Материал поступил в редакцию: 23-04-2015
Материал принят к печати: 30-07-2015
УДК: 616.12-008.331.3:616.24-007.272:616.127-007.51-085.254.3-079.7-073.432.19

The effect of spironolactone on left ventricular hypertrophy in patients with arterial hypertension and chronic obstructive pulmonary disease

Pavel Kravchun, Valentina Delevskaya
Kharkov National Medical University, Kharkov, Ukraine

The objective: To investigate the effect of spironolactone on echocardiograhic parameters of the heart in patients with arterial hypertension combined with chronic obstructive pulmonary disease.

Methods: A total of 80 patients, 41 patients, who received the basic therapy of arterial hypertension and chronic obstructive pulmonary disease (controls), and 39 patients, who additionally received spironolactone in a dose of 50 mg for 3 months, were included in the study. All the patients underwent spirometry and echocardiography before and after the treatment.

Results: The obtained results showed, that addition of spironolactone to the basic treatment of patients with arterial hypertension and chronic obstructive pulmonary disease led to the reduction of the left ventricular myocardial wall thickness, left ventricular myocardial mass and its dimensions ($P < 0.05$), the increase of its contractility along with decrease of pulmonary hypertension ($P < 0.05$).

Conclusion: Epy use of spironolactone in the basic treatment of patients with arterial hypertension and chronic obstructive pulmonary disease results in positive changes of structural and functional characteristics of the left ventricle of myocardium, prevents further adverse remodeling of the cardiovascular system and the progression of cardiac dysfunction.

Keywords: spironolactone - left ventricular dimensions of myocardium - chronic obstructive pulmonary disease - arterial hypertension.

J Clin Med Kaz 2015; 3(37):43-46

Corresponding author: Valentyna Yu. Dielievska, Department of Internal medicine № 2, Clinical immunology and allergology, Kharkiv National Medical University, Ukraine. Tel.: + 380688888201. E-mail: valentinka_1987@ukr.net

АРТЕРИАЛДЫ ГИПЕРТЕНЗИЯМЕН ЖӘНЕ ӨКПЕНІҢ СОЗЫЛМАЛЫ ОБСТРУКТИВТІ АУРУЫМЕН АУЫРАТЫН НАУҚАСТАРДА СПИРОЛАКТОННЫҢ ЖҮРЕКТІҢ СОЛ ЖАҚ ҚАРЫНШАСЫНЫҢ ҰЛҒАЮЫНА ӘСЕРІ

Кравчун П.Г., Делевская В.Ю.
Харьков ұлттық медициналық университеті, Харьков қ., Украина

Зерттеудің мақсаты: Артериалды гипертензиямен және өкпенің созылмалы обструктивті ауруымен ауыратын науқастардың жүрек бұлшықетінің эхокардиографиялық көрсеткіштеріне спиролактонның әсерін зерттеу.

Әдістері: Барлығы 80 науқас тексерілді, оның 41 – артериалды гипертензия мен өкпенің созылмалы обструктивті ауруының негізгі емін алды (бақылау), және 39 науқас –қосымша 50 мг мөлшерінде 3 ай спиролактон қабылдады. Барлық науқастарға емнің алдында және емнен кейін спирометрия мен эхокардиография жүргізілді.

Нәтижесі: Артериалды гипертензиямен және өкпенің созылмалы обструктивті ауруымен ауыратын науқастардың ем жоспарына спиролактонды қосу жүректің сол жақ қарыншасының қабырғасы қалыңдығының төмендеуіне, сол жақ қарыншаның салмағы мен көлемінің кішіреюіне ($P < 0,05$), оның жиырылу қызметінің жақсаруына және өкпелік гипертензияның төмендеуіне ($P < 0,05$) алып келді.

Қорытынды: Артериалды гипертензиямен және өкпенің созылмалы обструктивті ауруымен ауыратын науқастардың емінде спиролактонды қолдану жүректін сол жақ қарыншасының құрылымдық және қызметтік мінездемесінің жақсаруына әкеліп, жүрек-қантамыр жүйесінің әрі қарай патологиялық ремодельденуіне, жүрек жетіспеушілігінің үдеуіне жол бермейді.

Маңызды сөздер: спиролактон – сол жақ қарыншаның бұлшықетінің көлемі – өкпенің созылмалы обструктивті ауруы - артериалды гипертензия.

ВЛИЯНИЕ СПИРОНОЛАКТОНА НА ГИПЕРТРОФИЮ МИОКАРДА ЛЕВОГО ЖЕЛУДОЧКА У БОЛЬНЫХ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ И ХРОНИЧЕСКИМ ОБСТРУКТИВНЫМ ЗАБОЛЕВАНИЕМ ЛЕГКИХ

Кравчун П.Г., Делевская В.Ю.
Харьковский национальный медицинский университет, г. Харьков, Украина

Цель: изучить влияние спиронолактона на эхокардиографические показатели миокарда левого желудочка у больных артериальной гипертензией в сочетании с хроническим обструктивным заболеванием легких.

Методы: обследовано 80 пациентов, из них 41 – получали базисную терапию артериальной гипертензии и хронического обструктивного заболевания легких (контроль), и 39 – дополнительно принимали спиронолактон в дозе 50 мг в течение 3 месяцев. Всем пациентам проведена спирометрия и эхокардиография до и после лечения.

Результаты. Добавление спиронолактона в основной план лечения больных артериальной гипертензией и хроническим обструктивным заболеванием легких привело к снижению толщины стенки миокарда левого желудочка, массы левого желудочка и его размеров ($P < 0,05$), повышению его сократительной способности, а также снижению выраженности легочной гипертензии ($P < 0,05$).

Выводы. Применение спиронолактона у больных артериальной гипертензией и хроническим обструктивным заболеванием легких способствует положительным изменениям в структурных и функциональных характеристиках миокарда левого желудочка, предотвращает дальнейшее патологическое ремоделирование сердечно-сосудистой системы и прогрессирование сердечной недостаточности.

Ключевые слова: спиронолактон - размеры миокарда левого желудочка - хроническое обструктивное заболевание легких - артериальная гипертензия.

Introduction

It has been known, that the presence of left ventricular hypertrophy (LVH) is an adverse factor of higher risk of cardiovascular events, including mortality and morbidity from heart failure, atrial fibrillation and sudden death [1]. Indeed, LVH is one of the most distinct manifestation of hypertensive target organ damage. Arterial hypertension (AH) and chronic obstructive pulmonary disease (COPD) frequently coexist in the same patient and progressively lead to chronic heart failure, posing important diagnostic and therapeutic challenges. Prognosis of patients with concurrent heart failure and COPD has not been comprehensively addressed. Nevertheless patients presenting with both conditions seem to have an ominous course. In an increasing number of studies, COPD has been found to adversely impact on prognosis of heart failure patients, being an independent predictor of mortality and hospitalization [2, 3].

Nowadays aldosterone blockers are prescribed to the individuals, who develop heart failure, and variety of studies have shown their ability to reduce the risk of both hospitalization and death from cardiovascular diseases [4, 5]. Therefore we aimed to study the effectiveness of spironolactone treatment in reduction of LVH in the patients with AH in combination with COPD and its influence on the main echocardiographic cardiac dimensions.

Materials and methods

80 patients with II stage of AH and COPD of 2 - 3 degree of bronchial obstruction according to the spirometric criteria (GOLD 2 - 3) were recruited in the study. This study was approved by the Commission on Bioethics.

The exclusion criteria were oncological diseases, tuberculosis, respiratory tract infections, strokes and myocardial infarctions in anamnesis.

The diagnosis of COPD was established on the basis of typical symptoms, modified Medical Research Council (mMRC) dyspnea scale, COPD Assessment Tool (CAT) and spirometry according to GOLD 2014 guidelines (GOLD 2014) [6]. Diagnosis of AH was established according to ESH/ESC criteria that consider as hypertension the values of blood pressure over 140/90 mmHg [7].

The first group consisted of 41 patients with AH and GOLD 2-3 (24 male and 17 female, mean age 64.31 ± 1.74) treated with standard therapy of COPD and AH with using β2-agonists, corticosteroids, anticholinergics, ACE inhibitors and diuretics. The second group consisted of 39 patients (23 male and 16 female, mean age 61.42 ± 2.5) with AH and GOLD 2 - 3, who in addition to standard therapy were treated with spironolactone in a dose of 50 mg per day for 3 months. All the patients underwent general clinical and biochemical investigations, spirometry and echocardiography. Ultrasound investigation of the heart included measurement of left atrium diameter (LA), left ventricle end systolic diameter (LVESD), left ventricle end diastolic diameter (LVEDD), left ventricle end systolic volume (LVESV), left ventricle end diastolic volume (LVEDV), right atrial and ventricular diameters (RA and RV), left ventricular posterior wall thickness (PWT), interventricular septum thickness (IVS), pulmonary artery pressure (PAP), left ventricle ejection fraction (LVEF). Left ventricular mass (LVM), left ventricular mass index (LVMI) and relative wall thickness (RWT) were calculated using formulas [8]:

LVM (g) = 1.04 * [(LVEDD + IVS + PWT)3] – [LVEDD]3 – 13.6

LVMI (g/m2) = LVM / Body surface area

RWT (mm) = PWT + IVS / LVEDD

LVH was defined as a LVMI of 125 g/m2 or more in men and women in accordance with Devereux et al., 1977.

Results

The patients, who received basic therapy of heart failure (the first group), were further divided into two subgroups depending on the degree of the bronchial obstruction: 1A subgroup comprised 20 patients with AH and GOLD 2; 1B subgroup – 21 patients with AH and GOLD 3. The analysis of parameters of cardiohemodynamics in patients with AH and GOLD 2 after the basic treatment for 3 months showed the decrease of LVEDD from 47.8 + 0.34 mm to 46.5 + 0.41 mm ($P < 0.05$), LVM from 299.6 + 7.12 g to 277.06 + 6.27 g and LVMI from 168.23 + 6.24 g/m2 to 155.97 + 5.74 g/m2 ($P < 0.05$) (Table 1).

Table 1 The changes of the structural and geometric parameters of the heart in patients with AH combined with GOLD 2, (M ± m)

Parameter	Basic therapy (n=20)		Basic therapy + spironolactone (n=19)	
	before treatment	after treatment	before treatment	after treatment
LA, mm	40.0+0.27	39.1+0.34	40.0+0.32	37.7+0.20*
LVEDD, mm	47.8+0.34	46.5+0.41*	46.6+0.41	43.7+0.38*
LVESD, mm	33.2+0.30	32.4+0.32	32.3+0.28	30.4+0.26*
IVS, mm	12.7+0.28	12.4+0.27	12.5+0.25	11.5+0.21*
LV PWT, mm	13.7+0.27	13.4+0.25	13.4+0.22	12.6+0.17*
LVEDV, ml	123+2.1	117.90+3.27	123.4+2.7	107.0+1.81*
LVESV, ml	49.0+1.12	47.15+1.24	49.1+1.43	43+1.17*
LVEF,%	57.40+0.34	56.9+0.52	57.74+0.46	58.21+0.53*
LVM, g	299.69+7.12	277.06+6.27*	279.90+6.21	232.62+5.26*
LVMI, g/m2	168.23+6.24	155.97+5.74*	154.14+5.43	127.48+4.12*
RWT	0.56+0.1	0.56+0.1	0.56+0.1	0.54+0.1*
PAP, mm. Hg.	17.75+0.61	17.35+0.57	18.42+0.65	16.74+0.51*
RA, mm	37.9+0.21	37.1+0.24*	37.9+0.27	36.8+0.24*
RV, mm	25.7+0.20	25.2+0.18*	26.4+0.23	24.7+0.16*
Note: * – P < 0.05				

RA in patients with AH and GOLD 2 decreased from 37.9 ± 0.21 mm to 37.1 mm ± 0.24 and the size of the RV – from 25.7 ± 0.2 mm to 25.2 mm ± 0.18 (P < 0.05).

In the patients with AH and GOLD 3 after the basic treatment the echocardiographic parameters of the left ventricle (LV) of myocardium were not changed (Table 2). There was only a tendency of LVM decrease – from 331.68 ± 8.44 g to 315.97 ± 8.16 g (P > 0.05). Whereas diameter of RA decreased on 6.8% and diameter of RV – on 6.3% as compared to the data before the treatment (P < 0.05).

Table 2 Changes of the structural and geometrical parameters of the heart in patients with arterial hypertension combined with GOLD 3, (M ± m)

Parameter	Basic therapy (n=21)		Basic therapy + spironolactone(n=20)	
	before treatment	after treatment	before treatment	after treatment
LA, mm	41.5+0.16	41.1+0.13	43.4+0.23	41.5+0.21*
LVEDD, mm	50.4+0.25	49.8+0.22	50.4+0.27	47.4+0.23*
LVESD, mm	34.7+0.21	34.4+0.17	35.1+0.25	33.2+0.18*
IVS, mm	12.6+0.23	12.4+0.21	12.8+0.27	12.0+0.25*
LV PWT, mm	13.6+0.24	13.4+0.20	13.8+0.31	13.0+0.27*
LVEDV, ml	148.62+2.43	144.86+2.15	150.45+3.21	130.1+2.64*
LVESV, ml	58.56+1.48	58.1+1.34	59.6+1.03	54.2+0.83*
LVEF, %	54.29+0.27	54.60+0.31	55.85+0.64	56.40+0.57*
LVM, g	331.68+8.44	315.97+8.16	334.07+8.76	281.39+7.23*
LVMI, g/m2	192.05+7.20	182.51+8.35	188.71+7.35	158.69+6.51*
RWT	0.54+0.1	0.53+0.1	0.55+0.1	0.54+0.1
PAP, mm. Hg.	21.38+0.67	21.19+0.54	24.7+0.61	22.8+0.53*
RA, mm	40.8+0.30	38.0+0.27*	40.8+0.41	39.4+0.37*
RV, mm	28.3+0.24	26.5+0.22*	28.8+0.30	27.4+0.24*
Note: * – P < 0.05				

The next phase of the research was to study the echocardiographic parameters of the heart in the patients with AH and COPD after the treatment with spironolactone.

This group of the patients was also subdivided into two groups depending on the degree of the bronchial obstruction: 2A subgroup comprised 20 patients with AH and GOLD 2; 2B subgroup – 19 patients with AH and GOLD 3.

Thus, in patients with AH and GOLD 2 additional treatment with spironolactone reduced left heart dimensions. Thus, LA decreased on 5.75%, LVESD and LVEDD – on 5.8% and 6.2% respectively, LVESV and LVEDV – on 12.2% and 13% respectively, LVM – on 16.8%, LVMI – on 17.2%, PWT and IVS – on 5.9% and 8.0% respectively, RWT – on 3% (P < 0.05) (Table.1). The distinct dynamics of the right heart parameters was also observed. Thus, RA decreased on 3%, RV – on 6.4% and PAP – on 9.15% (P < 0.05).

Comparing with the group of the basic therapy patients with AH and GOLD 2 in spironolactone group showed LA decrease on 3.5% (P < 0.05), which is very important since dilatation of LA has been recognized as an unfavorable factor for cardiovascular prognosis [9] and reduction of LA in obstructive lung diseases presents difficult problem. We also observed decrease of LVESD and LVEDD – on 6.1% and 6%, LVESV and LVEDV – on 8.8% and 9.3%, PWT and IVS – on 6.0% and 7.2%, RWT – on 3.5%, LVM – on 16%, LVMI – on 18.2% (P < 0.05). Regarding initial normal values of LVEF it was nevertheless increased on 3.5% (P < 0.05), that along with statistically significant decrease of LVEDV indicates an improvement of LV function. Additional treatment with spironolactone also led to PAP decrease on 3.5% (P < 0.05).

In the same manner we assessed echocardiographic changes of the myocardium in patients with AH and GOLD 3, who received spironolactone treatment. In comparison with data before treatment patients of spironolactone group presented decrease of LA on 4.3%, LVESD and LVEDD – on 5.4% and 5.9%, LVESV and LVEDV – on 9% and 13.5%, LVM – on 15.7% , LVMI – on 15.9%, PWT and IVS – on 5.7% and 6.2%, RWT – on 1.8% (P < 0.05) (Table 2). We also observed the decrease of RA on 3.4%, RV – on 4.8% and PAP – on 7.6% (P < 0.05).

Compared with those who received only basic therapy patients with AH and GOLD 3 after spironolactone treatment, showed a statistically significant decrease of LVESD and LVEDD on 3.4% and 4.8% respectively, LVESV and LVEDV – on 6.7% and 10.1% (P < 0.05). It is important, that patients with AH and GOLD 3, as well as patients with GOLD 2 after spironolactone treatment demonstrated decrease of one of the most unfavorable factors of cardiovascular risk – LVH. Thus, LVM decreased on 11% and LVMI – on 13.05% (P < 0.05), while LVEF increased on 3.2% (P < 0.05).

Discussion

Obtained results show, that the basic therapy of chronic heart failure in the patients with AH and COPD reduces the enlargement of the right part of the heart and in patients with moderate degree of bronchial obstruction leads to the slight decrease of LVH.

Whereas additional prescription of spironolactone to the basic treatment of patients with AH and GOLD 2 - 3 led to the reduction of walls thickness, weight and size of the LV myocardium (P < 0.05) along with increase of its contractility (P < 0.05), that might be pathogenetically explained by the reduction of myocardial fibrosis. The results suggest that aldosterone antagonist spironolactone promotes reverse LV remodeling, that is very important, since there is strong evidence that progressive LV remodeling is directly related to the further deterioration of its work and progression of heart failure regardless of the neurohormonal status of the patient [10].

It is well known, that compensatory LVH is an established risk factor for atrial fibrillation, diastolic and systolic heart failure and sudden death. So decrease of LVH in AH and COPD using aldosterone antagonist might have significant positive effect on cardivascular prognosis and agrees with the data of other researches of its cardioprotective role [4].

Moreover, use of spironolactone within 3 months along with basic therapy in patients with AH and GOLD 2 resulted in reduced right heart dimensions and pulmonary hypertension. The ability of spironolactone to reduce pulmonary hypertension was also mentioned by Maron B. A. and colleagues (2012) in experiments on rats [11].

Conclusion

Our findings indicate, that addition of spironolactone to the basic treatment of heart failure in the patients with AH and COPD leads to positive structural, functional and hemodynamic changes, prevents further adverse remodeling of the cardiovascular system and the progression of cardiac dysfunction. Spironolactone provides decrease of pulmonary hypertension, LV hypertrophy and reappearance of normal LV geometry.

References

1. Katholi R. E., Couri D. M. Left ventricular hypertrophy: major risk factor in patients with hypertension: update and practical clinical applications, Int. *J. Hypertens*, 2011. – Article ID 495349, 10 p. http://dx.doi.org/10.4061/2011/495349.
2. Rutten F. H. Diagnosis and management of heart failure in COPD, Eur. Respir. Monogr, 2013, No. 59, pp. 50-63.
3. Rusinaru D., Saaidi I., Godard S. et al. Impact of chronic obstructive pulmonary disease on long-term outcome of patients hospitalized for heart failure, Am. *J. Cardiol*, 2008, No. 101, pp. 353-8.
4. Pitt B., Zannad F., Kemme W. J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure, *N. Engl. J*., 1999, No. 341, pp. 709-717.
5. Kurrelmeyer K. M., Ashton Y., Xu J. et al. Effects of spironolactone treatment in elderly women with heart failure and preserved left ventricular ejection fraction, *J. Card. Fail.*, 2014, No. 20, pp. 560-8.
6. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014, http://www.goldcopd.org.
7. Mancia G., Fagard R., Narkiewicz K., et al. Task Force Members. ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), *J. Hypertens,* 2013, No. 31, pp. 1281-357.
8. Devereux R. B., Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method, *Circulation*, 1977, No. 55, pp. 613.
9. Tsang T. S, Abhayaratna W. P., Barnes M. E., et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter?, J. Am. Coll. Cardiol, 2006, No. 47, pp. 1018-23.
10. Mann D. L. Left ventricular size and shape: determinants of mechanical signal transduction pathways, *Heart Fail Rev*, 2005, No. 10, pp. 95-100.
11. Maron B. A., Zhang Y. Y., White K., et al. Aldosterone inactivates the endothelin-B receptor via a cysteinyl thiol redox switch to decrease pulmonary endothelial nitric oxide levels and modulate pulmonary arterialhypertension, *Circulation*, 2012, No. 126, pp. 963-74.