The Receiver Operator Characteristics (ROC) curve defined the urea level cutoff with higher accuracy for the occurrence of hyperkalemia. The multivariate analysis was carried out by the logistic regression method[12], using the program SPSS 13.0® (Chicago-IL, USA).

Results

A total of 186 patients were selected and their characteristics are shown in Table 1.

The main characteristics of the patients in the two groups, with or without spironolactone, are shown in Table 2. Of the 186 patients, 56 were in group S and 130 in group C. The two groups differed regarding sex (p=0.01) and it is worth mentioning there was a tendency in the prevalence of diabetes mellitus (p=0.09) and the use of nitrate and hydralazine (p=0.09) in group C.

The mean hospital stay duration was 23.65 days. During

Table 1 – Patients' characteristics

Total	n = 186
Age – years (SD)	**55.5 (14)**
Sex – %	
Male	65.2
Ethnicity – %	
Caucasian	51.8
Brazilian mulatto	26.7
Black	20.6
Etiology – %	
Chagasic	32.1
Ischemic	26.9
Hypertensive	10.3
Others	30.7
LVEF % (SD)	**25.2 (4.4)**
Comorbidities – %	
Arterial hypertension	58.2
Diabetes mellitus	20.3
Hemoglobin < 12 g/dl	28.4
GFR < 50 ml/min	14.8
Laboratory assessment mg/dl	
Initial creatinine	1.25
Final creatinine	1.18
Initial urea	56.1
Final urea	57.5
Medications – %	
Diuretics	88.7
ACEI	80.9
Betablockers	79.4
Vasoactive drugs	63.2
Digitalis	53.5
Nitrate + hydralazine	29.6
Statins	25.0
ASA	24.3
Amiodarone	14.9
ARB	14.2

Table 2 – Characteristics of the groups

	Group S (n = 56)	Group C (n = 130)	*p*
Age – years (DP)	**53 (17)**	**58 (12)**	**0.12**
Sex – %			
Male	75.8	54.6	0.01
Ethnicity – %			
Caucasian	54.5	49.1	0.59
Brazilian Mulatto	24.3	29.1	0.56
Black	21.2	20.0	0.82
Etiology – %			
Chagasic	33.3	30.9	0.67
Ischemic	30.3	23.6	0.35
Hypertensive	6.1	14.5	0.07
Others	30.3	31.0	0.96
LVEF % (SD)	**25.4 (1.4)**	**25.0 (7.4)**	**0.82**
Comorbidities – %			
Arterial hypertension	54.6	61.8	0.31
Diabetes mellitus	15.2	25.4	0.09
Hemoglobin < 12g/dl	33.3	23.6	0.15
GFR < 50 ml/min	15.2	14.5	0.95
Laboratory assessment – mg/dl			
Initial creatinine	1.28	1.21	0.75
Final creatinine	1.18	1.18	0.98
Initial urea	54.8	57.3	0.48
Final urea	56.4	58.6	0.96
Medications – %			
Diuretics	87,5	90,0	0,61
ACEI	85,7	76,1	0,14
Betablockers	80,3	78,5	0,77
Vasoactive drugs	69,7	56,7	0,77
Digitalis	57,1	50,0	0,37
Nitrate + hydralazine	23,2	36,1	0,08
Statins	23,2	26,9	0,59
ASA	23,2	25,4	0,75
Amiodarone	16,1	13,8	0,69
ARB	10,7	17,7	0,23

the study, nine deaths occurred, 3 in group S and 6 in group C, without statistical difference between the groups.

The incidence of hyperkalemia in the general population studied was 7.69%, being more prevalent in group S (10.7% *vs*. 5.4%), p = 0.862. The evolution of the serum potassium is shown in figure 1. The incidence of hyperkalemia and calcium polystyrene (Table 3) was two-fold higher in the group that maintained spironolactone in the prescription during the hospitalization.

For the multivariate analysis, we selected 88 patients whose data were complete and of those, 12 presented hyperkalemia. The variables analyzed were: age, ethnicity, etiology of the heart failure, LVEF, diabetes mellitus, initial and final urea, initial and final creatinine, use of vasoactive drug, previous use of spironolactone and use of spironolactone during hospitalization. The final urea and creatinine values were the highest corresponding values during hospitalization.

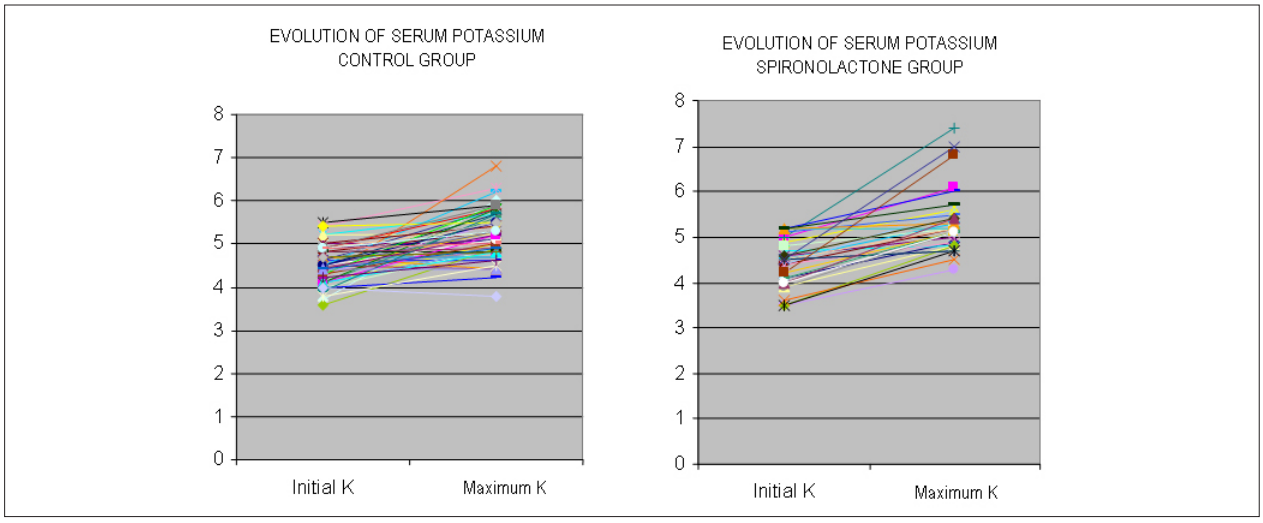

Figure 1 - Evolution of serum potassium in groups C and S.

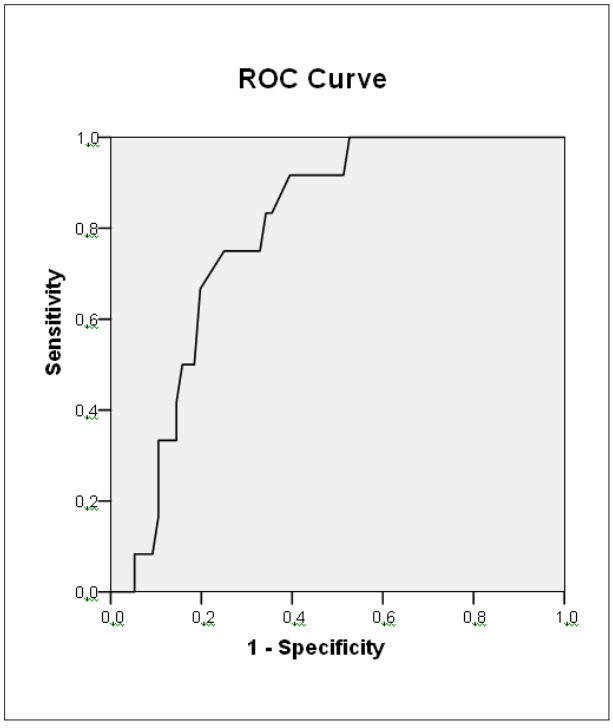

Figure 2 - ROC curve for final urea and the occurrence of hyperkalemia, urea value = 60.5 mg/dl, area under the curve = 0.792.

Table 3 – **Main outcome according to spironolactone use**

	Group S (n = 56)	Group C (n = 130)	p
K^+ > 6 mEq/l and use of Calcium polystyrene (%)	6 (10.7)	7 (5.4)	0.862

Through the logistic regression, the only variable with statistical significance was final urea (p=0.028), that is, the patients that presented renal function worsening during hospitalization had a higher probability of developing serum potassium increase.

The ROC curve (Fig. 2) shows that the urea value with the highest sensitivity and specificity for the development of hyperkalemia was 60.5 mg/dl.

Thus, the patients that presented urea values above this level during hospitalization had a RR of 9.6 (95% CI: 8.03 – 11.20) for potassium increase > 6 mEq/dl, when compared to patients with urea values lower than this level, with p = 0.005.

Patients that used spironolactone before hospitalization had a tendency towards the development of hyperkalemia, with a RR of 9.07 (95%CI: 6.55 – 11.59) and p = 0.087.

Discussion

Our main finding was the higher incidence of hyperkalemia in the group that used spironolactone during hospitalization (10.7%), although without statistical difference. Moreover, it is worth mentioning the higher frequency of hyperkalemia (7.69%) in decompensated patients, in relation to the data of stable patients studied in the RALES.

At the decompensated phase of HF, the renal function worsening is a frequent occurrence[13], possibly due to the presence of low cardiac output, use of medications and presence of comorbidities[14,15]. Svensson et al[4] identified the renal function, diabetes mellitus and the functional class of heart failure (NYHA) as independent risk factors for the development of hyperkalemia. As shown in Table 1, all these risk factors were prevalent and might have contributed to the increase in serum levels of potassium in the present study.

In the present study, hyperkalemia is defined as serum potassium > 6.0 mEq/l. In the studied population of patients

with decompensated HF, we found 13 (7.69%) cases with hyperkalemia. When we compared the patients that used spironolactone during the hospitalization with the ones that did not, we observed that the hyperkalemia and the use of calcium polystyrene were twice more frequent in the group that received spironolactone (10.7% *vs*. 5.4%).

We observed a higher frequency of prescription of hydralazine and nitrate in group C (Table 2). In general, the substitution of the ACEI by hydralazine and nitrate is carried out when hyperkalemia occurs, or with the worsening of renal function. As we treat more advanced-stage patients at our Service, probably the need for hydralazine and nitrate is higher.

Tamirisa et al[16], when analyzing the use of spironolactone in patients with HF, found a prevalence of hyperkalemia that was very similar to the one found in the present study. A total of 926 patients were studied and 67 (7.2%) discontinued the use of spironolactone due to hyperkalemia or renal function worsening. These patients were older and had DM and most used betablockers, similarly to our patients.

Cruz et al[17] carried out a study with 100 patients with decompensated HF using ACEI, associated or not to spironolactone. They considered as hyperkalemia serum potassium levels > 5.5 mEq/l. The patients were divided in two groups, according to the use or not of spironolactone. The incidence of hyperkalemia was 32% in the spironolactone group and 2% in the control group, with an OR of 24.2 (95% CI: 3.1 to 191.6). The HF functional class, elevated basal serum creatinine and the presence of DM were identified as predictors of risk for the development of hyperkalemia, which is in agreement with the present study.

We found an association between urea and the occurrence of hyperkalemia during the hospitalization period. The occurrence of the renal function worsening is not available; however, it can be inferred that a higher level of urea during the evolution can be considered as such. Therefore, our positive finding was the predictive value of the renal function worsening for the occurrence of hyperkalemia.

The beneficial effects of spironolactone in HF have been largely demonstrated; however, they occur at mid- and long-term. Our findings do not prove, but indicate, that spironolactone is related to hyperkalemia in the decompensation phase of HF.

Differently from the stable phase, the priority in the decompensation is the symptom improvement, which is the result of the hemodynamic improvement. Vasodilators such as ACEI and ARB have this effect. Acute hemodynamic improvement with spironolactone use has not been demonstrated. At our Service, which treats patients at more advanced stages of the disease, the hospitalization period for HF compensation is approximately 23 days. If there is hyperkalemia, essential medications such vasodilators are withdrawn and spironolactone is a less important medication in this period.

We believe that the spironolactone withdrawal for some days would probably not change the intra-hospital mortality and the preventive procedure of withdrawing this medication during hospitalization seems to be adequate. When spironolactone is maintained in the prescription, there must be a strict control of the renal function and serum potassium and it should be withdrawn before the onset of hyperkalemia. This procedure can prevent the withdrawal of medications that are important for the patient's compensation in the acute phase.

When the patient is released from the hospital at our Service, an early post-release return is scheduled at the referring outpatient clinic. Thus, spironolactone can be reintroduced at the outpatient clinic level, after routine tests have been ordered and always being prescribed after patient stabilization.

Study Limitations

We obtained a negative result probably caused by the lack of study power due to the sample size. We limited patient follow-up to the period of hospitalization and a longer follow-up period would have brought us more information regarding the importance of maintaining or not spironolactone during the hospitalization period for compensation. We believe that a randomized study could provide more information, subsequently.

Conclusions

The incidence of hyperkalemia was two-fold higher with spironolactone; however, it was not statistically significant. The increase in urea levels during the evolution was associated to hyperkalemia. We believe that the spironolactone withdrawal for some days would probably not change the intra-hospital mortality and the preventive procedure of withdrawing this medication during hospitalization seems to be reasonable. This strategy, however, must be assessed in large, randomized prospective studies before being applied to the routine clinical practice.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any graduation program.

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