

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 $24 \pm 7\%$, 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. $34.1 \pm 7\%$; $p < 0.001$), 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_{2max} 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.

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Adición de un ARAII al tratamiento con dosis máximas de IECA en la insuficiencia cardíaca

En la insuficiencia cardíaca, el beneficio de la combinación ARAII e inhibidores de la enzima convertidora de la angiotensina (IECA) ha sido estudiado sólo con dosis submáximas del IECA. Incluimos a 20 pacientes (FEVI $24 \pm 7\%$, NYHA II-III), sin cambios clínicos ni terapéuticos en los 3 meses previos, que recibían dosis máximas del IECA, y asociamos 50 mg/día de losartán. A los 6 meses, la presión arterial sistólica descendió (115 ± 8 frente a 106 ± 9 mmHg; $p = 0.001$), la FEVI aumentó ($24,4 \pm 7$ frente a $34,1 \pm 7\%$; $p < 0.001$), los volúmenes diastólicos (220 ± 58 frente a 190 ± 46 ml; $p = 0.007$) y sistólicos (164 ± 49 frente a 125 ± 38 ml; $p = 0.001$) disminuyeron y la PSAP descendió (43 ± 8 frente a 35 ± 7 mmHg; $p < 0.001$). Siete pacientes mejoraron un grado NYHA ($p = 0.008$), sin mejoría significativa del VO_{2max} ($20,8 \pm 5,2$ frente a $21,8 \pm 5,0$ ml/kg/min; $p = 0,120$). Las concentraciones de noradrenalina en reposo y en el momento de máximo esfuerzo, así como del péptido natriurético cerebral y de la renina, fueron similares. Con dosis máximas del IECA, la adición del ARAII fue segura, asociándose a una mejora de la función ventricular y la clase funcional, pero sin cambios en el estado neurohormonal.

Palabras clave: Insuficiencia cardíaca. Inhibidores de la angiotensina. Inhibidores de la enzima convertidora.

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.² 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-

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ABBREVIATIONS

ACEI: angiotensin-converting enzyme inhibitor.
 ARAII: angiotensin II type 1 receptor antagonist.
 NYHA: New York Heart Association functional class.
 VO_{2max} : maximum oxygen consumption.
 SBP: systolic blood pressure.
 PASP: pulmonary artery systolic pressure.

cological mechanisms are complementary, the possibility of combining both drugs has drawn attention. Experimental and clinical studies have disclosed benefits on exercise, heart function, hemodynamic, and neurohormonal parameters from a combination of both agents as opposed to either drug alone.⁵⁻¹² Nevertheless, in all these studies, the mean dose of ACEI administered was clearly lower than the therapeutic maximum dose of the active principle, which is the dose associated with the greatest clinical, functional, and neurohormonal benefit.^{13,14} Therefore, any conclusions regarding additional benefits to be obtained by using ARAII in patients receiving ACEI must be contrasted with the effects of maximum doses of ACEI.

The objective of this investigation was to study the possible relation between the addition of the ARAII losartan and improvement in echocardiographic and neurohormonal parameters, and the exercise capacity of patients with stable heart failure receiving the maximum dose of an ACEI.

PATIENTS AND METHOD

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, as well as functional limitations due to non-cardiac disease. The patients received 50 mg/day losartan in a single dose from onset. The appearance of K^+ >6 mEq/dL, creatinine >2 mg/dL, or symptomatic hypotension (systolic blood pressure [SBP]<90 mm Hg with attributable symptoms) were criteria for discontinuing the drug.

Before initiating ARAII administration, an echocar-

diographic study (Sonos 5500, Hewlett Packard, MA, U.S.), stress test with measurement of gas exchange (CPX Express, MedGraphics, St. Paul, MN, U.S.), and plasma neurohormone determinations were made by persons who did not know the patient's identity. Baseline samples were extracted from a vein catheterized before the stress test, in fasting conditions after 30 min of rest, and at the point of maximum noradrenaline stress. Noradrenaline samples were stored at -80°C and processed together by high-performance liquid chromatography with electrochemical detection (ESA Inc., Bedford, U.S.). Samples of total renin (Nichols Institute Diagnostics, California, U.S.) and brain natriuretic peptide (Shionogi and Co., Ltd., Osaka, Japan) were stored at -20 °C and processed by radioimmunoanalysis.

After 6 months of combined treatment, the same tests and determinations were repeated, which were interpreted with the baseline results by a person who did not know the patient's identity. In addition, every week during the first month and every month up to 6 months, an outpatient visit was scheduled that included an interview, physical examination, electrocardiogram, and basic biochemistry.

The values obtained at baseline and after 6 months of treatment were compared by means of the Student t test for paired data in the case of the quantitative variables, and by the non-parametric Wilcoxon test for the qualitative variable NYHA functional class. A value of $P<.05$ was accepted as statistically significant. The statistical analysis was made with the SPSS computer application (version 7.5, SPSS, Inc).

RESULTS

The 20 patients received maximum doses of ACEI, almost half of which were taking beta-blockers, and most of which took digitalis and furosemide (Table 1). All of them tolerated the introduction of losartan 50 mg without significant side effects. SBP descended significantly (from 115 ± 8 to 106 ± 9 mm Hg; $P=.001$), 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 ($P=.008$), 3 passed from grade

TABLE 1. Baseline characteristics

Patients	20
Age, years	52±9 (39-67)
Male sex	15 (75)
Etiology	
Idiopathic	15 (75)
Ischemic	5 (15)
NYHA	
II	12 (60)
III	8 (40)
Treatment	
ACEI	20 (100)
Ramipril, 5 mg/12 h	11 (55)
Enalapril, 20 mg/12 h	5 (25)
Fosinopril, 20 mg/12 h	4 (20)
Beta-blockers	9 (45)
Digitalis	15 (75)
Furosemide	19 (95)
LVEF, %	24.4±7.3
VO _{2max} , mL/kg/min	20.8±5.2
Sinus rhythm/atrial fibrillation	16 (80)/4 (20)
SBP, mm Hg	116±8

LVEF indicates left ventricular ejection fraction; ACEI, angiotensin II converting enzyme inhibitor; NYHA, New York Heart Association functional class; SBP, systolic blood pressure; VO_{2max}, maximum oxygen consumption. Data are expressed as number (%). Age, LVEF, VO_{2max}, and BP are expressed as mean±standard deviation.

II to grade I and 4 passed from grade III to grade II (Table 3). Nevertheless, the increase in VO_{2max} (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.⁵⁻¹² 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,¹⁵ which in our population was 9 mm Hg for SBP, similar to that re-

TABLE 2. Echocardiographic parameters

	Baseline	6 months	P
LVEF, %	24.4±7.3	34.1±7.6	<.001
EDV, ml	220±58	190±46	.007
ESV, ml	164±49	125±38	.001
EDD, mm	68.9±9.9	65.7±3+9.6	.048
ESD, mm	58.9±10.1	54.9±9.9	.005
MI	1.2±0.97	1.0±0.86	.163
PASP, mm Hg*	42.9±7.5	34.7±7.4	<.001

*Evaluated in 12 patients. EDD indicates: end-diastolic diameter; ESD, end-systolic diameter; LVEF, left ventricular ejection fraction; MI, mitral insufficiency; PASP, pulmonary artery systolic pressure; EDV, end-diastolic volume; ESV, end-systolic volume. Values expressed as mean±standard deviation.

TABLE 3. Functional and neurohormonal parameters

	Baseline	6 months	P
NYHA			.008
I	0	3 (14)	
II	12 (60)	13 (66)	
III	8 (40)	4 (20)	
VO _{2max} , mL/kg/min	20.8±5.2	21.8±5.0	.120
AT, %	43.7±10	45.0±8.5	.621
FC, %	64.0±18	66.1±16	.415
HR _{max} × BP _{max}	25 293±35 649	26 730±6231	.716
NAO, pg/mL	768±484	709±289	.624
NAS, pg/mL	1775±289	1889±320	.828
ΔANA0-S, pg/mL	945±240	1011±274	.888
BNP, pg/mL	45.6±16	40.5±34	.471
TR, μU/mL	483±394	565±529	.230

NYHA indicates New York Heart Association functional class is expressed as the number of patients (%), the other parameters are expressed as mean±standard deviation; FC, functional capacity; HR_{max}×BP_{max}, double product; AT, anaerobic threshold; VO_{2max}, maximum oxygen consumption; BNP, brain natriuretic peptide; NA₀, plasma noradrenaline at rest; NA_s, plasma noradrenaline at maximum effort; TR, total renin.

ported in other studies.⁸

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 losartan¹⁰ or enalapril with candesartán.¹¹ 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.^{5,7,8} 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.^{5,6}

The patients also showed improvement in their symptoms in terms of NYHA functional class, as reported in other studies.⁹ Nevertheless, the increase in VO_{2max} in the stress test (1 ml/kg/min) was not statistically significant. Earlier, Hamroff et al¹⁵ observed a significant increase in VO_{2max} (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 al¹² also found a significant increment in VO_{2max} 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 catecholamines, and peptides, and an increase in plasma renin.^{7,11,12} 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 al¹⁶ 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.¹⁷ 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,^{18,19} 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.

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