The RALES Study: Importance of aldosterone antagonism in the management of congestive heart failure

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Congestive heart failure (CHF) is a leading cause of morbidity and mortality in the Western world.[1] In the United States, CHF afflicts over 4 million people[2] and is the most common reason for admission to hospital in patients >65 years of age; CHF is responsible for over $17 billion of direct hospital costs. In Europe, CHF accounts for 70% of all hospital admissions in patients >70 years of age. Thus, CHF is an enormous global healthcare problem, which is likely to continue to inflict a significant burden on the healthcare delivery system.[3,4] Recently published results of the RALES study expand our therapeutic armamentarium with the addition of aldosterone antagonists in the management of severe CHF.

An overview of the pathophysiology of CHF (Figure 1)

A hallmark of heart failure is progressive decompensation of left ventricular function that results in progressive left ventricular remodeling and progression of symptoms. Initial myocardial injury may result from a number of pathological mechanisms (some of which are shown in Figure 1), leading to initial left ventricular dysfunction. For a period of time, activation of compensatory mechanisms, including sympathetic activation, salt and water retention, as well as others, may result in initial stabilization. Then, because of secondary damage or the progressive nature of left ventricular remodeling, there is decompensation.

At the cellular level, the transition from compensated to decompensated heart failure has been associated with alterations in calcium homeostasis, down regulation of beta-adrenergic receptors, myocyte dysfunction, on-going myocyte loss, and extracellular matrix remodeling.[5,6] In recent years, a number of biologically active peptides including norepinephrine, angiotensin II, endothelian I, aldosterone, and pro-inflammatory cytokines have been implicated as molecules whose physiological actions may contribute to disease progression of the failing heart.[6]

A number of important steps and considerations have been identified (Table 1), but will not be expanded on in this overview of the pathophysiology of CHF.

Similarly, a number of important disadvantages resulting from left ventricular remodeling are summarized in Table 2.

Consensus, recommendations for the management of chronic CHF[7]

General measures for the management of heart failure

• Measures to decrease the risk of a new cardiac injury including cessation of smoking; weight reduction in obese patients; control of hypertension, hyperlipidemia, and diabetes mellitus; and discontinuation of alcohol use.

• Measures to maintain fluid balance: Patients should restrict their daily intake of salt to a moderate degree (to ≤ 3 grams daily), and weight should be measured daily to detect the early occurrence of fluid retention.

• Measures to improve physical conditioning: Patients with heart failure should not be instructed to limit their physical activity, but should be encouraged to engage in moderate degrees of exertion to prevent or reverse physical deconditioning.

• Measures recommended in selected patients: Control of ventricular response in those with atrial fibrillation or other supraventricular tachycardias; anticoagulation in patients with atrial fibrillation or a previous embolic event (and, possibly, other high-risk patients); coronary revascularization in patients with angina (and, possibly, in patients with ischemic but viable myocardium); restoration of sinus rhythm in selected cases.

• Pharmacologic measures to be avoided: Use of anti-arrhythmic agents to suppress asymptomatic ventricular arrhythmias; use of most calcium antagonists; and use of non-steroidal anti-inflammatory agents.

• Other recommended measures: These include influenza and pneumococcal immunization; and close outpatient surveillance to detect early evidence of clinical deterioration.

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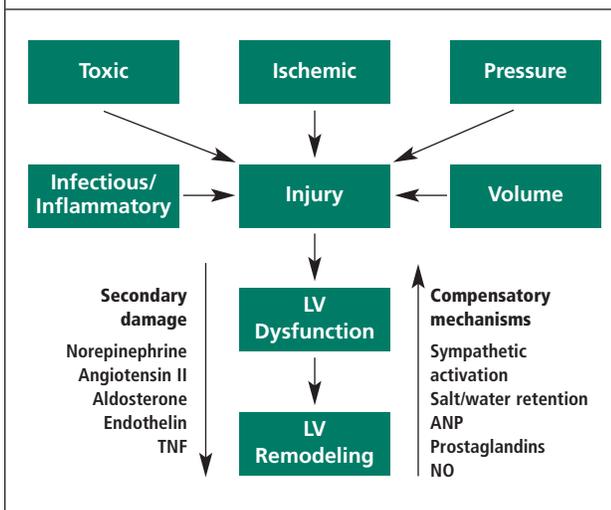Michael R. Freeman, MD
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Figure 1: Pathophysiology of CHF

Toxic, Ischemic, Pressure, Infectious/Inflammatory, Volume → Injury → LV Dysfunction → LV Remodeling

Secondary damage: Norepinephrine, Angiotensin II, Aldosterone, Endothelin, TNF

Compensatory mechanisms: Sympathetic activation, Salt/water retention, ANP, Prostaglandins, NO

Table 1: Overview of left ventricular remodeling

Alterations in myocyte biology
- Excitation contraction coupling
- Myosin heavy chain (fetal) gene expression
- ß-adrenergic desensitization
- Hypertrophy
- Myocytolysis
- Cytoskeletal proteins

Myocardial changes
- Myocyte loss
   - Necrosis
   - Apoptosis
- Alterations in extracellular matrix
   - Matrix degradation
   - Replacement fibrosis

Alterations in LV chamber geometry
- LV dilation
- Increased LV sphericity
- LV wall thinning
- Mitral valve incompetence

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Use of ACE inhibitors in heart failure

All patients with heart failure due to left ventricular systolic dysfunction should receive an ACE inhibitor unless they have been shown to be intolerant to, or have a contraindication to the use of, this class of drugs. In patients with evidence for, or a prior history of, fluid retention, ACE inhibitors are generally used together with diuretics. ACE inhibitors are also recommended for use in patients with left ventricular systolic dysfunction who have no symptoms of heart failure.

Patients receiving therapy with an ACE inhibitor should be advised that side effects may occur early in therapy but that they do not generally prevent long-term use of the drug; symptomatic improvement may not be seen until patients have received treatment for several weeks or months; and ACE inhibitors may reduce the risk of disease progression even if the symptoms of the patient have not responded favorably to treatment.

ACE inhibitors are indicated for the long-term management of chronic heart failure. These drugs should generally not be used to stabilize acutely ill patients ("rescue" therapy), eg, those who are in the intensive care unit with refractory heart failure requiring intravenous pressor support.

Although clinical trials suggest that all ACE inhibitors are likely to exert favorable effects in heart failure, preference should be given to the target doses of the specific ACE inhibitors evaluated in large-scale studies.

Use of beta-blockers in heart failure

All patients with stable NYHA class II or III heart failure due to left ventricular systolic dysfunction should receive a ß-blocker unless they have a contraindication to its use or have been shown to be unable to tolerate treatment with the drug. ß-blockers are generally used together with diuretics and ACE inhibitors. Patients receiving therapy with a ß-blocker should be advised that side effects may occur early in therapy, but that they do not generally prevent long-term use of the drug. Symptomatic improvement may not be seen until the patient has received treatment for 2-3 months. ß-blockade may reduce the risk of disease progression even if the patient's symptoms have not responded favorably to treatment.

More data are needed on the effect of ß-blockers in unstable patients or in patients with current or recent class IV symptoms before the drugs can be recommended for use in such patients.

Beta-blockers are indicated for the long-term management of chronic heart failure, but should not be used in acutely ill patients ("rescue" therapy), including those who are in the intensive care unit with refractory heart failure requiring intravenous support.

Use of digitalis in heart failure

Digoxin is recommended to improve the clinical status of patients with heart failure due to left ventricular systolic dysfunction and should be used in conjunction with diuretics, an ACE inhibitor, and a ß-blocker. The drug is also recommended in patients with heart failure who have atrial fibrillation with a rapid ventricular response, although ß-blockers may be more effective in controlling the ventricular response during exercise.

Although some physicians have advocated using serum levels to guide the selection of the appropriate dose of digoxin, there is no evidence to support the validity of such an approach. Despite pervasive fears about toxicity, digoxin is well tolerated by most patients with heart failure.

Use of diuretics in heart failure

Diuretics should be prescribed for all patients with symptoms of heart failure who have evidence for, or a predisposition

Table 2: Mechanical disadvantages created by LV remodeling

- Increased wall stress (afterload)
- Afterload mismatch
- Episodic subendocardial hypoperfusion
- Increased oxygen utilization
- Sustained hemodynamic overloading
- Worsening activation of compensatory mechanisms

to, fluid retention, since these drugs are the only reliable means of controlling the fluid retention of heart failure. However, diuretics should not be used alone even if the symptoms of heart failure are well controlled, but should generally be combined with an ACE inhibitor and a ß-blocker.

The goal of diuretic therapy is to eliminate the symptoms, as well as the physical signs of fluid retention as assessed by jugular venous pressures or peripheral edema, or both. If hypotension or azotemia is observed before these goals are achieved, the physician may elect to slow the rapidity of diuresis, but the diuresis should nevertheless be maintained until fluid retention is eliminated, as long as the changes in blood pressure and renal function are mild or moderate in severity and do not produce symptoms.

The most useful approach to selecting the dose of, and monitoring the response to, diuretic therapy is by measuring body weight, preferably on a daily basis. Diuretics may alter the efficacy and toxicity of nearly all the drugs used for the treatment of heart failure. Underdosing of diuretics can lead to fluid retention which may diminish the response to ACE inhibitor therapy and increase the risk of treatment with ß-blockers. Overdosing of diuretics can lead to volume depletion which may increase the likelihood of hypotension with ACE inhibitors and vasodilators and the risk of renal insufficiency with ACE inhibitors and angiotensin II receptor antagonists.

Diuretic resistance (which accompanies the progression of heart failure) can be overcome by the intravenous administration of diuretics, the use of ≥2 diuretics in combination (eg, furosemide and metolazone), or by the short-term use of drugs that increase renal blood flow (eg, dopamine and dobutamine). Diuretic resistance may also be caused by concomitant therapy with nonsteroidal anti-inflammatory drugs.

Aldosterone in heart failure

Aldosterone has an important role in the pathophysiology of heart failure since its secretion promotes retention of sodium, the loss of magnesium and potassium, sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, and vascular damage.[8-12] Since aldosterone receptor blockers are used infrequently in patients with heart failure, either because of the potential for serious hyperkalemia or because of frequent use of loop diuretics, a randomized aldactone evaluation study – the Randomized Aldactone Evaluation Study (RALES) – was conducted. The hypothesis was that the daily treatment with 25 mg of spironolactone would significantly reduce the risk of death from all causes among patients who had severe heart failure as a result of systolic left ventricular dysfunction and who were receiving standard therapy, including an ACE inhibitor, if tolerated.

The RALES Study[13]

Patients were eligible for enrollment if they had NYHA class IV heart failure within the 6 months before enrollment and were treated with an ACE inhibitor and a loop diuretic, and had a left ventricular ejection fraction (VEF) of no more than 35% six months before enrollment. Patients were excluded from the study if they had primary operable valvular heart disease or congenital heart disease, unstable angina, primary hepatic failure,

Figure 2: RALES results: 30% reduction in risk of all-cause mortality (p <0.001)[13]
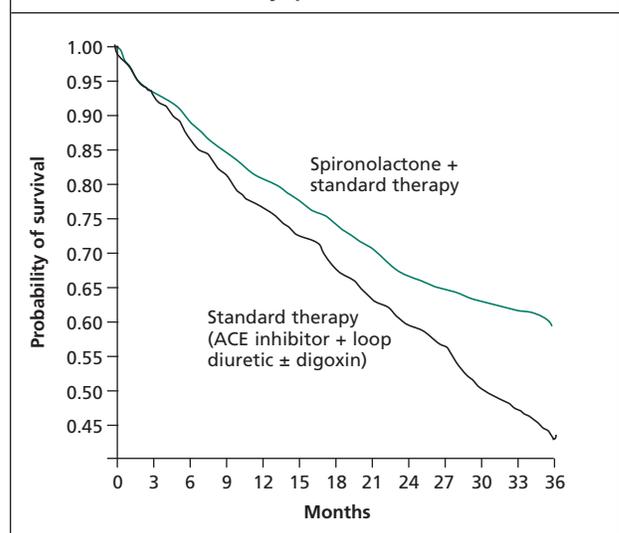
active cancer, or any other life-threatening disease. Patients who had undergone heart transplantation or were awaiting the procedure were also ineligible. Other criteria for exclusion were serum creatinine concentration of >220 mmol/L and a serum potassium concentration of >5 mmol/L.

Randomization into the study began on March 24, 1995 and recruitment was completed on December 31, 1996 with follow-up schedule to continue through December 31, 1999. However, at the fifth planned interim analysis, it was observed that the effect of spironolactone on the risk of death from all causes exceeded the prespecified critical Z value; therefore, the trial was discontinued on August 24, 1998 with a mean follow-up of 24 months.

A total of 1663 patients from 195 centers in 15 countries underwent randomization: 841 were assigned to placebo and 822 were assigned to receive spironolactone. There were no significant differences in baseline characteristics with the mean age of the patient population being 65 ± 12 years, 73% being male, approximately 70% being in class III NYHA, and approximately 30% in class IV NYHA. Approximately 55% of the patients had ischemic pathophysiology as the cause of their heart failure and almost every patient received an ACE inhibitor and loop diuretic, with approximately 70% receiving digoxin, and approximately 10% receiving beta-blockers.

Survival

There were 386 deaths in the placebo group (46%) and 284 deaths in the spironolactone group (35%), representing a 30% reduction in the risk of death (RR = 0.7, 95% CI, 0.6-0.82, p<0.001). Figure 2 demonstrates Kaplan-Meier analysis of the probability of survival, demonstrating clear benefit in favor of spironolactone treated patients.

A total of 314 deaths in the placebo group (37%) and 226 deaths in the spironolactone group (27%) were attributed to cardiac causes, representing a 31% reduction in the risk of car-

Table 3: Evidence-based approach to heart failure management					
	Agent	**Trial**	**Percent of patients With NYHA Class**		
			II	**III**	**IV**
ACE inhibitors	enalapril	CONSENSUS		100	
	enalapril	SOLVD	57	31	2
ß-Blockers	bisoprolol	CIBIS-II		83	17
	metoprolol CR/XL	MERIT-HF	41	56	3
Aldosterone antagonists	spironolactone	RALES		70	30

Table 4: Anti-aldosterone Agents

Spironolactone
- Binding to renal and gonadal steroid receptors
- Inhibition of P450 enzymes in endocrine organs
- Induction of P450 enzymes in the liver
- Complex metabolism

9-11 Epoxymexrenone (Eplerenone)
- Greater aldosterone binding capacity in vivo
- Less progestational and anti-androgenic actions
- No effect on P450 hydroxlyases in endocrine organs
- Minimal increase in liver P450 enzymes

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diac death (RR = 0.69; 95% CI, 0.58-0.82, p<0.001). The reduction in the risk of death among the patients in the spironolactone group was attributed to a significantly low risk of both death from progressive heart failure and sudden death from cardiac cause.

The reduction in the risk of death among patients in the spironolactone group was similar in the analysis of all six pre-specified subgroups that included age, ejection fraction, cause of heart failure, creatinine level, and the use of digoxin or ACE inhibitor. The benefit of spironolactone treatment was also seen in retrospective analysis based on gender, NHYA class, baseline serum potassium concentration, or the use of beta-blockers.

Safety

There were no significant differences between the two groups in serum sodium concentration, blood pressure, or heart rate during the study. While there was a statistically significant increase in median creatinine concentration and median potassium concentration in the spironolactone group by comparison to placebo, the differences were not clinically important. Serious hyperkalemia occurred in 10 patients in the placebo group (1%) and 14 patients in the spironolactone group (2%, p=0.42). Gynecomastia or breast pain was reported by 10% of the men in the spironolactone group and 1% of the men in the placebo group (p<0.001), causing more patients in the spironolactone group than in the placebo group to discontinue treatment (10 vs 1, p=0.006).

Results

The results of the RALES study clearly demonstrate efficacy of spironolactone in improving outcome in patients with severe heart failure and, therefore, represent a significant addition to our therapeutic armamentarium in the management of heart failure. Pharmacological agents that have been shown clearly to improve survival in patients with chronic heart failure are summarized in Table 3.

While spironolactone is the most widely known aldosterone antagonist, newer aldosterone antagonists such as selective aldosterone receptor antagonists (SARAs) are becoming available. eplerenone is the first such drug of its class and exhibits greater binding *in vivo* and has less progestational and anti-androgenic effects, hopefully leading to more desirable effect profile. A comparison of anti-aldosterone agents is shown in Table 4.

The use a selective aldosterone receptor antagonist, such as eplerenone, may therefore minimize the risk of gynecomastia.

Conclusion

The results of the RALES study clearly demonstrate that an aldosterone receptor antagonist, when used in conjunction with an ACE inhibitor, reduces the risk of both death from progressive heart failure and sudden death from cardiac causes. The effectiveness and risk of treatment with spironolactone in patients at lower risk than those in RALES study (eg, those with less severe heart failure), will require further prospective study. The results of the RALES study contribute to our understanding of the pathophysiology of heart failure and have implications for the treatment of patients with other conditions in which ACE inhibitors are beneficial, such as those with hypertension and those who have had a myocardial infarction.[13]

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