Aldosterone is a steroid hormone that is secreted by the zona glomerulosa of the adrenal cortex and is directly involved in regulation of blood pressure. Aldosterone exerts its main effects on the distal tubular site of the nephron where it increases water and sodium chloride reabsorption thereby leading to expansion of the extracellular fluid volume. Recent views indicate that, in addition to its renal effects and regulatory role on body water and electrolyte balance, aldosterone acts on a variety of cell types affecting cellular mechanisms that mediate important tissue responses, including hypertrophy and fibrosis. Landmark studies have detected expression of receptors with high affinity for aldosterone in cardiac myocytes and fibroblasts obtained from human hearts [1]. Recent evidence obtained from experimental animal studies indicates that chronic exposure to inappropriately high aldosterone levels or activation of the mineralocorticoid receptors can induce myocardial tissue damage with mechanisms that are independent of blood pressure elevation [2]. These animal studies have demonstrated that chronic infusion of aldosterone induces tissue inflammatory changes [3] that lead to fibrosis of myocardium [4] and can be prevented by removal of adrenal glands or administration of aldosterone antagonists [5].

Almost a decade ago, two trials have investigated the effects of aldosterone antagonists in patients with functional class III-IV systolic heart failure, showing a significant decrease in the mortality rate as compared to patients who received placebo on top of conventional treatment. The Randomized Aldactone Evaluation Study (RALES) [6] and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) [7] were performed, respectively, in patients with New York Heart Association (NYHA) class III-IV heart failure.
Aldosterone antagonists and the heart

failure who were treated with spironolactone and in post-myocardial infarction patients with severely impaired left ventricular (LV) function who were treated with eplerenone. Although indirectly, these two studies have provided important evidence of the unfavorable cardiac effects of aldosterone. In this article, we summarize briefly the current knowledge of the effects of aldosterone antagonists on cardiac protection and highlight the most recent findings that have been obtained in different cardiac conditions with use of these agents.

Aldosterone antagonists in heart failure

The RALES [6] and the EPHESUS [7] trials have clearly demonstrated the benefits of aldosterone antagonists in patients with advanced stages of systolic heart failure. Recently, these observations have been extended to patients with milder degrees of cardiac dysfunction in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study [8]. In this study, 2737 patients with NYHA class II cardiac insufficiency and LV ejection fraction of less than 35% were randomized to receive either eplerenone or placebo in addition to conventional treatment. This trial ended prematurely after a median follow-up of 21 months because the composite endpoint of cardiovascular death and hospitalization for heart failure were significantly less frequent (hazard ratio 0.63) in patients who were treated with eplerenone.

In addition to the important findings of the EMPHASIS-HF, two studies of smaller size have reported evidence of protective effects of aldosterone antagonists in patients with early stages of cardiac failure. The Anti-Remodeling Effect of canrenone IN patients with mild Chronic Heart Failure (AREA IN-CHF) was a randomized, double-blind, placebo-controlled study that investigated whether canrenone improves LV remodeling in NYHA class II cardiac failure patients [9]. After 12 months, the composite endpoint of cardiac mortality and hospitalization was significantly lower in the canrenone than the placebo arm (8% versus 15%), with LV ejection fraction that increased significantly more in patients who were treated with canrenone. Another study randomized patients with NYHA class I-II cardiac failure and LV ejection fraction of less than 40% to spironolactone or placebo [10]. Spironolactone increased significantly LV ejection fraction, decreased LV volumes, and improved LV diastolic filling pattern after 6 months. Thus, the currently available evidence strongly supports the notion that aldosterone receptor antagonists are of considerable therapeutic value in patients with systolic heart failure with a cardioprotective effect that is already appreciable in the early functional stages.

Recent evidence suggests that the benefits of aldosterone antagonists in the context of cardiac failure are not restricted to patients with impaired systolic function. In fact, some studies have tested the effects of these drugs in patients with heart failure and preserved systolic function (HFPSF). Forty-four elderly patients with HFPSF (ejection fraction > 45%) were randomized to conventional treatment with or without eplerenone and LV function was reassessed with conventional echocardiography and tissue Doppler imaging at 6 and 12 months [11]. In patients who were treated with eplerenone, deceleration time had a significantly greater decrease than in patients on conventional treatment and, after 12 months, the spironolactone-induced improvement of diastolic function was associated with a significantly slower increase in plasma procollagen levels. Edwards et al. [12] reported similar data in 112 patients with stage 2-3 chronic renal failure and HFPSF who were included in the Chronic Renal Impairment in Birmingham (CRIB II) study. In this study, the effects of spironolactone on LV function and circulating markers of collagen turnover were compared with those of placebo. After 40 weeks, spironolactone improved significantly markers of LV relaxation and attenuated significantly the increase in aminoterminal propeptide of type-III procollagen that was observed with placebo. The evidence provided by these initial studies on HFPSF suggests a possible benefit of aldosterone blockade also on this subtype of cardiac failure that would deserve further investigation in studies of a larger size. Taken together, the findings obtained in the studies that have tested the effects of aldosterone antagonists in cardiac failure provide indirect evidence of untoward effect of aldosterone on the heart. Notably, all these studies have employed doses of spironolactone (from 25 to 50 mg/day) or eplerenone (from 25 to 50 mg/day) that did not lower blood pressure suggesting that the cardioprotective effects of aldosterone antagonists occur independent of the blood pressure-related hemodynamic load to the heart.
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Aldosterone antagonists in hypertensive heart disease

LV hypertrophy in essential hypertension

Evidence that LV hypertrophy imposes a definite and independent risk of increased cardiovascular morbidity and mortality in patients with hypertension has been established more than 20 years ago [13]. There is also little doubt that blood pressure-lowering therapy reduces LV mass in these patients in comparison to treatment with placebo [14] and decreases cardiovascular risk [15]. Large clinical trials that evaluated the effects of blockade of the renin-angiotensin system (RAS) with angiotensin-converting enzyme (ACE) inhibitors [16] or angiotensin receptor blockers (ARB) [17] have demonstrated a specific ability of these agents in preventing progression and inducing regression of LV mass in essential hypertensive patients. It must be noticed, however, that a significant percentage of hypertensive patients with LV hypertrophy fail to achieve full regression of LV mass when treated with RAS blockers, a fact that might be ascribed to plasma aldosterone escape from the inhibitory effect of these drugs [18]. This hypothesis received the support of studies in which it was demonstrated that with use of RAS blockers LV mass does not decrease in hypertensive patients with aldosterone escape as opposed to a decline in LV mass that is observed in patients without aldosterone escape [19]. Also, two small studies that were conducted in Japan have reported that addition of spironolactone to RAS blockers in the treatment of hypertension-induced LV hypertrophy provides additional effects on LV mass reduction. In a first study [20], Sato et al. compared the effects of an ACE-inhibitor alone or an ACE-inhibitor plus spironolactone (25 mg/day) on blood pressure and LV mass changes in essential hypertensive patients with LV hypertrophy. In this 60-week study, final values of blood pressure were similar and LV mass index decreased in both treatment groups, but the extent of reduction was significantly greater in patients who were treated with the combination of the ACE-inhibitor and spironolactone. In a 1-year study [21], Taniguchi et al. compared the effects of candesartan (8 mg/day) alone or combined with spironolactone (25 mg/day) in patients with essential hypertension and different patterns of left ventricular geometry. At the end of study, changes in blood pressure did not differ between the two groups, whereas only the combination of candesartan and spironolactone decreased LV mass with a change that was significant only in those patients with concentric LV hypertrophy.

Strong evidence that aldosterone antagonists decrease LV mass in hypertensive patients with LV hypertrophy [22] and improve LV function in hypertensive patients with diastolic dysfunction [23] has been obtained recently. In the 4-E Left Ventricular Hypertrophy Study, regression of LV hypertrophy was compared in essential hypertensive patients who were treated with eplerenone, enalapril, or their combination for 9 months [22]. LV mass index decreased significantly and comparably in patients treated with eplerenone or enalapril, whereas the combination of the two agents showed additive effects on LV mass reduction. In another study, 30 hypertensive patients with exertional dyspnea, preserved LV ejection fraction, and impaired diastolic function were randomized to receive either 25 mg/day of spironolactone or placebo for 6 months [23]. Peak systolic strain and cyclic variation of integrated backscatter were improved by spironolactone with significant differences with patients treated with placebo. Thus, current evidence indicates that aldosterone receptor antagonists could gain a considerable place in the treatment of hypertensive patients with LV hypertrophy and/or LV diastolic dysfunction.

Use of spironolactone has demonstrated cardiac benefits also in patients with hypertension resistant to treatment. In 34 patients with hypertension unresponsive to the combination of three drugs, Gaddam et al. have recently assessed in a longitudinal follow-up study the morphological and functional cardiac variables [24]. Baseline measurements obtained with magnetic resonance imaging indicated that among patients with resistant hypertension those with elevated plasma aldosterone had greater left and right ventricular end-diastolic volumes than patients with normal plasma aldosterone, but blood pressure values and LV mass were comparable. Spironolactone was added to the ongoing antihypertensive treatment at 25 mg/day and was titrated up to 50 mg/day within 4 weeks. Patients were reassessed after 3 and 6 months showing that treatment with spironolactone reduced ventricular end-diastolic volume only in patients with elevated baseline plasma
and this hypothesis will have to be confirmed in patients without aldosterone excess [25].

Patients with elevated plasma aldosterone, but also in patients without aldosterone excess [25] and this hypothesis will have to be confirmed in further studies.

LV hypertrophy in primary aldosteronism

Primary aldosteronism offers a unique clinical opportunity to study the effects of aldosterone on the heart because, in this condition, the effects of the hormone are isolated from those of the renin-angiotensin axis. For many years, primary aldosteronism has been considered a relatively benign form of hypertensive disease associated with modest incidence of cardiovascular complications [26, 27]. This tenet was generally ascribed to the suppression of angiotensin II generation occurring as a result of the expansion of body fluid compartments induced by the sodium-retentive effects of aldosterone [28].

More recently, however, many studies have indicated that protracted exposure to high aldosterone levels might cause cardiac structural damage [29], independent of the blood pressure level. Nowdays it is clear that primary aldosteronism is associated with a variety of cardiovascular complications [30], indicating that inappropriate high aldosterone levels can induce damage in specific tissues that is independent of the hypertension-related hemodynamic load.

Cardiac abnormalities are common consequences of hypertensive states and have been demonstrated in patients with primary aldosteronism. Most cross-sectional echocardiographic evaluations have reported a greater increase of LV mass in patients with primary aldosteronism as compared with other types of hypertensive disease. An increased frequency of inappropriate LV mass has been reported in patients with primary aldosteronism, even in the absence of LV hypertrophy as defined by conventional criteria [31], suggesting that elevated aldosterone increases LV mass beyond the amount needed to compensate the blood pressure-dependent hemodynamic load. In primary aldosteronism, excess LV hypertrophy occurs in association with an abnormal pattern of LV filling [32, 33], indicating abnormal diastolic function, whereas systolic function is generally not different from that of patients with other types of hypertension. Also, in primary aldosteronism abnormalities of diastolic function have been associated with the evidence of abnormal densitometric properties of the LV wall [32] suggesting myocardial fibrosis.

Everybody is aware of the intrinsic limitations of cross-sectional evaluations in the definition of causal associations, and findings obtained in these studies need to be strengthened by observations of longitudinal studies. Most cardiac ultrasound assessments of cardiac changes after treatment of primary aldosteronism are confined to studies of short duration after adrenalectomy. Initial studies reported that in patients treated with removal of an aldosterone-producing adrenal adenoma, both LV mass and diastolic filling [32] were normalized after one year, whereas patients who were treated with spironolactone had no significant changes in LV hypertrophy. We have reported on a seven-year follow-up of patients with primary aldosteronism who were treated with either adrenalectomy or spironolactone [33]. We observed that patients treated with either surgery or aldosterone antagonists have significant and comparable decrease of LV mass, although change is significant within the first year only after adrenalectomy. In these patients, we found also that the extent of decrease in LV mass that was obtained with both surgical and medical treatment of primary aldosteronism, was directly related with plasma aldosterone levels that were measured before treatment both at baseline and after an intravenous saline load. In agreement with our findings, another study has reported recently significant decrease of LV mass in a substantial group of patients with primary aldosteronism who have been re-evaluated after a follow-up of 36 months following either adrenalectomy or treatment with aldosterone antagonists [34]. Similar to our study, in this study significant decrease of LV mass in patients who
were treated with surgery occurred earlier than in those treated with aldosterone antagonists. Thus, as indicated by these studies, blood pressure reduction accounts for the decrease of LV mass obtained with treatment of primary aldosteronism only in part. These observations support a role of aldosterone in the induction of LV hypertrophy over that induced by hypertension itself.

Given the relevance of LV hypertrophy in the stratification of cardiovascular risk, even in patients with primary aldosteronism regression of hypertrophy might translate in substantial protection from cardiovascular events. In fact, as consistently reported in retrospective evaluations [35-38], this endocrine disease is associated with an increased prevalence of coronary heart disease, cerebrovascular disease, congestive heart failure, and atrial fibrillation. As we reported in a long-term follow-up study, treatment of primary aldosteronism with either adrenalectomy or aldosterone antagonists decreases the risk of cardiovascular events to a level that is comparable to that of patients with essential hypertension [36].

Aldosterone antagonists in atrial fibrillation

Atrial fibrillation often complicates hypertensive heart disease and retrospective studies have consistently reported an increased prevalence of this arrhythmia in patients with primary aldosteronism [35, 36, 38]. The relative risk for this rhythm disorder in patients with primary aldosteronism as compared to patients with essential hypertension was 12.1 [35], 4.9 [36], and 6.6 [38], respectively, in three different studies. Moreover, treatment with both surgery and spironolactone restored incidence of atrial fibrillation to a level that was comparable to that of patients with essential hypertension [36].

Many studies suggest that blockade of the renin-angiotensin-system appears to have specific benefit over other types of antihypertensive drugs in the prevention of atrial fibrillation [39]. This benefit has been ascribed to attenuation of the pro-inflammatory and pro-fibrotic effects of angiotensin II on atrial myocardium [39]. As outlined in the introduction of this article, experiments conducted in animal models demonstrate that aldosterone, similar to angiotensin II, induces inflammation and fibrosis of the myocardium [2-5]. Based upon these assumptions, clinical studies have been designed to investigate the effects of aldosterone antagonists on recurrences of atrial fibrillation. The SPIR-AF trial [40] was a 12-month, prospective, open-label study that randomized 164 patients with a history of at least 4 years of recurrent atrial fibrillation to 4 different treatments, two of which had spironolactone (25 mg/day) on top of a beta-blocker alone or of a beta-blocker plus enalapril, respectively. The primary outcome as defined by recurrences of symptomatic atrial fibrillation was significantly less frequent in both spironolactone-treated groups than in patients treated with a beta-blocker alone or the combination of a beta-blocker plus enalapril. This study is the first to suggest a potential benefit of mineralocorticoid receptor antagonists in the prevention of recurrences of atrial fibrillation. Previous studies were conducted in patients with heart failure, showing that aldosterone antagonists reduce the risk of sustained atrial rhythm disorders in these patients [41] and that a specific polymorphism possibly related to the activity of aldosterone-synthase is associated with greater incidence of atrial fibrillation [42]. More recently, the relationship of aldosterone with atrial arrhythmias has been investigated with an elegant approach that has combined examination of clinical samples and in vitro experiments. Tsai et al. have measured aldosterone levels and expression of steroidogenesis proteins in atrial tissue that was obtained at surgery from patients with and without atrial fibrillation [43]. No difference in atrial aldosterone levels was found between patients with or without atrial fibrillation, whereas patients with atrial fibrillation had increased expression of the atrial mineralocorticoid receptor as compared to patients with sinus rhythm. This observation leads to the hypothesis that the possible effects of aldosterone in the atria are not due to the amount of hormone that is generated locally, but might depend from an increased tissue expression of mineralocorticoid receptors. In a separate set of experiments that were performed in vitro using an atrial cell line, the Taiwanese researchers demonstrated that expression of mineralocorticoid receptor is increased by sustained electrical field depolarization and that exposure of cells to aldosterone activates the inward calcium and outward potassium current. In these in vitro experiments, co-incubation with spironolactone attenuated the changes induced by exposure of atrial cells to aldosterone, indicating the involvement of a mineralo-
corticoid receptor-dependent pathway. These findings represent an important step in the understanding of cellular and electrophysiological mechanisms that might account for the beneficial effects of spironolactone in the prevention of atrial fibrillation [44]. Findings also prompt larger studies designed to investigate whether aldosterone antagonists can reduce also cardioembolic risk.

In vitro evidence of mineralocorticoid-receptor mediated" to "mineralocorticoid-receptor mediated electrophysiological effects of aldosterone on myocardial cells might generate some interest for possible additional clinical uses of aldosterone antagonists. A recent metaanalysis that has included 7 trials and 8635 patients with heart failure or coronary artery disease has examined the effects of spironolactone and eplerenone on ventricular arrhythmias [45]. This metaanalysis has demonstrated that these drugs reduce the rate of ectopic ventricular beats, the risk of ventricular tachycardia, and, ultimately, the risk of sudden cardiac death in these patients. Thus, although this issue will need further investigation in appropriately designed clinical trials, use of aldosterone antagonists could be seen in perspective as a valuable choice also for the prevention of ventricular arrhythmias.

Conclusions

Spironolactone and other aldosterone antagonists are established treatments for patients with congestive states due to either cardiac, hepatic, or renal conditions associated with secondary aldosteronism. Current evidence indicates that aldosterone can cause myocardial tissue abnormalities, including hypertrophy and fibrosis, over that induced by high blood pressure itself. Therefore, aldosterone antagonists might prove beneficial in a variety of cardiac conditions by counteracting the untoward cardiac effects of the hormone. In addition to clear demonstration of cardioprotection in patients with systolic heart failure and primary aldosteronism, evidence is accumulating in support of a possible use of these agents in patients with diastolic heart failure, hypertension-related LV hypertrophy, and atrial fibrillation. Further and adequately focused studies will have to be conducted to define precisely the spectrum of cardiac conditions that could benefit from use of these interesting agents.

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