

Effect of Angiotensin Blockade on the Orthostatic Response in Patients with Systemic Arterial Hypertension

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Introduction and objectives. The effect of the treatment of arterial hypertension with angiotensin inhibitors on the autonomic response to orthostatism was studied.

Patients and method. In 20 hypertensive patients, enalapril (10 to 20 mg) was administered daily for four weeks. Then, irbesartan (150 to 300 mg) was given for four weeks. Finally, 10 mg of enalapril combined with 150 mg of irbesartan was prescribed for another four weeks. Heart rate variability at rest and during the head-up tilt test with controlled respiration was assessed at the beginning and end of each period.

Results. Mean arterial pressure showed a similar reduction in the three treatment periods. There were no changes in heart rate. Heart rate variability at rest showed differences in the spectral high-frequency component between the control and the treatment periods ($p = 0.10$). There was an increase in the high-frequency component between the control and the third ($p = 0.047$) and the fourth periods ($p = 0.03$). In the head-up tilt test there was a decrease in total spectral high-frequency power.

Conclusions. There was no increase in orthostatic intolerance with these drugs in hypertensive patients. The absence of changes in heart rate in spite of a decrease in blood pressure suggests resetting of the baroreflex function. The long-term control of hypertension with these drugs may have a favorable effect on heart rate variability, with an increase in parasympathetic activity.

Key words: *Orthostatic response. Systemic arterial hypertension. Angiotensin inhibition.*

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Efecto de la inhibición de la acción de la angiotensina sobre la respuesta al ortostatismo en pacientes con hipertensión arterial sistémica

Introducción y objetivos. El presente trabajo se llevó a cabo para estudiar el efecto del control de la presión arterial por inhibición de angiotensina en la respuesta autonómica al ortostatismo en pacientes hipertensos.

Pacientes y método. En 20 pacientes hipertensos se administró enalapril, 10 o 20 mg diarios, durante 4 semanas. Después se usó irbesartán, 150 o 300 mg, durante otras 4 semanas. Finalmente, se prescribieron 10 mg de enalapril y 150 de irbesartán durante otras 4 semanas. Al principio y al final de cada etapa se midió la variabilidad de la frecuencia cardíaca en reposo y en ortostatismo pasivo con mesa basculante con respiración controlada.

Resultados. La presión arterial media disminuyó de manera similar en las 3 etapas. No se observaron cambios significativos en la frecuencia cardíaca. La variabilidad de la frecuencia cardíaca en reposo reveló diferencias en potencia espectral del componente de frecuencias altas sin tratamiento, comparada con los períodos con tratamiento ($p = 0,10$). El componente de alta frecuencia aumentó entre el primero, tercero ($p = 0,047$) y el cuarto períodos ($p = 0,03$). En la prueba de inclinación, la densidad de potencia espectral total disminuyó el componente de alta frecuencia.

Conclusiones. No se observó un incremento de la intolerancia ortostática de los pacientes con los fármacos utilizados. El hecho de que la frecuencia cardíaca no se modificara pese a la disminución de la presión sugiere un reajuste de la función barorrefleja. El control sostenido de las cifras de presión en pacientes hipertensos con estos fármacos puede tener un efecto favorable en la variabilidad de la frecuencia cardíaca, con un aumento de la actividad parasimpática.

Palabras clave: *Respuesta ortostática. Hipertensión arterial sistémica. Inhibición de la angiotensina.*

INTRODUCTION

In spite of the benefits of hypertensive treatment for cardiovascular and renal complications, the majority of clinical trials have not shown a significant reduction in morbidity and mortality of cardiac origin in patients

with systemic arterial hypertension.¹ Various studies that have used the cardiac frequency variability²⁻⁴ and measurement of baroreflex activity^{5,6} to evaluate autonomous modulation of the heart have shown diminished vagal cardiac activity in patients with arterial hypertension.

Vasodilator antihypertensive medications, by reducing arterial pressure, activate a series of mechanisms mediated by the autonomous nervous system (ANS). There are few published studies on the effects of hypertensive medications on autonomous nervous system function in the hypertensive heart. Adrenergic beta-blockers increase tonic and reflexive vagal cardiac activity.⁷ The effects of calcium antagonists are heterogeneous, and depend on the class of pharmacological agent used and the way it is administered. Nifedipine increases sympathetic activity and reduces vagal activity.⁸ Verapamil, diltiazem, and amlodipine decrease sympathetic activity without modifying vagal activity.⁹

Recently, Guastí et al,¹⁰ in a study carried out on hypertensive patients at rest, did not find a modulating effect of the rennin-angiotensin system on the autonomous control of arterial pressure. Our study was designed to ascertain whether treatment of arterial hypertension via inhibition of angiotensin influences the response of the ANS on orthostasis. To inhibit angiotensin action we used an angiotensin-converting enzyme inhibitor (ACEI), an angiotensin II AT₁ receptor blocker, and a combination of both. The study was not designed to compare the different pharmaceutical agents, as was the study by Guastí et al,¹⁰ but to study the effect of the inhibition of angiotensin on the autonomous control of the cardiovascular apparatus.

PATIENTS AND METHOD

The study protocol was approved by our bioethics committee and the patients signed an informed consent form. The study was performed on 20 patients (13 women, 7 men) with system arterial hypertension between the ages of 30 and 70 years (mean age 57.3 years±9.55 years) recruited from outpatient clinics of the Instituto Nacional de Cardiología Ignacio Chávez (Ignacio Chavez National Institute of Cardiology). The diagnosis of systemic arterial hypertension was established in accordance with the 6th report of the Joint National Committee for the prevention, detection, evaluation, and treatment of elevated arterial pressure in the United States of America.¹¹

We excluded from the study patients with lesions in the target organs with functional changes (the brain, heart, or kidney), as well as those patients who presented with secondary hypertension, diabetes mellitus, thyroid dysfunction, or who were taking medications acting on the ANS, digitalis, diuretics, anti-arrhythmia agents, steroids, or cimetidine. On the patients recrui-

ted, we obtained a complete clinical history, ECG and chest X-ray in the AP and oblique positions, blood cytology, general urine analysis and glucose, urea and blood creatinine testing; all studies were normal or negative. All patients were in sinus rhythm.

Arterial pressure was obtained by the sphygmomanometer method 3 times, with the patient seated and the humeral artery in the thoracic location of the heart. We used as the final arterial pressure the average of the 3 pressure readings taken. All the readings, in all patients, were performed by the same observer.

After a one-week drug washout the patients were given 10 mg of enalapril. One week later the patients were reevaluated: if the average arterial pressure had decreased 10 mm Hg or more the same drug dose was maintained, and if the reduction was less than 10 mmHg the dose was increased to 20 mg for 4 weeks. After another one-week washout we administered 150 mg of irbesartan per day, and the same dose was continued if at the end of one week the average arterial pressure decreased by 10 mm Hg; if the reduction was less than 10 mm Hg, we increased the dose to 300 mg for 4 weeks. In the final phase, after another week of washout, the patient received 10 mg of enalapril and 150 mg of irbesartan for 4 weeks. The exact amount of drugs per the dosage regimen were given to the patient at each visit, with instructions to return any medication not taken in order to assure that the medication regimen was adequately followed. A washout period of one week was occurred between each treatment regimen, taking into account that the effective half-life of enalapril is 11 hours and of irbesartan is 11 to 15 hours.

The final office consult in each time period was scheduled to occur between the hours of 9:00 and 10:00 a.m., after a 12-hour fast; the patients abstained from imbibing alcoholic beverages 48 hours prior to the consult and caffeine 12 hours prior to the consult.

At the beginning of the study and at the end of each stage of treatment we measured the cardiac frequency variability in repose and in passive orthostasis. In an environment with a stable temperature (24 to 25°C) and dim light, after 20 minutes of repose in the supine decubitus position, we instructed the patient to breathe at a frequency of 12 respirations per minute, guided by a metronome audiocassette recording. The patient remained in repose with controlled respiration another 5 minutes, and then while continuing controlled respiration, undergoing passive inclination on a tilt-table inclined to 70° for 30 minutes or until a positive response was elicited. The patients were instructed not to talk and to keep their eyes closed during the tests. We measured arterial pressure with a sphygmomanometer at one-minute intervals. The tilt test was considered positive when the decrease in systolic arterial pressure (SAP) was greater than 30 mm Hg, the absolute systolic number was less than 90 mm Hg, bradycardia was

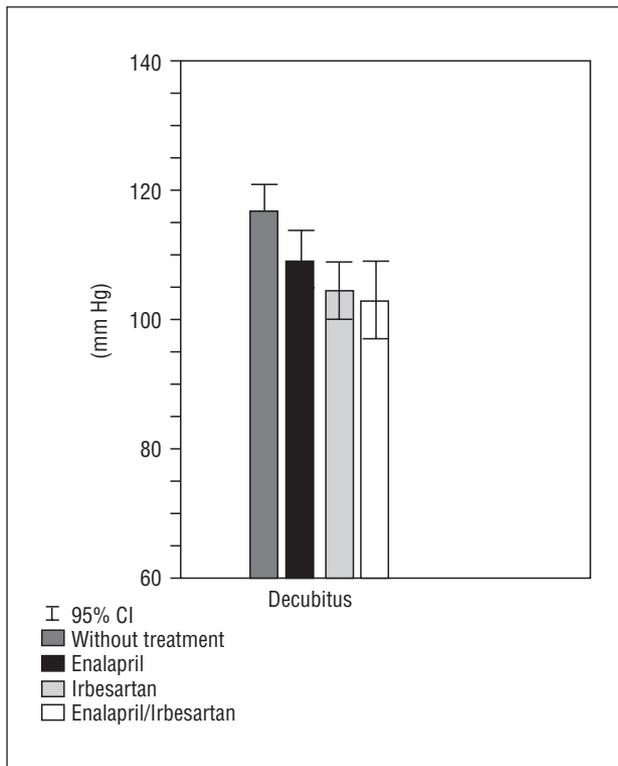


Fig. 1. Mean and confidence interval of the average arterial pressure of patients studied in the decubitus position and at the end of each treatment period.

less than 50 beats/minute, or we observed a decrease to numbers lower than baseline, or both.^{12,13}

The electrocardiographic signal was measured continuously via a commercial 2-channel Holter system (Medilog Oxford V7, London, UK). The signal was digitized. After visual review of the ECG, the R-R intervals were calculated during 5-minute periods. R-R interval variability was analyzed in the frequency domain via Fourier rapid transform with 2 Hz resampling. The spectral potency was calculated for frequency bands: total 0.04 to 0.4 Hz, low frequencies of 0.04 to 0.15 Hz, and high frequencies of 0.15 to 0.4

Hz. We calculated the ratio of low frequencies to high frequencies (LF to HF).

The high frequency band reflects vagal cardiac activity related to respiration¹⁴ and the low frequency band is considered an indication of sympathetic and vagal modulation.¹⁵ The values obtained were converted to their natural algorithms by not having a normal distribution pattern.

Statistical analysis of the measurements of arterial pressure and cardiac frequency were performed using variance analysis. The analysis of the measurements of cardiac frequency variability were performed after logarithmic transform, with the Friedman test and the Wilcoxon test, with a significant value being $P=.05$.

RESULTS

Measurement at rest

The decubitus arterial pressure before beginning the study was $162 \text{ mm Hg} \pm 15.8 \text{ mm Hg}$ systolic arterial pressure (SAP) and $101 \text{ Hg} \pm 9.2 \text{ mm Hg}$ diastolic arterial pressure (DAP), with a mean pressure of $121 \text{ mm Hg} \pm 9.8 \text{ mm Hg}$.

The effect of the pharmaceutical agents, on both SAP and DAP, in decubitus was similar at the end of the three treatment periods (Figure 1). The decrease in mean arterial pressure with the administration of enalapril was $10 \text{ mm Hg} \pm 9.5 \text{ mm Hg}$ and $11 \text{ mm Hg} \pm 12 \text{ mm Hg}$ with irbesartan. When combined treatment was administered, the average decrease in arterial pressure was $14 \text{ mm Hg} \pm 11.5 \text{ mm Hg}$. In all patients we obtained a hypotensive response of a similar magnitude. Although the arterial pressure decreased, we did not observe significant changes in cardiac frequency (Figure 2).

Analysis of cardiac frequency variability at rest showed a tendency toward an increase in the density of the spectral power of high frequencies in the three stages of treatment (Table 1); ($P=.10$, Friedman). On comparison of each of the treatment stages with res-

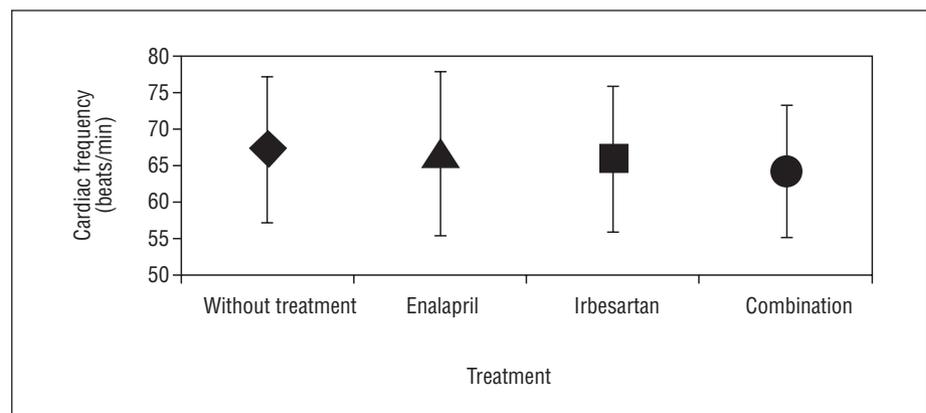


Fig. 2. Mean and standard deviation of cardiac frequency at rest during the four stages of the study.

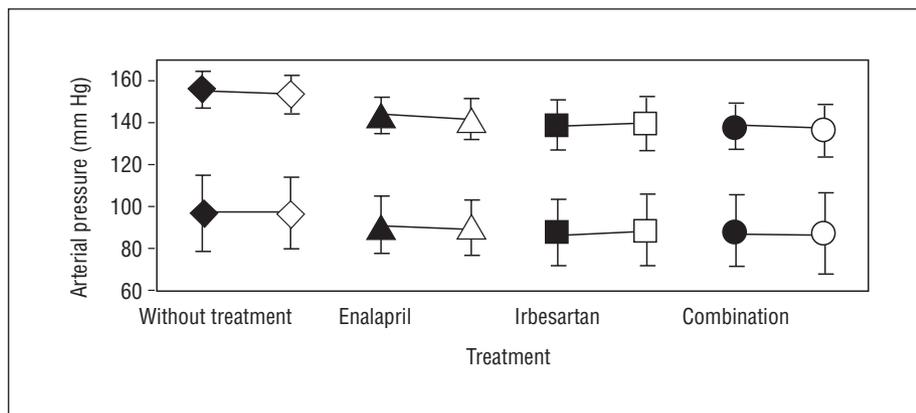


Fig. 3. Mean and standard deviation of the systolic and diastolic arterial pressure at rest, in the dorsal decubitus position (e), and during the first minute of total body passive tilt (e) in the four stages of the study.

pect to the stage without treatment, we identified a significant increase in the high frequency component both in the third stage with irbesartan treatment alone ($P=.047$, Wilcoxon) and in the fourth stage with combined treatment ($P=.03$, Wilcoxon) (Table 1).

Tilt test

We did not observe a positive response to the tilt test at any treatment stage, and there were no significant changes in arterial pressure or cardiac frequency during the first minute of the test (Figures 3 and 4).

Nevertheless, there was an additional finding that did not alter the final result of the test upon comparison of the results of the tilt test without treatment with the tests performed at the end of each stage of the study. During the three last measurements, the density of total spectral power had a tendency to diminish, principally due to the decrease in the low frequency component with an increase in the LF to HF ratio (Table 2).

DISCUSSION

Angiotensin II activates both the central nervous system and the peripheral sympathetic nervous sys-

tem, and is an important regulator of noradrenalin liberation in the sympathetic nerve endings. Therefore, it modulates cardiac and sympathetic vascular activity.¹⁶

Angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers are the medications that are considered to be effective antihypertensive agents.¹⁷⁻¹⁹ It has been demonstrated that despite long-term use of ACEI, plasma concentrations of active angiotensin persist, and when an angiotensin receptor blocker is added, the hemodynamic effects of the ACEI blocker are increased.²⁰

In patients of advanced age, the prevalence of orthostatic hypotension varies from 13% to 30%. The diagnosis most frequently associated with this is systemic arterial hypertension, which can contribute to an increase in the mortality rate for high-risk patients.²¹ In the group of patients we studied we did not find an increase in orthostatic intolerance despite the vasodilator effect of the pharmaceutical agents used.

The 70° tilt table test was negative for all patients in all the stages of the study. This test is based on the fact that upon adopting the bipedal stance there is an accumulation of venous blood in the legs due to the gravitational effect, with a consequent decrease in the

TABLE 1. Cardiac frequency variability in the spectral frequency domain during 5 minutes at rest in the decubitus supine position

Measurement	Without treatment	Enalapril	Irbesartan	Enalapril/irbesartan
	Average 25th-75th percentiles	Average 25th-75th percentiles	Average 25th-75th percentiles	Average 25th-75th percentiles
Low frequencies (0.04-0.15 Hz)	284 121-514	334 154-602	452 305-680	384 224-940
High frequencies (0.15-0.4 Hz)	164 63-480	175 86-476	256* 96-647	511* 68-867
Total band (0.04-0.4 Hz)	448 301-1044	612 245-1117	927 434-1168	1127 325-1706
LF:HF	1.65 0.65-4.5	1.85 1-3.85	1.7 0.9-3.25	1.5 0.8-2.45

* ≤ 0.05 Wilcoxon test.

LF indicates low frequencies; HF, high frequencies.

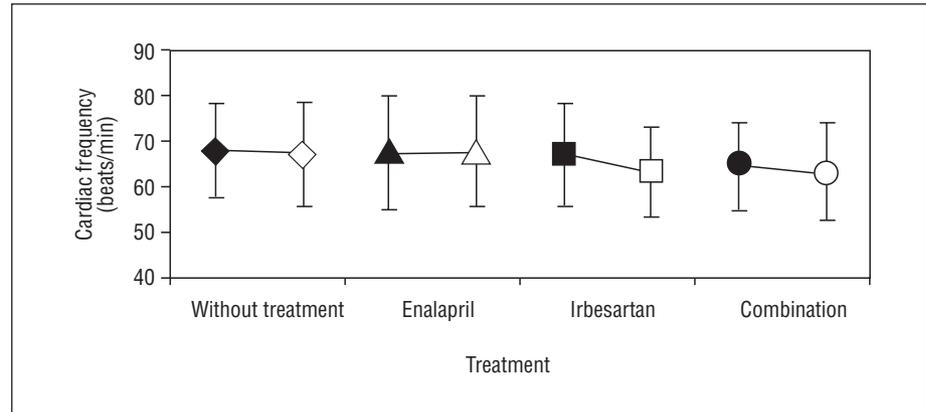


Fig. 4. Mean and standard deviation of cardiac frequency at rest, in the dorsal decubitus position (◊), and during the first minute of total body passive tilt (◊) in the four stages of the study.

venous return, triggering a Bezold-Jarisch effect. Myocardial contraction in a small volume cavity stimulates the C-receptor fibers of the myocardium which, in turn, produces an intense vagal reflex with arterial hypotension and a decrease in cerebral blood flow.^{12,13}

The fact that the cardiac frequency is not altered despite the decrease in arterial pressure during the observation period suggests that during inhibition of angiotensin effects a readjustment of the baroreflex function is produced. These findings are similar to those described by Guastí et al¹⁰ in a comparative study of the effects of enalapril and losartan. In the same study, the investigators did not identify differences in the effects of these drugs on cardiac frequency variability at rest.

Our study was not designed to compare drugs, as was the study by Guastí et al,¹⁰ but to identify whether or not the vasodilator effect of the drugs could interfere with cardiovascular control of orthostasis.

In the patients studied we found that sustained long-term control of arterial pressure numbers in the hypertensive patient could have a favorable effect on car-

diac frequency variability. After two months of treatment, spectral power in the high frequency band began to increase; this increase continued throughout the rest of the study.

This observation shows that, apart from the long-term control of arterial hypertension, use of these drugs also increases parasympathetic activity.

The variability of R-R intervals is the result of many different factors that are individual as well as environmental in nature. Their study is useful for evaluating the autonomous modulation of the heart, both in the frequency domain as well as in the time domain.^{22,23} When spectral techniques are used for the analysis of recorded short stable periods, the relative power of the different variation frequencies of the R-R intervals can be identified. The high frequency component, approximately 0.25 Hz, has been related to respiration and efferent vagal activity.²⁴⁻²⁶ The low frequency component, approximately 0.1 Hz, has been related to neurohumoral factors, the baroreceptor reflex, parasympathetic influence, and to central control mechanisms.^{21,27} As far as very low frequency oscillations are concerned, the evidence suggests that they principally

TABLE 2. Change in cardiac frequency variability in the frequency domain during the first 5 minutes of passive tilt as compared to measurements in the decubitus position

Measurement	Without treatment	Enalapril	Irbesartan	Enalapril/irbesartan
	Average 25th-75th percentiles	Average 25th-75th percentiles	Average 25th-75th percentiles	Average 25th-75th percentiles
Low frequencies (0.04-0.15 Hz)	-28 -145 to 52	-144 -237 to 66	-128 -484 to 69	-63 -276 to 12
High frequencies (0.15-0.4 Hz)	-24 -352 to 3	-29 -229 to 16	-79 -231 to 9	-107 -533 to -10
Total band (0.04-0.4 Hz)	-45 -468 to 29	-213 -573 to 73	-278 -799 to 112	-164 -727 to -2.8
LF:HF ratio	0.3 -0.4 to 2.35	-0.15 -1.7 to 1.4	0.05 -0.6 to 1.35	0.2 -0.4 to 3.5

LF indicates low frequencies; HF, high frequencies

depend on parasympathetic activity.²⁸ Nevertheless, for the interpretation of R-R interval variability is necessary to consider the study conditions and the respiration characteristics. The appropriate reproducibility of measurements is only achieved when the recording is performed with controlled respiration,²⁶ as was the case in our study.

The results obtained show that the inhibition of angiotensin action, despite its hypotensive effect via vasodilatation, does not change the neurohumoral and cardiac responses to orthostasis,²⁹ and can be used with increasing the risk of orthostatic hypertension in high-risk patients.

We did not find an increase in orthostatic intolerance in our patients with the use of the pharmaceutical agents we administered. The fact that the cardiac frequency was unchanged despite the decrease in arterial pressure suggests a readjustment of the baroreflex function.

The sustained control of arterial pressure numbers in hypertensive patients with these drugs may have a favorable effect on cardiac frequency variability, with an increase in parasympathetic activity.

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