**BRIEF REPORTS**

Addition of an Angiotensin II Receptor Blocker to Maximal Dose of ACE Inhibitors in Heart Failure

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In heart failure, the benefits of adding angiotensin-receptor blockade to ACE inhibitors have been studied only with submaximal doses of ACE inhibitors. We included 20 patients (LVEF 24 ± 7%, NYHA II-III), with no clinical or therapeutic variations in the previous three months, who were receiving maximal doses of ACE inhibitors. We added losartan 50 mg once a day. At six months, SBP decreased (115 ± 8 vs. 106 ± 9 mmHg; p = 0.001), LVEF increased (24.4 ± 7 vs. 34.1 ± 7%; p < 0.001), ventricular end-diastolic volumes decreased (220 ± 58 vs 190 ± 46 ml; p = 0.007), and SPAP decreased (43 ± 8 vs. 35 ± 7 mmHg; p < 0.001). Seven patients improved one degree on the NYHA scale (p = 0.004), but VO\(_{2}\max\) did not change (20.8 ± 5.2 vs. 21.8 ± 5.0 ml/kg/min; p = 0.120). Plasma levels of norepinephrine, at rest and maximal exercise, brain natriuretic peptide, and renin were similar. After maximum ACE inhibitor doses, the addition of losartan is safe and associated with an improvement in ventricular function and NYHA functional class, but with no change in neurohormonal status.

**Key words:** Heart failure. Angiotensin inhibitors. Angiotensin-converting enzyme inhibitors.

**Full English text available at:** www.revespcardiol.org

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**INTRODUCTION**

In patients with ventricular systolic dysfunction, whether symptomatic or asymptomatic, blockade of the renin-angiotensin system using angiotensin-converting enzyme inhibitors (ACEI) produces a significant clinical and prognostic benefit.\(^1\) Beyond ACE, the type 1 receptor seems to mediate the principal harmful effects of angiotensin II, which has led to the development of receptor antagonists (ARAII).\(^2\) ARAIIs have a more selective and potent blocking effect than ACEIs, since they antagonize angiotensin II generated by both ACE and alternative pathways.\(^3\) On the other hand, the blockade of bradykinin degradation and its subsequent accumulation are an exclusive effect of ACEIs that cause side effects, but also account for some of their benefits.\(^2,3\)

In heart failure, ARAIIs have not been shown to be superior to ACEIs, although they are equivalent and can be used as substitute therapy.\(^4\) Since their pharma-
The study included patients with left ventricular (LV) systolic dysfunction (ejection fraction [EF] <40%) who were symptomatic (NYHA II-III), stable (no hospital admissions, congestive decompensation, or therapeutic changes in the previous 3 months), and receiving maximum doses of an ACEI (defined as the maximum therapeutic dose for the active principle). All patients were informed about and consented to the intervention. A valvular cause was excluded in preparation for heart transplantation by plasma creatinine >1.5 mg/dl, without the development of symptoms requiring discontinuation of the drug. There were no significant elevations in serum potassium (4.2±0.34 versus 4.4±0.3 mEq/dL; P=NS) or plasma creatinine (1.12±0.16 versus 1.15±0.15 mg/dl; P=NS).

A significant improvement in the echocardiographic parameters of left ventricular systolic function was demonstrated (Table 2), with an increase in the EF (by a mean of 9.7%) and a reduction in ventricular dimensions. Likewise, a significant decrease in the systolic pressure of the pulmonary artery was appreciated (PASP), but the improvement in the degree of mitral insufficiency did not reach statistical significance (Table 2).

A total of 7 patients reported an improvement in NYHA functional class (P=0.008), 3 passed from grade...
II to grade I and 4 passed from grade III to grade II (Table 3). Nevertheless, the increase in VO$_{2\text{max}}$ (1 mL/kg/min) in the stress test did not reach statistical significance. The anaerobic threshold, functional capacity, and double product were similar at baseline and 6 months (Table 3). Neurohormone values at rest did not change significantly and noradrenaline response to maximum effort did not change (Table 3).

**DISCUSSION**

This prospective study shows that in patients with heart failure due to systolic dysfunction who are stable with optimized treatment with maximum doses of ACEI, the ARAII losartan can be administered safely and is associated with a significant improvement in ventricular function and functional class.

In our population all the patients received the maximum dose of ACEI, unlike earlier published studies in which the mean doses administered were either in an intermediate range or were the maximum tolerated by the patient. In any case, the dose given was lower than the maximum possible ACEI dose used. The present study extends the safety range of the association of ACEI and ARAII to include patients who are receiving maximum ACEI doses. Administration of the combination is followed by a greater decrease in blood pressure than with each drug separately, which in our population was 9 mm Hg for SBP, similar to that reported in other studies.

The most noteworthy finding of this study was an improvement in the echocardiographic parameters of systolic function, mainly at the expense of an increase in the EF, but also due to a reduction in ventricular dimensions. Other studies have reported similar findings with intermediate doses of captopril combined with losartan or enalapril with candesartan. The decrease in PASP supports the existence of an additional improvement in the hemodynamic profile of these patients. In fact, a significant hemodynamic improvement has been described after both acute and chronic administration of an ARAII to patients receiving an ACEI, with an important reduction in ventricular postload. Our study supports this hypothesis. However, although this reduction in load conditions could explain the improvement in ventricular systolic function, an effect on cardiac remodeling and function, as has been observed in experimental studies, cannot be excluded.
The patients also showed improvement in their symptoms in terms of NYHA functional class, as reported in other studies. Nevertheless, the increase in VO_{2\text{max}} in the stress test (1 ml/kg/min) was not statistically significant. Earlier, Hamroff at al^{15} observed a significant increase in VO_{2\text{max}} (2.2 ml/kg/min) with losartan and ACEI versus placebo and ACEI, but in this study most patients received submaximal doses of ACEI. Similarly, Guazzi et al^{12} also found a significant increment in VO_{2\text{max}} when they added intermediate doses of losartan to enalapril. Therefore, although the association of losartan improves the capacity for exercise according to these studies, the benefit decreases with the greater ACEI dose that the patient is receiving, as shown by our study.

Previous studies with intermediate doses of ACEI have shown that the addition of an ARAII produces more neurohormonal suppression and a reduction in the concentrations of aldosterone, natriuretic cathecolamines, and peptides, and an increase in plasma renin. In our study, maximal ACEI doses were given and the association of ARAII did not produce any additional block in the neurohormonal state. In support of our findings, Bertram et al^{16} found that the suppression of the renin-angiotensin-aldosterone system achieved was similar with the addition of 50 mg of losartan to treatment with enalapril 20 mg or with an increase in the dose of enalapril from 20 mg to 40 mg. In heart failure, in which the sympathetic response to peak exercise is enhanced, ACEIs have been shown to dampen this response. Previously, no study has evaluated this effect of ARAII. In our study, the addition of losartan did not influence the sympathetic response to maximum effort. The discrepancy between the improvement in ventricular function and the absence of changes in neurohormone concentrations may mean that the effect of ARAII in these patients was only hemodynamic, not due to a more effective neurohormonal block. Since the clinical deterioration in heart failure correlated with the degree of neurohormonal activation, the fact that the addition of ARAII did not produce a further blockade in neurohormonal activation may indicate the absence of an effect on the evolution and prognosis of the heart disease.

The findings of our study suggest that when maximal doses of ACEI are used, the addition of an ARAII is associated with significant hemodynamic and symptomatic improvement, but its effect on prognosis is dubious since the objective parameters of functional capacity and neurohormonal activation were not affected. This discrepancy is consistent with the results communicated in the Val-Heft study,^{20} which reported symptomatic improvement with a reduction in hospitalization, but no greater survival with the combination of valsartan and ACEI with respect to placebo and ACEI.

Limitations

The sample size and variability of some neurohormonal parameters could have limited the statistical power of the study. In addition, the absence of a control group does not allow cause-effect relations to be established. Our study used the maximum doses established for each active principle, but it is possible that the true maximum doses are those that produce effective ACE block, which was not assessed because plasma ACE activity was not measured. This investigation examined the results at 6 months with losartan 50 mg, so we cannot draw conclusions as to the effects of more prolonged administration or higher doses of ARAII.

Conclusion

In patients with stable heart failure who received maximum doses of ACEI, the addition of the ARAII losartan was well tolerated and associated with an improvement in ventricular function and functional class, but there were no changes in the degree of neurohormonal activation.

REFERENCES


