Role of Angiotensin Receptor Blockers in Heart Failure
Not Yet RESOLVD

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There is convincing evidence that the renin-angiotensin aldosterone system (RAAS) plays a major role in the pathogenesis and progression of heart failure. Angiotensin (Ang) II is a potent vasoconstrictor agent, and through the release of aldosterone, it promotes salt and water retention. Moreover, Ang II is a growth factor for both cardiac myocytes and fibroblasts. Exposure of these cells to Ang II leads to the induction of genes that produce characteristic phenotypic alterations that are similar to those seen during cardiac remodeling. Ang II also contributes to the generalization (and mostly deleterious) activation of other neurohormonal systems both within the heart and throughout the body by promoting release of agents such as norepinephrine and endothelin. The immediate effects of RAAS activation are increased cardiac afterload and preload. The long-term effects appear to include adverse cardiac remodeling characterized by ventricular dilatation, hypertrophy, and changes in chamber configuration, all of which predispose to progressive left ventricular (LV) dysfunction. Perhaps the strongest evidence for the role of the RAAS in heart failure, however, comes from studies in experimental animal models and in human patients demonstrating that interruption of this system will have favorable effects on the clinical course, including prolonged survival.

ACE inhibitors (ACEIs) have been a cornerstone of therapy for patients with LV dysfunction for nearly 2 decades. The benefits of ACEIs have been demonstrated in myocardial infarction (MI) survivors and in patients with LV dysfunction ranging from those who are asymptomatic to those with New York Heart Association functional class IV symptoms of heart failure. In these populations, the ACEIs have been shown to improve cardiac performance, relieve symptoms, decrease hospitalizations, and prolong survival. Many of the beneficial effects appear to be related to the ability of the ACEIs to inhibit further cardiac remodeling. What is not so clear, however, is the mechanism through which ACEI therapy leads to favorable changes in cardiac structure and function. In addition to blocking production of Ang II through the converting-enzyme pathway, ACEIs also block the breakdown of bradykinin. Bradykinin reduces vasomotor tone by enhancing the release of vasodilator substances from the vascular endothelium. It also has been shown to have anti-growth properties, which, at least in some animal experiments, accounts for the favorable effects of the ACEIs on cardiac remodeling. Although the relative importance of this property of the ACEIs is uncertain, it is certainly possible that it contributes to the clinical benefits of these agents.

In addition to ACEIs, there are alternative pharmacological approaches to blocking the RAAS. The type 1 Ang II (AT1) receptor is responsible for most of the known physiological and pathophysiological effects of Ang II, including vasoconstriction and promotion of cell growth. Selective blockers of this receptor are now available, and they might be expected to have many of the same effects as the ACEIs. Although less widely investigated (particularly in heart failure patients) than the ACEIs, the Ang II receptor blockers have been shown to have similar effects as the ACEIs in improving hemodynamic variables and cardiac function. There is limited and as yet incomplete evidence from clinical trials with Ang II receptor blockers assessing their effects on either surrogate end points such as ventricular structure and function or the “hard” end points of hospitalizations and mortality.

The pharmacological profile of AT1 receptor blockers, however, differs substantially from that of the ACEIs. The AT1 receptor blockers, for instance, do not have the same effects on bradykinin metabolism as do the ACEIs. Moreover, formation of Ang II can take place through alternative pathways as well as through the converting-enzyme route. This is particularly true in tissue in which proteases such as chymase may be responsible for the majority of Ang II production. Ang II that is generated through this alternative pathway, of course, would not be altered by the administration of an ACEI, but its effects would be prevented by an AT1 receptor blocker. There are also other effects of AT1 receptor blockers that may be beneficial. Administration of AT1 receptor blockers leads to an increase in circulating Ang II levels. Although interaction with the AT1 receptor is prevented, Ang II can then interact with other unblocked Ang II receptors. The best characterized of these is the type 2 Ang II (AT2) receptor. The expression of this receptor is regulated during the life cycle of the organism, and abundant reexpression may occur in certain pathological states. Although the consequences of activation of these receptors are only beginning to be understood, there is evidence that the AT2 receptor mediates antigrowth effects in some experimental settings. Thus, it is possible that shunting of Ang II from the AT1 to the AT2 receptor might represent another potential
benefit of the receptor blockers. In view of these pharmacological differences, the issue of whether the AT$_1$ receptor blockers will ultimately prove to be more, less, or equally effective compared with the ACEIs in improving the clinical course of patients remains unknown at this time. The pharmacological differences between the ACEIs and AT$_1$ receptor blockers, however, raise the intriguing possibility that combination therapy with both classes of drug could offer benefits beyond those seen with either of the agents alone. Theoretically at least, this approach would provide greater inhibition of Ang II activation of AT$_1$ receptor than with an ACEI alone while maintaining the beneficial effects of augmented bradykinin levels.

The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study reported in this issue of Circulation compares the effects of candesartan, enalapril, and their combination in a cohort of 768 patients with symptomatic heart failure due to LV systolic dysfunction. The goal was to compare the effects of the drugs and the combination of agents on exercise performance, ventricular function, quality of life, neurohormones, and tolerability. A secondary goal was to identify the optimal dose of candesartan for a larger proposed clinical trial. Although the study was neither designed nor powered to assess effects on morbidity and mortality, it was terminated prematurely after the External Safety and Efficacy Monitoring Committee voiced concerns about the increased number of events in the patients treated with candesartan. The impact of premature termination, however, was minimal, because the vast majority of patients had completed or were about to complete the study. The main findings were the absence of any appreciable difference between therapies in exercise performance, NYHA functional class, or quality of life. There was a trend toward a greater number of events in either the candesartan alone or combination groups compared with the enalapril-treated patients. For hospitalizations alone, the 3-way comparison was significant ($P=0.048$). Interestingly, the combination of candesartan and enalapril prevented increases in LV volumes that occurred with either of the drugs alone. Combination therapy also appeared to have favorable effects on the neurohormonal profile of these patients, with reductions seen in aldosterone levels (at 17 weeks of therapy) and in levels of brain natriuretic peptide.

What to conclude from these results? Probably not too much, because RESOLVD was a pilot study and not a full-scale clinical trial powered to detect changes in relevant clinical parameters with a high degree of confidence. In addition, the separation of patients into 6 treatment regimens for comparison, the effects of an additional randomization to metoprolol or placebo after 19 weeks of initial therapy, and the fact that multiple variables were analyzed in the report erode much of the confidence one might have in the ability of this study to determine the positive or negative effects of the Ang II receptor blocker, either alone or in combination with enalapril, in this population. Although the increase in the number of events is worrisome and should serve as a reminder of the possibility that the effects of the receptor blocker (either alone or in combination) may not be as favorable as those seen with an ACEI, it would be wrong to conclude that this is the case on the basis of the results of the RESOLVD pilot trial.

Perhaps the most intriguing aspect of these results is the effect of combination therapy with enalapril and candesartan on LV volumes. Whereas therapy with each individual drug was associated with increases in LV systolic and diastolic volumes during the course of the study, these changes were largely prevented by treatment with the combination of agents. The effects of combination therapy in reducing aldosterone levels at 17 weeks and in preventing the increases in brain natriuretic peptide that were seen with either of the therapies alone might be considered to be compatible with the volumetric data. If these results are correct, they would be consistent with the possibility that the use of combined therapy with an ACEI and an Ang II receptor blocker in patients with LV dysfunction more effectively inhibits progressive LV dilatation than does either class of drug alone. With the mortality and hospitalization data, however, it would be premature to draw such conclusions from the RESOLVD results because of the issues raised in this editorial discussion. In addition, these results were obtained while patients were still taking study medication. The combination of enalapril and candesartan had a significantly greater effect than either agent alone in reducing blood pressure. Thus, it is possible that the differences in LV volumes that were observed between the study groups might represent the acute unloading effects of combined therapy as opposed to an effect of therapy on the remodeling process.

It is also worth pointing out that the increases in LV volumes in the patients receiving enalapril alone in this report are different from those reported from representative subpopulations of previous clinical trials of enalapril and other ACEIs in patients with LV dysfunction.$^{10,11}$ Unlike the results of RESOLVD, which showed that LV volumes increased over time with ACEIs, reports from SOLVD (Studies Of Left Ventricular Dysfunction) and elsewhere provide information that ACEIs prevent increases in LV volume and mass over time. The reason for the differences between the RESOLVD and previous results is not certain, but differences in patient populations and relatively small sample sizes would appear to be a reasonable explanation. It is curious, however, that unlike previous studies that have shown that changes in ventricular volumes track along with improvements in the clinical course, the results of RESOLVD are somewhat discordant in this regard. Again, caution is advised in reading too much into this for the reasons outlined above. Currently, there are at least 2 large-scale, well-designed clinical trials assessing the effects of combination therapy with an ACEI and Ang II receptor blocker in heart failure and 1 additional trial comparing the therapies. The results of these trials should give more definitive answers regarding the comparison between ACEIs and Ang II receptor blockers and the value of combination therapy with the 2 agents.

RESOLVD is, however, a valuable addition to the literature because it shows that the combination of an ACEI and an Ang II receptor blocker was acceptable to most patients in that they were able to continue on this regimen for nearly a year. The possibility that the combination had more favorable effects on cardiac volumes than the individual therapies alone...
is an interesting hypothesis that deserves further attention. It also demonstrates that we may need to consider yet another reassessment of our concepts of the pathways through which RAAS activation leads to progressive LV dysfunction and the mechanisms by which various drugs interrupt this process.

References


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