

“Escape” of Aldosterone Production in Patients with Left Ventricular Dysfunction Treated with an Angiotensin Converting Enzyme Inhibitor: Implications for Therapy

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Summary. Despite the findings in randomized trials of a significant effect of angiotensin-converting enzyme (ACE) inhibitors in reducing morbidity and mortality of patients with symptomatic left ventricular dysfunction, the morbidity and mortality of these patients remains relatively high. One potential strategy to further improve morbidity and mortality in these patients is blockade of aldosterone. Many clinicians have assumed that ACE inhibitors would block both angiotensin II and aldosterone. However, there are data to suggest that aldosterone production may “escape” despite the use of an ACE inhibitor. An escape of aldosterone production has several important consequences, including: sodium retention, potassium and magnesium loss, myocardial collagen production, ventricular hypertrophy, myocardial norepinephrine release, endothelial dysfunction, and a decrease in serum high density lipoprotein cholesterol. Due to the potential importance of these mechanisms, the finding that there is a significant correlation between aldosterone production and mortality in patients with heart failure, as well as evidence that an aldosterone antagonist, spironolactone, when administered to patients with heart failure treated with conventional therapy including an ACE inhibitor results in increased diuresis and symptomatic improvement, an international prospective multicenter study has been organized, the Randomized Aldactone Evaluation Study (RALES Pilot Study), to evaluate the safety of blocking the effects of aldosterone in patients with heart failure treated with an ACE inhibitor.

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Large-scale randomized trials such as the Cooperative North Scandinavian Enalapril Survival Study (Consensus) [1], Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial [2], Vasodilator-Heart Failure Trial (V-HeFT-II) [3], Survival After Left Ventricular Enlargement (SAVE) [4], and Acute Infarction Ramipril Efficacy (AIRE) Study [5], have confirmed the effectiveness of angiotensin-converting enzyme (ACE) inhibitors in reducing total mortality

and morbidity in patients with symptomatic left ventricular dysfunction early and late postinfarction as well as in chronic heart failure. There is also evidence suggesting that ACE inhibitors may have an effect in reducing the incidence of recurrent myocardial infarction in patients with left ventricular dysfunction [4,6]. On the basis of these studies and previous studies showing that ACE inhibitors improve exercise performance and symptoms in patients with symptomatic left ventricular dysfunction [7,8], ACE inhibitors in conjunction with diuretics with or without concomitant therapy with digoxin have become the standard for care of patients with symptomatic left ventricular dysfunction unless contraindicated because of hyperkalemia or not tolerated because of symptomatic hypotension, progressive renal dysfunction, angioedema, or intractable cough. The finding in randomized trials of a significant effect of ACE inhibitors on mortality and morbidity in patients with symptomatic left ventricular dysfunction has prompted efforts to apply this strategy to the vast majority of patients with asymptomatic left ventricular dysfunction, who have up to now not been treated with an ACE inhibitor.

While efforts to extend the use of ACE inhibitors to patients with asymptomatic left ventricular dysfunction are important, there is also evidence suggesting that despite the use of ACE inhibitors in patients with symptomatic left ventricular dysfunction, there remains a relatively high incidence of mortality and recurrent heart failure [2]. This realization has prompted efforts to explore other mechanisms and treatment strategies, including the use of beta-adrenergic receptor blocking agents, inotropic agents, direct-acting vasodilators, and metabolically effective

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agents, to further reduce mortality and morbidity [9]. One potential strategy to further improve mortality and morbidity in the patient with symptomatic left ventricular dysfunction has been largely overlooked, that is, blockade of aldosterone.

Many clinicians have assumed that ACE inhibitor therapy would block both angiotensin II and aldosterone. However, there are data to suggest that aldosterone production remains important despite the use of an ACE inhibitor. After several months of ACE inhibitor therapy and continued inhibition of angiotensin II production in patients with hypertension, aldosterone levels may increase or "escape" [10]. A similar escape of aldosterone production has recently been shown in patients with heart failure treated with an ACE inhibitor [11]. Recent studies have also shown that relatively high doses of an ACE inhibitor, such as captopril 50 mg three times daily for several days, suppresses resting levels of both angiotensin II and aldosterone, but during exercise both angiotensin II and aldosterone levels increase [12].

In another recent study using zofinopril in patients with acute myocardial infarction, it was shown that while ACE levels were almost completely suppressed angiotensin II and aldosterone levels escaped after several days [13]. The SOLVD trial has also suggested an escape of angiotensin II and catecholamine levels despite treatment with enalapril in doses of up to 10 mg bid after 1 year [14]. Although aldosterone levels were not measured in this study, it can be postulated that if angiotensin II levels increase there would also be an increase in aldosterone levels. Thus there appears to be an "escape" of aldosterone production, and in some instances angiotensin II, despite continued use of an ACE inhibitor. The mechanisms for the "escape" of aldosterone and angiotensin II are incompletely understood. Alternative pathways for the production of angiotensin II have been identified [15,16] and may become important after prolonged blockade of ACE, with a resultant increase in renin. Aldosterone production may be stimulated by decreased plasma levels of potassium and magnesium, and increased levels of ACTH, independent of the level of angiotensin II [17,18].

Aldosterone is produced in the zona glomerulosa of the adrenal gland [17–20]. Plasma aldosterone levels are normally between 5 and 15 ng/dl. Synthesis of aldosterone is mainly determined by angiotensin II. Other factors, such as an increase in ACTH, norepinephrine, or atrial natriuretic factor, or a decrease in intracellular potassium and magnesium, are also of importance and may be critical in determining aldosterone synthesis in situations in which angiotensin II production is inhibited. Inactivation of aldosterone occurs mainly in the liver. Its metabolite tetrahydroaldosterone is conjugated with glucuronic acid and excreted in the urine. Impaired hepatic blood flow and metabolism of aldosterone in the liver may also be of importance in determining serum aldosterone levels.

In situations such as chronic heart failure, in which hepatic blood flow and metabolism are impaired, the plasma half-life of aldosterone may increase from a normal value of 30–35 minutes to over 70 minutes, with a concomitant increase in aldosterone levels from a normal range of 5–15 ng/dl to over 30 ng/dl. Conversely, heparin, which blocks angiotensin II receptors in the zona glomerulosa of the adrenal gland and digitalis, through action on sodium/potassium ATPase, intracellular sodium, and potassium concentration, may decrease aldosterone production [17,18].

The consequences of an elevation of angiotensin II levels are well known and include peripheral and coronary vasoconstriction, stimulation of growth factors [21], release of endothelin [22] and plasminogen activator inhibitor [23], and oxidation of low density lipoprotein [24]. The effect of increased aldosterone production has, however, received less attention and will be briefly reviewed. An escape of aldosterone despite the use of an ACE inhibitor has several potentially important consequences that could result in the relatively high incidence of morbidity and mortality seen in patients with symptomatic left ventricular dysfunction despite treatment with an ACE inhibitor. Aldosterone would be expected to play a role in recurrent heart failure through its well-known effects in promoting distal renal tubular sodium absorption [25]. Elevated levels of aldosterone have also been implicated, at least in animal models, in myocardial collagen production [26] and ventricular hypertrophy [27]. Increased myocardial collagen production and consequent left ventricular hypertrophy could lead to an impairment in diastolic filling, diastolic dysfunction, and decreased coronary flow reserve, and eventually systolic dysfunction and recurrent heart failure.

Aldosterone may also be of importance in the relatively high incidence of sudden cardiac death found in patients with both ischemic and nonischemic heart failure. Increased aldosterone levels cause a loss of potassium and magnesium from the distal renal tubule. Both hypokalemia and hypomagnesemia predispose to recurrent ventricular arrhythmias, digitalis toxicity, and therefore sudden cardiac death [28,29]. The use of adjunctive potassium is common in patients with heart failure treated with diuretics and digitalis; hypokalemia nevertheless remains a major problem. In part, the hypokalemia can be corrected by the concomitant use of magnesium, which facilitates potassium retention [30]. Aldosterone may also predispose to ventricular arrhythmias through its effect on norepinephrine uptake [31].

Barr et al. have recently shown that norepinephrine uptake, as assessed by the myocardial uptake of meta-iodobenzylguanidine (mIBG), is depressed in patients with heart failure and that this can be improved by the use of the aldosterone receptor antagonist spironolactone despite the use of an ACE inhibitor [31]. The finding in the SOLVD treatment trial [2] that sudden cardiac death was only minimally reduced by

enalapril and the failure of type I antiarrhythmic agents to reduce mortality in patients with left ventricular dysfunction in the Cardiac Arrhythmia Suppression Trial (CAST) [32] are an impetus to develop further strategies to prevent ventricular arrhythmias and sudden cardiac death in patients with left ventricular dysfunction. Although there is considerable controversy regarding the effectiveness of ACE inhibitors in reducing sudden cardiac death in that sudden cardiac death was found to be reduced in the V-HeFT II trial [33], sudden cardiac death nevertheless remains an important cause of death in patients with symptomatic left ventricular dysfunction treated with an ACE inhibitor.

An escape of aldosterone could also play a role in recurrent ischemic events in patients with left ventricular dysfunction. The SOLVD trial pointed out the importance of recurrent ischemic events, myocardial infarction, and hospitalization for unstable angina in patients with left ventricular dysfunction due to ischemic as well as nonischemic cardiomyopathy [6]. Patients with recurrent ischemic events had a severalfold increase in the risk of death compared with patients without a recurrent ischemic event. Prior to this observation most clinicians focused on symptomatic improvement in patients with left ventricular dysfunction. The finding that recurrent ischemic events are common in both patients with ischemic as well as nonischemic cardiomyopathy has promoted efforts to prevent recurrent ischemia. Risk factor reduction in patients with ischemic cardiomyopathy, and correction of recurrent ischemia by revascularization, deserve increased emphasis.

Of importance in the SOLVD treatment [2–6] and prevention trials [34], as well as in the SAVE trial [4], was the finding that ACE inhibitors were effective in preventing recurrent myocardial infarction. These findings are of particular importance both for the patient with symptomatic left ventricular dysfunction as well as for the secondary prevention of ischemic heart disease in patients with asymptomatic left ventricular dysfunction, and have prompted a randomized trial to explore the role of ACE inhibitors in patients with ischemic heart disease and preserved left ventricular dysfunction ($EF \geq 40\%$) [35]. While the effectiveness of ACE inhibitors in preventing recurrent ischemic events can be explained by their effect in preventing angiotensin II production, there is evidence to suggest that aldosterone production might also be of importance and that an escape of aldosterone could predispose to recurrent myocardial infarction.

As mentioned earlier, aldosterone has been shown to cause left ventricular hypertrophy in experimental animals [26] and is significantly correlated with left ventricular mass in patients [36]. Left ventricular hypertrophy has been shown to be associated with a decrease in coronary flow reserve [37]. A decrease in coronary flow reserve has been demonstrated in both patients with nonischemic and ischemic cardiomyopa-

thy [38]. Prevention of left ventricular hypertrophy by ACE inhibitors and/or aldosterone receptor antagonists could be expected to maintain coronary flow reserve and thereby prevent recurrent myocardial ischemia.

There are, however, several other mechanisms whereby aldosterone could cause myocardial ischemia and infarction. Patients with primary aldosteronism have been found to have endothelial dysfunction, as evidenced by a decrease in forearm vascular response to the administration of acetylcholine as compared with normal individuals [39]. Removal of the aldosterone-producing tumor restores endothelial function. Endothelial dysfunction could be expected to lead to increased peripheral and coronary arterial resistance in response to neurohumoral stimuli such as angiotensin II, norepinephrine, or release of platelet products such as thromboxane and serotonin, all of which are endothelial-dependent vasodilators. Endothelial dysfunction has been suggested to be an important precursor of atherosclerosis [40] and has been demonstrated in patients with heart failure [41]. Release of endothelin from the endothelium has been shown to increase aldosterone levels [42]. Endothelin is a potent growth factor stimulant [43] and could play a role in the development of atherosclerosis [44] directly and/or through release of aldosterone.

Aldosterone has also been inversely correlated with serum high density lipoprotein cholesterol (HDL-C) concentrations [44]. A reduction in HDL-C concentration would be expected to predispose to atherosclerosis. A further potential link between aldosterone and atherosclerosis comes from the demonstration that there are specific aldosterone receptors on monocytes and that aldosterone administration results in an increase in intracellular monocyte calcium, sodium, and potassium [46,47]. The effect of these intracellular changes on electrolyte concentration are uncertain but could potentially influence monocyte function and/or cytokine release.

Aldosterone might also predispose to recurrent ischemia and infarction through its effects on magnesium. Individuals living in areas with low magnesium concentrations in their water have a significantly higher incidence of myocardial infarction than individuals living in areas with a high magnesium content [29]. Magnesium depletion in experimental animals has been shown to result in an increase in coronary vasomotor tone [47], and experimental hypomagnesemia has been used to cause coronary arterial spasm [48]. Experimental magnesium depletion has also been shown to cause cytokine release, which could further depress myocardial function [49,50]. Patients with symptomatic left ventricular dysfunction treated with high doses of loop diuretics activate their renin-angiotensin-aldosterone system [51] and would be expected to have magnesium depletion. The incidence of magnesium depletion in patients with symptomatic left ventricular dysfunction treated with loop diuretics

is, however, controversial. Recent studies have not detected a high incidence of hypomagnesemia in patients with chronic heart failure despite the use of loop diuretics [52,53]. While hypomagnesemia does not appear to be common, despite the use of loop diuretics, there is evidence for a decrease in intracellular magnesium concentrations, which may not be reflected in serum levels [54]. The administration of magnesium supplementation to patients with chronic heart failure treated with loop diuretics has been shown to result in a significant reduction in complex ventricular arrhythmias [55].

Due to the mechanisms outlined earlier and the finding in the CONSENSUS trial that there was a significant correlation between aldosterone and mortality [56], it has been postulated that an aldosterone receptor blocking agent would be of benefit in reducing the incidence of recurrent heart failure, ventricular arrhythmias, ischemic events, and therefore death in patients with heart failure despite the use of conventional therapy including an ACE inhibitor. There is evidence that the addition of spironolactone, an aldosterone receptor antagonist, to the therapy for patients with severe heart failure treated with conventional therapy including diuretics, digoxin, and an ACE inhibitor results in increased diuresis and symptomatic improvement [57]. A high incidence of hyperkalemia has not been observed in these patients despite concomitant treatment with an ACE inhibitor, nor in previous studies of patients with hypertension treated with an ACE inhibitor and aldactone. Nevertheless, the relative paucity of data on the safety of spironolactone in patients with symptomatic left ventricular dysfunction treated with an ACE inhibitor has prompted a prospective blinded randomized international multicenter study in order to explore its safety when used in conjunction with an ACE inhibitor, the Randomized Aldactone Evaluation Study (RALES Pilot Study). The data from this pilot safety study will be used to develop the dosing strategy for a subsequent study (RALES Mortality Trial) testing the efficacy of aldactone in reducing total mortality in patients with NYHA class IV heart failure treated with conventional therapy including an ACE inhibitor.

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