

# Aldosterone receptor antagonists induce favorable cardiac remodeling in diastolic heart failure patients

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## ABSTRACT

**Background.** Serum levels of aldosterone in heart failure are increased up to 20 times compared to normal subjects. After an acute myocardial infarction, aldosterone increases progressively as well as interstitial fibrosis and collagen synthesis from cardiac fibroblasts, forming a patchy heterogeneous interstitial collagen matrix that affects ventricular function. Even if angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARA) can reduce aldosterone levels early during treatment, they increase again after a 12 week treatment. The aim of this study was to evaluate the changes in structure and function of the left ventricle in symptomatic (NYHA I-III) diastolic heart failure patients receiving an aldosterone receptor antagonist. **Methods.** Twenty-eight subjects with diastolic heart failure, on BB, ACEI and/or ARA were randomized to receive spironolactone (group A) on a mean dose of 37.5 mg once a day (n = 14, age 63.7 ± 21.6 years and body mass index, BMI 27.5 ± 9.4), or not (group B, n = 14, Age 64.8 ± 11.9, BMI 26.9 ± 4.7). All patients were followed-up for a mean of 13.79 ± 0.99 months. **Results.** Group A showed a 42.8% ischemic origin of heart failure, while in group B was 55% (p = 0.2). No other co-morbidities were significantly different among both groups. Mean percentage of changes by echocardiogram was as follows: Interventricular septum (IVS) -12.2 ± 11% vs. 1.3 ± 15.2 (p = 0.03), pulmonary systolic artery pressure (PSAP) was 0.99 ± 3.8% vs. 10.5 ± 9.1, p = 0.05). Other parameters did not show statistically significant differences. **Conclusion.** Aldosterone receptor antagonists reduce or avoid increasing of PSAP and inducing a favorable remodeling of the left ventricle, especially in the IVS in diastolic heart failure patients.

**Antagonistas de receptores de aldosterona inducen remodelación cardiaca favorable en pacientes con insuficiencia cardiaca diastólica**

## RESUMEN

**Antecedentes.** En pacientes con insuficiencia cardiaca existen aumentos de aldosterona hasta 20 veces mayores que en sujetos control. Después de un infarto miocárdico la aldosterona aumenta progresivamente, así como la fibrosis intersticial y la síntesis de colágena por fibroblastos cardiacos, provocando parches intersticiales heterogéneos en la matriz de colágena que afecta la función ventricular. El tratamiento inicial con inhibidores de enzima convertidora de angiotensina (IECA) y/o antagonistas de receptores de angiotensina II (ARA) puede reducir estos niveles; sin embargo, aumentan nuevamente después de 12 semanas de tratamiento. El propósito de este estudio fue evaluar los cambios estructurales y funcionales en el ventrículo izquierdo en pacientes con insuficiencia diastólica tratados con ARA angiotensina (NYHA I-III). **Métodos.** Veintiocho pacientes con insuficiencia cardiaca diastólica en tratamiento con BB, IECA y/o ARA se aleatorizaron a recibir una dosis media de 37.5 mg una vez al día de espirolactona (grupo A) (n = 14, edad 63.7 ± 21.6 años e índice masa corporal IMC 27.5 ± 9.4), o no (grupo B, n = 14, edad 64.8 ± 11.9, IMC 26.9 ± 4.7). Todos los pacientes fueron seguidos por 13.79 ± 0.99 meses. **Resultados.** De los pacientes del grupo A, 42.8% y el 55 del grupo B (p = 0.2), tenían cardiopatía isquémica. No se encontraron diferencias significativas en otras comorbilidades. El porcentaje promedio de cambios en el ecocardiograma se observó en septum interventricular (SIV) -12.2 ± 11% vs. 1.3 ± 15.3% (p = 0.02), y la presión sistólica de la arteria pulmonar (PSAP, 0.99 ± 3.8% vs. 10.5 ± 9.1, p = 0.05, para los

grupos A y B, respectivamente). Los otros parámetros no mostraron diferencias estadísticamente significativas. **Conclusión.** El tratamiento con antagonistas de receptores de aldosterona disminuye o limita aumentos de PSAP e induce una remodelación favorable del ventrículo izquierdo, especialmente del SIV en pacientes con insuficiencia cardíaca diastólica.

**Key words.** Aldosterone antagonist receptors. Diastolic heart failure.

**Palabras clave.** Antagonistas de receptores de aldosterona. Insuficiencia cardíaca diastólica.

## INTRODUCTION

Myocardial hypertrophy is a common consequence of several co-morbidities, arterial hypertension and obesity are frequently involved through several mechanisms.<sup>1</sup> The pathophysiology involves left ventricular remodeling in combination with several degrees of myocardial fibrosis that are finally associated to left ventricular dysfunction and a symptomatic heart failure state.<sup>2</sup>

Myocardial hypertrophy can be present in asymptomatic patients, including those with abnormal systolic or diastolic function; however, particularly in subjects with diastolic dysfunction, the early presence of effort symptoms like fatigue, and dyspnea are the rule.<sup>3</sup>

Experimental studies relate aldosterone in the genesis of myocardial fibrosis, hypertrophy and myocardial dysfunction.<sup>4,5</sup> Hypothetic positions have considered that aldosterone antagonism could improve the outcome of systolic and diastolic heart failure because of its antifibrotic effects.<sup>6</sup> In addition, clinical and experimental studies have associated aldosterone with abnormal vascular function<sup>7</sup> and with diastolic dysfunction frequently accompanied by impairment of left systolic dysfunction despite a normal ejection fraction.<sup>8</sup> Even if angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor antagonists (ARA) medication can reduce aldosterone levels early during treatment, these increase again after a 12 week treatment.<sup>9</sup>

We designed this study in order to examine the effects of aldosterone antagonism with spironolactone on myocardial structural and functional changes in heart failure patients with PRESERVED systolic function.

## METHODS

Patients with diastolic heart failure attending to Heart Failure Clinic were considered eligible, independently of the etiology, if they had history of arterial hypertension (and/or were on antihypertensive treat-

ment), but no history of angina, myocardial infarction or myocardial revascularization (PTCA and / or aorto-coronary by pass grafting) during the 3 months previous to recruitment and they referred fatigue, dyspnea on exercise and/or orthopnea. All patients were followed-up for a mean of  $13.79 \pm 0.99$  months.

All patients had a TRANSTHORACIC echocardiogram study and an exercise treadmill test, at the beginning and at the end of the follow-up. Patients were consecutively randomized, independently of heart failure treatment, to receive spironolactone 25-50 mg once a day (Group A, n = 14) or to not receive spironolactone (Group B, n = 14). During the follow-up, clinical and laboratory evaluation were made bimonthly, with special emphasis in serum electrolytes (particularly potassium).

The echocardiogram was made by a Cardiologist blinded to the clinical evaluation and treatment received. Wide angle, two dimensional echoes were videotaped on a 3/4 inches videocassette recorder with patients in left lateral decubitus position, using HP Sonos ultrasound 5000 imaging system. Apical four chambers and apical two chambers were the views selected for left ventricular long axis at the end diastole and at the end systole to calculate ejection fraction, and stroke volume. The echocardiograms were made according to the recommendations of the American Society of Echocardiography.

Ventricular dysfunction was diagnosed according recommendations of Heart Failure Society of America<sup>10</sup> and I-Preserved trial<sup>11</sup>. Diastolic dysfunction was considered when the ejection fraction was over 45%, and shortening fraction = 28%, without severe segmental dyskinesia of the left ventricle, left atrial enlargement, or increased thickness of posterior wall, interventricular septum, and left ventricular mass index.

For comparisons between the groups we used Fisher's Exact Test for categorical and Mann-Whitney U Test for continuous variables. A p value < 0.05 was considered statistically significant. All analyses were performed using a commercially avail-

**Table 1.** Baseline clinical characteristics of the studied patients.

| Variable                              | With spironolactone (n=14) | Without spironolactone (n=14) |
|---------------------------------------|----------------------------|-------------------------------|
| Age (years)                           | 63.71 ± 21.61              | 64.79 ± 11.89                 |
| Male (%)                              | 28.6                       | 71.4                          |
| Weight (kg)                           | 64.51 ± 18.36              | 71.31 ± 14.08                 |
| Blood pressure                        | 112 ± 12                   | 114 ± 8                       |
| Heart rate                            | 86 ± 4                     | 82 ± 6                        |
| BMI (kg/m <sup>2</sup> )              | 27.54 ± 9.37               | 26.87 ± 4.67                  |
| NYHA I (%)                            | 42.9                       | 75.0                          |
| II                                    | 0.0                        | 16.7                          |
| III                                   | 57.1                       | 8.3                           |
| Beta Blockers (%)                     | 79.5                       | 79.7                          |
| ACE inhibitors (%)                    | 38.5                       | 29                            |
| Angiotensin receptors Antagonists (%) | 69.2                       | 73.9                          |
| Diuretics (thiazide) (%)              | 76.9                       | 62.3                          |
| Diuretics (loop) (%)                  | 5.1                        | 13                            |
| Nitrates (%)                          | 38.2                       | 47.8                          |
| Anticoagulants (%)                    | 7.7                        | 1.5                           |
| Aspirin (%)                           | 26                         | 4.5                           |
| Calcium Channel Blockers (%)          | 5.1                        | 13                            |
| Hypertension (%)                      | 85.7                       | 92.9                          |
| Diabetes (%)                          | 28.6                       | 64.3                          |
| Renal disease (%)                     | 14.3                       | 21.4                          |
| Ischemic heart disease (%)            | 42.9                       | 57.1                          |
| Dislipidemia (%)                      | 100                        | 76.9                          |
| Dysthyroidism (%)                     | 0                          | 21.4                          |
| LVSF (%)                              | 29.67 ± 7.99               | 29.38 ± 12.72                 |
| LVEF (%)                              | 48.79 ± 4.65               | 51.57 ± 11.71                 |
| LVEDd (mm)                            | 51.00 ± 6.78               | 47.43 ± 5.87                  |
| LVESd (mm)                            | 38.14 ± 7.15               | 31.62 ± 5.58                  |
| IVS (mm)                              | 13.79 ± 0.99               | 13.21 ± 2.42                  |
| PW (mm)                               | 12.50 ± 1.26               | 12.00 ± 1.75                  |
| LAD (mm)                              | 44.43 ± 3.82               | 42.92 ± 6.13                  |
| IVRTI (mm Hg)                         | 118.33 ± 7.64              | 116.11 ± 17.28                |
| PAP                                   | 57.00 ± 6.78               | 43.20 ± 11.19                 |

Values are expressed as mean ± standard deviation or percentage when correspond.

BMI: Body mass index. NYHA: New York Heart Association functional class. LVSF: Left ventricular shorting fraction. LVEF: Left ventricular ejection fraction. LVEDd: Left ventricular end diastolic diameter. LVESd: Left ventricular end systolic diameter. IVS: Interventricular septum. PW: Posterior wall. LAD: Left atrium diameter. IVRTI: Isovolumetric relaxation time index. PAP: Pulmonary artery pressure.

able package (SPSS for Windows, version 10.0, 1999 Chicago: SPSS Inc.).

## RESULTS

Twenty-eight patients were included, 20 (71.42%) females and 8 males (28.57%). Characteristics of patients are presented in Table 1. Group A showed a

42.8% ischemic origin of heart failure, while in group B was 57.1% ( $p = 0.2$ ). There were more women on spironolactone treatment compared with those without it, with no statistical significance. Co-morbidities and concomitant treatment were similar in both groups. In group A more patients were in functional class III compared with group B. No other characteristics, co-morbidities or treatment were significantly different among both groups. Blood pressure and results on exercise treadmill test, were similar in both groups at the beginning and at the end of the follow-up. Mean serum levels of potassium, creatinine, and the rest of laboratory test did not show significant differences at the beginning and at the end of follow-up ( $13.79 \pm 0.99$  months).

Regarding the echocardiographic parameters, the only significant change was the reduction in the interventricular septum dimension observed in patients receiving spironolactone compared with the control where an increased thickness was found ( $-12.2 \pm 11\%$  vs.  $1.3 \pm 15.3\%$ ,  $p = 0.02$ ), as well as pulmonary arterial pressure ( $0.99 \pm 3.8\%$  vs.  $10.5 \pm 9.1$   $p = 0.05$ ) although this change was not statistically significant. No case required reduction of the drug dosage because of adverse events.

## DISCUSSION

Aldosterone has been involved in vascular response to acetylcholine infusion, free oxygen radicals, TNF- $\alpha$  and other cytokines production; however, the aldosterone receptors antagonists were able to block these effects.<sup>12</sup> It has also been demonstrated an increase of pro-collagen pro peptide type I levels in blood samples from the coronary sinus, which is a fibrosis marker in hypertensive heart disease.<sup>13</sup> An improved endothelial function in brachial artery flow at 4 weeks was demonstrated in CHF patients on conventional medical therapy. This benefit was still present after 8 weeks of treatment, presumably due to reversal of aldosterone impairment of endothelial nitric oxide activity.<sup>14</sup> Duprez, et al.<sup>15</sup> also demonstrated the presence of a good correlation between left ventricular mass index and aldosterone serum levels as well as an inverse correlation with this and the compliance of one proximal artery.

Heart failure patients on treatment with ACEI or AT1 antagonist receptors, showed a regression to initial aldosterone serum levels after 12 weeks,<sup>9</sup> indicating an aldosterone escape after this time. In addition, after acute myocardial infarction, an early remodeling process starts, and it could be reduced using earlier aldosterone receptors antagonists.<sup>16</sup>

Diastolic dysfunction is frequently accompanied by impaired left ventricular systolic function despite a normal ejection fraction.<sup>7,8</sup> Monttram, et al.<sup>17</sup> demonstrated that in an ambulatory hypertensive population with left ventricular preserved systolic function, myocardial function was improved after 6 months of aldosterone blocked with spironolactone, independently of the antihypertensive effect, as was demonstrated by no significant changes in ambulatory blood pressure.

In our cases, the most important structural change was observed in the diastolic interventricular septum thickness, while in other cases was most important in the left ventricular posterior wall.<sup>17</sup> It is thus possible that in the presence of an adverse stimulus, myocardial wall responds with a heterogeneous hypertrophy distribution, perhaps depending on the coronary blood flow reserve, related to the angiographic coronary representation, as has been suggested in several types of systolic overload or in post infarction myocardial patients,<sup>18</sup> and it could explain the differential beneficial effect in different segments.

Spironolactone antagonism has been associated with improvement of some indirect parameters of diastolic function as left atrial area<sup>19</sup> and decrease in pulmonary venous A wave reversal velocity, consistent with reduction in left ventricular stiffness and /or end diastolic pressure.<sup>17</sup> In this way, it is possible to infer that a lack of increase in pulmonary blood pressure, as observed in our group on spironolactone, could be related to an easier filling of the left ventricle as an indicator of improvement in diastolic function, even if such a change was not statistically significant, and unrelated to blood pressure levels.

Although there is not enough evidence to use specific agents to treat patients with diastolic heart failure,<sup>19</sup> there is hypothetical support that optimization of antihypertensive treatment reduces the progression of myocardial hypertrophy and diastolic dysfunction. It has been suggested that blockade of type 1 angiotensin receptors reduces the left ventricular stiffness in hypertensive patients, and it was associated to myocardial fibrosis regression.<sup>20</sup> In the same way, aldosterone blockade with spironolactone, an agent with more antifibrotic power and less antihypertensive effect, improved myocardial function in symptomatic patients with diastolic dysfunction, but not necessarily left ventricular hypertrophy.<sup>17</sup>

In our study, patients with diastolic heart failure were all treated with ACE inhibitors/ARA and Beta blockers, with a good antihypertensive treatment response in rest and in exercise in both groups.

They all showed a significant difference regarding the reduction of interventricular septum thickness that increased in the control group, suggesting that the most complete blockade of renin-angiotensin-aldosterone system improves myocardial structure and function in heart failure patients treated with spironolactone. These findings are in concordance with improvement in arterial stiffness with spironolactone in experimental studies with angiotensin receptor blockade.<sup>5</sup>

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