Role of Aldosterone Antagonists in the Current Management of Heart Failure

Yabluchansky, Nykola

Chronic heart failure (HF) is one of the most important syndromes in cardiology. Their main causes are: ischemic heart disease, high blood pressure, myocarditis, vavular heart diseases, cardiomyopathies and other pathological conditions. Although its modern management with angiotensin converter enzyme inhibitors (ACEI), beta blockers (BB), digoxin and diuretics improved the quality and duration of the life of the patients, less than half of them survive longer than 5 years. For this reason, it is very important to develop new therapeutic strategies, one of which is the management with aldosterone antagonists (AA). The objective of my presentation is to determine the role of AAs in the management of HF.

Aldosterone and heart failure

HF is defined as a clinical syndrome, characterized by the functional impairment of the left ventricle (LV) to fulfill a proper perfusion, according to the needs of the organism, which manifests by symptoms of hypoperfusion and congestion. This definition is far from being complete. LV functional impairment causes important disorders of other organs and systems, mostly in their regulation. So, in advanced stages of HF, these disorders are more significant –regarding the evolution of the syndrome- than LV functional impairment. As a clear example of this, it is worth mentioning that all the drugs mentioned in the previous paragraph, act by optimizing regulation. Even digoxin, that does not seem to fit this mechanism, in low doses has a systemic regulating effect, instead of a local inotropic one.

Aldosterone holds a significant place in HF pathophysiology. This hormone integrates the renin-angiotensin-aldosterone system (RAAS), that activates in renal hypoperfusion conditions. The greater the degree of this hypoperfusion, the greater the activation of the RAAS. This RAAS stimulation causes a deterioration of the regulatory system, thus reflecting in a greater decrease of contractile cardiac function. Thus, the “vicious circle” not only closes, but it turns at an increasing speed.

The final products of the RAAS are angiotensin I and aldosterone. Angiotensin activates the sympathetic nervous system, and stimulates the release of neurohormones; aldosterone stimulates other important biologic substances. As a result of these pathological processes, the following

occur: vasoconstriction, increase of blood pressure and of HR, and appearance of arrhythmias that endanger the life of the patient. Aldosterone is synthesized not only in the suprarenal cortex, but also in other tissues: myocardium, blood vessels, brain…Aldosterone receptors are located at the same sites. The main functions of this hormone are: water and sodium retention, induction of protein synthesis, regulation of renal excretion function, and potassium secretion. An increase in the levels of aldosterone –both for activation of synthesis, and for slowing its elimination- activates pathological mechanisms for HF. Inhibiting the RAAS just with ACEI does not restore normal plasmatic levels of aldosterone, suggesting a double mechanism of increase of this hormone. An increase of aldosterone worsens circulatory hemodynamic parameters (increasing postload and HR, etc.), thus resulting in cardiac remodeling and a greater progression of HF.

Nevertheless, the effects of aldosterone are not exclusively hemodynamic. According to the newest data, aldosterone plays a very significant role in inflammation, which is related to myocardial fibrosis, of blood vessels and other tissues. All this is the structural basis for HF. Aldosterone activates pro-inflammatory mediators: cyclooxygenase-2, macrophage-stimulating chemotaxic protein-1 l, TNF-alpha. Moreover, aldosterone releases from the bone marrow, cells that gather in colonies, activates different forms of white cells in blood and tissues. All these cells make up a pro-inflammatory cellular pool, that could be an important factor for dystrophy and myocardial and blood vessel destruction, as a consequence of replacement of healthy tissue by fibrous one. We have to highlight that fibrosis is one of the most important factors for the appearance of arrhythmias, which could endanger the life of these patients. Besides, aldosterone has a direct effect on endothelial function and several brain structures, such as arachnoid matter, paraventricular nucleus of the hypothalamus, autonomous nervous system nuclei, etc.

Angiotensin activation induces the synthesis and release of aldosterone, both at systemic and local level. In turn, aldosterone activates stress-dependent reactions of angiotensin. In brief, angiotensin and aldosterone make up a self-sustainable system with harmful effects for the evolution of HF.
These conclusions about such important role of angiotensin and aldosterone in the evolution of HF are supported by many experimental clinical studies. For this reason, the combination of ACEI and aldosterone antagonists not only decreases the deleterious effect of these hormones, but is the basis for the restoration of changes of continuity in connective tissue and the whole cardiovascular system.

Aldosterone antagonists

At a time not so distant from today, aldosterone antagonists (AA) were used as potassium-sparing diuretics for the correction of hypokalemia, produced by loop diuretics and thiazides. But time provides corrections, and nowadays, AAs are a pharmacological set on their own (separated from diuretics).

There are two representatives known of AAs: spironolactone (nonselective) and epleronone (selective). Spironolactone is rapidly absorbed with its maximal plasmatic concentration within the first 2 hours. It biotransforms in the liver, where the next active metabolites are formed: 7-alpha-thiospironolactone, canrenone or canrenoate, 7-alpha-thiomethylspironolactone or 6-beta-oxy-7-alpha-thiomethyl-spironolactone. The concentrations of these metabolites reach their maximal level within 2-3 hs. The first 3 metabolites (26%, 68%, and 33% of basal substance) have an antimineralocorticoid effect. The binding of spironolactone and canrenone with plasmatic proteins is 90 to 98%. The basal substance (nonmetabolized spironolactone) is eliminated within 2 hs; canrenone in 20 hs; 7-alpha-thiomethyl-spironolactone in 3 hs; 6-beta-pxy-7-alphathiomethyl-spironolactone in 10 hs. Metabolites are excreted with urine and bilis.

Spironolactone, besides its action on aldosterone receptors, also inhibits the receptors of androgen, glycocorticoids, and progesterone. For this reason, in the cases of prolonged use of aldosterone, there is a probability of different complications. One of the most frequent ones (up to 10%) in men is gynecomastia, in women mammary pain and dysmenorrhea. Other frequent complications are a decrease of libido and impotence. All of these complications hinder the possibility for a systematic management of HF with spironolactone.

Eplerenone (epoxymexrenone) is a 9-alpha-, 11-alpha epoxy derived from spironolactone. Its bioavailability is 67%, and maximal plasmatic concentration is achieved within the first 1.5 hs. Eplerenone biotransforms in the liver, its half life is from 4 to 6 hs, and it has no active metabolites. Renal excretion of the drug is below 5%.

The rate of adverse effects from eplerenone does not exceed that of placebo. The rate of adverse effects, such as gynecomastia in men, and vaginal bleeding in women is lower than 1%. There were no cases reported on eplerenone overdose. It does not require dose adjustment of ACEI, ARB, statins, BB, or amiodarone in the case of their use in combination with eplerenone. The combination of eplerenone with ACEI and ARB is not advised in patients with renal function

impairment, due to the risk of hyperkalemia. No interactions were recorded between eplerenone, warfarin, digoxin, or oral contraceptives.

Aldosterone antagonists are contraindicated in the following cases: plasmatic potassium greater than 5.5 meq/l, plasmatic creatinine greater than 2.0 mg/dl in men, and greater than 1.8 mg/dl in women, creatinine clearance lower than 50 ml/min, diabetes mellitus type 2 with microalbuminuria. AAs are not indicated in combination with potassium-sparing diuretics, or in eplerenone along with spironolactone.

AAs are aldosterone receptor blockers, which are found in different tissues of the organism. Besides the concurring interaction with these receptors, AAs also inhibit aldosteronsynthetase activity, decreasing the synthesis of aldosterone. Due to its anti-inflammatory action, they prevent the development of myocardial fibrosis and vascular median. Its beneficial effects on systemic hemodynamic parameters help preventing myocardial remodeling and favor reversion of myocardial hypertrophy. All that has been commented here, determines the main indications for the use of AAs in the management of patients class III-IV HF (NYHA), especially in the cases of ineffectiveness of standard treatment.

In patients with decompensated HF, AAs can be indicated in high doses (from 150 to 300 mg/d), 1 qd or in 2 takes, during the first half of the day (no more than 4 to 6 weeks). Later, it is advised to go to maintenance doses, from 25 to 50 mg/d. Combined with ACEI, AAs are indicated in doses of 25 to 50 mg/d. Eplerenone is indicated in the same dose in post-infarction patients complicated with HF (compensated) with ejection fraction below 40%.

Clinical use of aldosterone antagonists

When ACEI were starting to be used to treat HF, indicating AAs (as potassium-sparing diuretics) was no longer necessary to prevent a potential hypokalemia, secondary to the management with loop diuretics or thiazides. However, soon after it became known that ACEI block just one part of RAAS. Therefore, to achieve a full outcome from the management of HF, a combination of ACEI and AAs was necessary. All of this is the foundation for the return of AAs to clinical practice. Nowadays, according to the indications by the European Society of Cardiology, AAs are indicated in patients with class III-IV HF, and also in post-infarction patients with stable HF, and the criteria in the prior paragraph. According to these criteria, AAs are indicated virtually in all patients with HF (for all functional classes).

The RALES (Randomized Aldactone Evaluation Study) was the first randomized controlled study, in which the impact on mortality in an arm of 841 patients with standard treatment combined with placebo, was compared with an arm of 822 patients with standard treatment combined with spironolactone (25 mg/d) in patients with class III-IV HF and EF of 35%. This study was terminated early, in year 1998, due to the decrease in mortality in the arm with spironolactone. The follow-up period was 2 years. In the arm with spironolactone, all-cause mortality decreased in 27% (compared to placebo); cardiac mortality in a 31%; the total number of hospitalizations in a 17%; hospitalizations due to HF decompensation in a 36%, total mortality and total number of hospitalizations in a 22%. All these data were statistically very significant. Nevertheless, in spite of the management in low doses of spironolactone, adverse effects were observed frequently, related to the nonselective stimulation of steroid blockers. The rate of gynecomastia or mastodynia in the arm with spironolactone was 10% (compared with 1% in the placebo arm).

A year later, Pitt B., and Roniker B., compared spironolactone with eplerenone, in patients with class II-IV HF. In this study, 321 patients were included. Eplerenone was indicated in doses between 25 and 100 mg/d. The patients in the control arm received spironolactone (25 mg/d) or placebo. There were no differences between spironolactone and eplerenone, as to their effect on the functional class of HF. In men from the spironolactone arm, increases in the levels of plasmatic testosterone were detected more frequently (compared to eplerenone). In year 2003, the results were published from the international controlled multicentric EPHESUS study (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), in which the impact was determined of standard HF management combined with eplerenone, on the prognosis of post-infarction prognosis with HF signs and LVEF lower than 40%. In this study 6632 patients were included (3319 in the arm with eplerenone and 3313 in the placebo arm), from 647 centers from 37 countries. The patients were included in the study within 3 to 14 days post infarction, with the condition of stability of clinical parameters. This study was terminated in year 2002, when the total number of deaths reached the level of statistical significance in 1012 cases. In the eplerenone arm a significant decrease of total mortality was observed (14.4% vs.16.7%), as well as of mortality and hospitalizations by cardiovascular causes (26.7% vs. 30%). During the first 30 days post infarction, total mortality decreased by 31% and the incidence of sudden cardiac death by a 37%. The rate of gynecomastia and impotence (in men) and mammary pain (in women) did not differentiate significantly between the eplerenone and placebo arms.

Highlights

AAs supplement the action of ACEI and RAAS, thus obtaining more significant and continued results in the management of patients with HF. The therapeutic significance of spironolactone has been shown in patients with severe HF and in the case of eplerenone, for patients with stable HF with ejection fraction lower than 40%, within 3 to 13 days post infarction. Adverse effects are less frequent for eplerenone than for spironolactone, and those of eplerenone are comparable to placebo. The combination of the standard management of HF with AAs improves the structure and hemodynamic indicators of the cardiovascular system, and moreover, decreases total mortality, incidence of sudden cardiac death, and the frequency and duration of hospitalizations.

Currently, we can already consider aldosterone block as a component of optimal management of patients with HF. Therefore, in a near future, it is expected that indications for the systematic management of these patients with AAs (mainly eplerenone) will keep on enhancing.

Bibliography

1. Blacher J, Amah G, Girerd X, et al. Association between increased plasma levels of aldosterone and decreased systemic arterial compliance in subjects with essential hypertension. Am J Hypertens 1997;10:1326-34.
2. Blasi ER, Rocha R, Rudolph AE, et al. Aldosterone/salt induces renal inflammation and fibrosis in hypertensive rats. Kidney Int 2003;63:1791-1800.
3. Booth E, Johnson JP, Stockand JD. Aldosterone. Adv Physiol Educ 2002;26:8-20.
4. Brown NJ, Kim KS, Chen YQ, et al. Synergistic effect of adrenal steroids and angiotensin II on plasminogen activator inhibitor-1 production. J Clin Endocrinol Metab 2000;85:336-44.
5. Degasparo M, Joss U, Ramjoue, et al. Three new epoxy-spironolactone derivates: characterization in vivo and in vitro. J Pharmacol Exp Ther 1987,240:650-6.
6. Delyani J, Myles K, Funder J, et al. Eplerenone (SC 66110), a highly selective aldosteron antagonist. Am J Hypertens 1998;11:94A.
7. Duprez D, De Buyzere M, Rietzschel ER, et al. Aldosterone and vascular damage. Curr Hypertens Rep 2000;2:327-34.
8. Guidelines for the diagnosis and treatment of Chronic Heart Failure: full text (update 2005): The Task Force for the Diagnosis and Treatment of CHF of the European Society of Cardiology. Eur Heart J 2005; doi: 10.1093/eurheartj/ehi205, p. 1–45.
9. Krum H, Liew D. Eplerenone in the treatment of chronic heart failure. Expert Rev Cardiovasc Ther. 2004 May;2(3):315-20.

10. McFaiden R, Barr C, Struthers A. Aldosterone blocade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. Cardiovasc Research 1997;35:30-4.
11. McMachon E. Recent studies with eplerenone, a novel selective aldosterone receptor antagonist. Current Opinion in Pharmacology 2001;1:190-6. Pitt B et al. for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction. N Engl J Med 2003; 348: 1309–21.
12. Pitt B, Roniker B. Eplerenone, a novel selective aldosteron receptor antagonist (SARA): dose - finding study in patients with heart failure. J Am Coll Cardiol. 1999;33: 188A-9A.
13. Pitt B 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: 709–17.
14. Pitt B et al. Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction. N Engl J Med 2003;348:1309-21.
15. Rajagopalan S, Duquaine D, King S, et al. Mineralocorticoid receptor antagonism in experimental atherosclerosis. Circulation 2002;105:2212-26.
16. Randomized ALdactone Evaluation Study. Eur Heart J 1995;16(suppl N):107-10.
N Eng J Med 1999;341:709-717 Seckl JR and Walker BR. Minireview: 11beta-hydroxysteroid dehydrogenase type 1-a tissue-specific amplifier of glucocorticoid action. Endocrinology 2001;142:1371-6.
17. Schunkert H, Hense HW, Danser J, et al. Association between circulating components of the rennin-angiotensine-aldosterone system and left ventricular mass. Br Heart J 1997;77:24-31.
18. Spertus A, Tooley Phar J, Jones P, et al. Expanding the outcomes in clinical trials of heart failure: The quality of life and economic components of EPHESUS (EPlerenone's neuroHormonal efficacy and survival study). Am Heart J 2002;143:636-42.
19. Struthers AD. Aldosterone blockade in heart failure. J Renin Angiotensin Aldosterone Syst. 2004 Sep;5 Suppl 1:S23-7.
20. Struthers AD. Angiotensin blockade or aldosterone blockade as the third neuroendocrine-blocking drug in mild but symptomatic heart failure patients. Heart. 2006 Dec;92(12):1728-31.
21. Weber KT. Efficacy of aldosterone receptor antagonism in heart failure: potential mechanisms. Curr Heart Fail Rep. 2004 Jul;1(2):51-6.