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Paper

BNP and ANP as diagnostic and predictive markers in heart failure with left ventricular systolic dysfunction

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Abstract

Background

The prevalence of chronic heart failure (CHF) with systolic dysfunction is increasing. Plasma natriuretic peptides have been envisaged as diagnostic and predictive markers.

Aims

To investigate the relationship between the levels of B-type natriuretic peptide (BNP) and A-type natriuretic peptide (ANP) and the clinical and functional parameters of CHF in outpatients with CHF at baseline, compared with normal healthy controls; to find out the differences in a randomised controlled trial between patients treated with an angiotensin-converting enzyme (ACE) inhibitor, captopril, or an angiotensin receptor blocker (ARB), irbesartan. These differences were assessed throughout the six-month treatment period and at the sixth month.

Methods

Plasma BNP (pmol/L) and ANP (pmol/L) were determined in 68 hypertensive patients with dilated cardiomyopathy, NYHA class III–IV and ejection fraction (EF) ≤40%, and in 26 normal controls. Statistical analysis for BNP and ANP was done by Student's *t*-test. The patient group was randomly subdivided into two subgroups of 34 patients, each treated with either an ARB, irbesartan, or an ACE inhibitor (ACE I), captopril. BNP and ANP were measured in both subsamples and correlated with clinical, functional and neurohormonal parameters throughout a follow-up period of six months and at the sixth month.

Results

The mean EF in the patient sample was 33.43±6.52% and in the controls was 61.96 ±3.53% (p=0.000). The mean BNP (pmol/L) in patients was 44.78±54.36 and in the controls was 7.12±8.28 (p=0.000) and the mean ANP (pmol/L) was 30.32±25.97 in patients and 11.18±7.92 in controls (p=0.000). A statistically significant difference was found between patients and healthy controls. Significant correlations were found between natriuretic peptides and EF. Between the baseline phase and the sixth month, BNP and ANP decreased significantly in the ARB group. At the sixth month, both BNP and ANP were lower in the ARB group. Evidence of clinical benefit was found with both ARB or ACE-I treatment throughout the six months, with patients moving from classes III and IV to class II NYHA. Improvement of EF was also found, with transition of patients with lower EF (even <30%) to higher values. EF was higher in the ARB group at the sixth month.

Conclusions

BNP and ANP can be useful diagnostic tools in hypertensive CHF patients with moderate-to-severe LV dysfunction. The decrease in BNP and ANP in the ARB group throughout six months, as well as the lower value at the sixth month, suggest a prognostic value of these parameters.

Introduction

The prevalence of chronic heart failure (CHF) is increasing worldwide. Previous studies have stressed the value of natriuretic peptides as useful tools for the diagnosis and prognosis of CHF and the guidelines for the diagnosis and treatment of CHF of the European Society of Cardiology (ESC) in 2001 emphasised the role of B-type natriuretic peptide (BNP) as a possible diagnostic marker, taking into account the correlation between decreasing cardiac ventricular function and increasing plasma natriuretic peptide concentrations. This same document admits the possibility of identification of patients at high risk of serious cardiac events through the measurement of natriuretic peptide levels and the prognostic benefits of tailored therapy.

In this paper, we describe a trial to investigate the clinical importance of these peptides in a study population with a previous history of hypertension. The aims were to establish the relationship between the levels of BNP and A-type natriuretic peptide (ANP) and the clinical and functional parameters of CHF in an outpatient setting at baseline, compared with a sample of normal healthy controls, and to investigate the differences, in a randomised controlled trial (RCT), between two groups treated with an angiotensin-converting enzyme (ACE) inhibitor, captopril, or an angiotensin AT_1-receptor blocker (ARB), irbesartan. These differences were assessed throughout six months and at the sixth month to evaluate the change in clinical, functional and neurohormonal parameters.

Methods

Between the 5th January 1999 and the 28th March 2001, a study was performed on a sample of 68 patients.

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Study design

Inclusion criteria were: a history of hypertension, CHF classes III and IV (NYHA) and left ventricular systolic dysfunction (LVSD) (ejection fraction [EF] ≤ 40%), in sinus rhythm, with or without clinical diagnosis of ischaemic heart disease and in the absence of significant mitral or tricuspid regurgitation by Doppler.

Following baseline measurements, the patients were randomised into two groups of 34 individuals each to receive either an ARB (irbesartan) or an ACE inhibitor (ACE-I) (captopril). A clinical, functional and neurohormonal evaluation was implemented with a follow-up of six months.

Exclusion criteria included anaemia, valvular heart disease, chronic atrial fibrillation, complete left bundle branch block, renal failure in pre-haemodialysis stage, liver failure, chronic obstructive pulmonary disease, hospitalisation at the time of randomisation, and cerebral stroke. Alcohol consumption could not exceed 50 g/day. Patients suffering from malignant disease were also excluded.

A sample of 26 normal controls was also set up in order to establish the reference parameters of normality compared with the patients' sample.

All patients and controls signed a declaration of consent after having been duly informed of the protocol. The study was approved by the qualified Ethics Committee.

The investigation conforms with the principles outlined in the Declaration of Helsinki.

The patients were first subjected to a doctor's appointment, during which they completed a form with all relevant biographical and biometric data, as well as information related to the possible aetiology of CHF, risk factors and duration of disease. Inquiries concerning the history and subsequent treatment of arterial hypertension, myocardial infarction or angina, and alcohol consumption, were carried out.

The number of previous hospitalisations related to CHF and the NYHA functional class without effect of medication were also investigated.

The ESC criteria were adopted to confirm the diagnosis of CHF.

Before the baseline evaluation, and for at least 14 days afterwards, no patient involved in the study underwent treatment with an ACE-I or an ARB. β-blocker treatment was excluded under the conditions of the protocol approved for the first six months of treatment.

Further to the first doctor's appointment, the protocol for the patient groups covered four main study phases: the basal phase, first month, third month and sixth month. For the control sample, only the basal study was carried out.

The patients started the treatment with the ACE-I, captopril, (12.5 mg t.i.d.) or with the ARB, irbesartan, (75 mg q.d.). An adjustment was made at the end of the first week and at the doctor's appointment of the first month by increasing the dose (first week: 25 mg t.i.d. of captopril or 150 mg q.d. of irbesartan; first month: 50 mg t.i.d. of captopril or 300 mg q.d. of irbesartan). On the third month, the dose was maintained whenever possible.

Outcome measurements

The following diagnostic studies were analysed: 12-lead electrocardiogram (ECG), chest X-ray, M-mode, two-dimensional and Doppler echocardiogram (echo) with ejection fraction (EF) measured by biplane disc summation method (Simpson's rule), 24-hour ECG monitoring (Holter), radionuclide ventriculography of equilibrium (RNVE) and a laboratory study including the neurohumoral evaluation of ANP, BNP, norepinephrine (NE), angiotensin II (Ang II) and aldosterone. Creatinine was also evaluated.

The patients started the treatment with captopril (12.5 mg t.i.d.) or with irbesartan (75 mg q.d.) with further dose adjustment as previously described.

All adverse effects were registered. The number of hospitalisations between the basal phase and the sixth month was also recorded.

Statistical analysis

The statistical analysis was divided into two parts. In the first part, demographical, clinical, functional and laboratory data of variables obtained at the beginning of the study amongst the 68 patients were compared with the group of healthy controls, using methods suitable to each variable (absolute and relative frequency tables for variables measured on a nominal, mean and median scale, standard deviation and limits for variables measured on an interval scale; chi square test to compare the proportions between the two groups and Student's *t*-test for unpaired samples, to compare the mean values).

Multiple linear regression or logistic regression was performed to work out the influence of age and gender in the comparative analysis between patients and controls and also to analyse the possible influence of diabetes mellitus and ischaemic heart disease in the sample of patients.

In the second part, the results of the patient group were analysed through the comparison of the clinical, functional and laboratory features obtained in the basal evaluation in each group of 34 patients. An analysis of variance (ANOVA) was performed. The differences between the basal phase and the sixth month for each group of 34 patients were determined and the difference between the two drugs in the sixth month of treatment was also tested.

A comparative study between the two drugs throughout the four stages of the observation was also carried out.

We correlated the variables of the sample of 68 patients and of each sub-sample of 34 patients at baseline and in the sixth or third month according to the examinations stipulated in the protocol for these phases.

The correlations between the continuous variables were carried out using Pearson's coefficient. We used Spearman's ordinal coefficient for the correlations between variables in which at least one of them was not continuous.

The safety analysis consisted of the description of the adverse effects observed during the treatment.

Table 1 Biometric parameters – patients and controls

	Patients (n=68)	%	Controls (n=26)	%
Age (years)	65.79±11.78		58.15±14.07	
Male	55	80.88	10	38.46
Female	13	19.12	16	61.54
White	66	97.06	26	100
Black	2	2.94	0	0
BSA (m^2)	1.86±0.18		1.74±0.20	
BMI (kg/m^2)	27.99±4.36		25.57±4.0	
HR (bpm)	75.97±15.18		70.38±7.82	
BP (mmHg)	137.93±17.96/81.29±12.31		128.58±8.12/76.65±7.85	

BSA = body surface area; BMI = body mass index; HR = heart rate; BP = blood pressure

Results

Clinical

The sample of 68 patients comprised 55 males and 13 females, with an average age of 65.79 years. There were 66 white and two black patients (Table 1).

The sample of 26 healthy controls was composed of white individuals, 10 males and 16 females. The average age was 58.15 years.

The duration of CHF history before enrolment ranged from a a few months to a maximum of 12 years (mean 2.82±2.75 years). This is in agreement with the literature and with our previous personal experience. There is, in many cases, a long period of time between the asymptomatic phase of CHF and the advanced stages of the disease.

We found cases of no prior hospitalisations and a maximum of 30 (mean 2.41±4.7) in this randomised sample. This diversity is due to the severity, compliance to medication, intercurrent disease and duration of CHF.

The average of clinical parameters of heart rate (HR) and blood pressure was higher in the patient sample than in the controls (see Table 1). This was a result to be expected in a group with history of high blood pressure and CHF when compared to a healthy sample.

According to the inclusion criteria, all patients were in NYHA classes III and IV at baseline, and most (57 [83.8%]) belonged to class III, reflecting moderate-to-severe CHF (Figure 1).

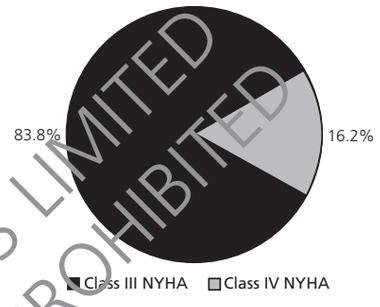
Hypertension was associated with ischaemic heart disease in 17 patients (25%) and with Type 2 diabetes mellitus in 15 patients (22%) (Figure 2).

Only one hospital admission was observed in the first month and four admissions in the sixth month, all of which were from the captopril group. The total of five hospitalisations represents 14.7% of the cases in this group.

Analysing the distribution of the sample of 68 patients according to their NYHA class in the basal phase and at the third and sixth month of therapy, a marked improvement in NYHA class was observed, with a transition from classes III and IV to class II, with both irbesartan and captopril. There were no significant differences between the ARB and the ACE-I, in each of the four study stages.

The comparative analysis between irbesartan and captopril treatments revealed that there were no statistically significant differences between the two groups in the clinical-functional parameters.

Figure 1 Clinical parameters – NYHA classes



Cardiothoracic index

The average cardiothoracic index (CTI) of the sample of patients at baseline (0.57±0.03) was higher than in the controls (0.50±0.01) (p=0.000).

In the 68 patients, an inverse correlation between CTI and echocardiographic EF was observed (r=–0.478; p=0.000) and a similar correlation with EF by RNVE was also noted (r=–0.545; p=0.000).

CTI decreased significantly between the basal phase and the third month of treatment in the irbesartan group.

Echocardiography

While comparing the echocardiographic parameters of the sample of patients with the healthy controls, it was noted that there were higher values in the patients, with a statistically significant difference in the following parameters: left atrium MM, left atrium 2D, right atrium 2D, left ventricle end diastolic diameter (LVEDD), left ventricle end systolic diameter (LVESD), left ventricle end diastolic volume (LVEDV), left ventricle end systolic volume (LVESV), left ventricular mass (LVM). LV shortening fraction (LVSF) and LV ejection fraction (LVEF) were significantly lower in the patients than in the controls. The same was observed when the values relative to body surface area (BSA) were taken into account (Table 2).

Within the sample, 65 patients, in the basal phase, had an EF ≥20% and 59 patients had EF

Figure 2 Patients: cardiovascular risk factors

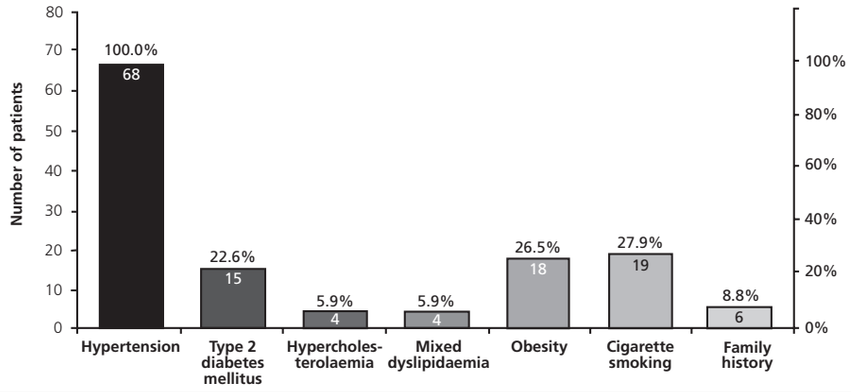


Table 2 Doppler echocardiogram – baseline results (related to body surface area)

Index	Patients (n=68) Controls (n=26)	Mean	Median	Range	SD	p-value*
LAI MM (mm/m²)	Patients	24.62	24.91	14.46–40.41	4.68	<0.000
	Controls	21.06	21.06	15.92–26.84	2.66	
LAI 2D (mm/m²)	Patients	33.09	32.79	21.93–49.96	6.19	<0.000
	Controls	26.69	26.71	21.41–33.37	2.96	
RAI 2D (mm/m²)	Patients	29.09	28.33	19.45–43.68	5.19	<0.0012
	Controls	25.46	25.05	18.42–31.54	3.03	
LVEDDI (mm/m²)	Patients	34.96	34.36	25.01–55	6.30	<0.0000
	Controls	28.60	28.19	24.11 –35.99	2.69	
LVESDI (mm/m²)	Patients	27.17	26.19	18.19–45.61	5.89	<0.0000
	Controls	16.62	16.9	11.37–21.47	2.53	
SF (%)	Patients	22.62	23.33	7.23–29.51	5.37	<0.000
	Controls	41.95	40.84	31.91–52.94	6.41	
Septal thickness (mm/m²)	Patients	5.49	5.59	3.63–7.47	0.92	<0.588
	Controls	5.60	5.64	3.93–7.65	0.89	
Posterior wall thickness (mm/m²)	Patients	5.36	5.49	3.70–7.47	0.78	<0.1770
	Controls	5.61	5.58	3.95–7.65	0.82	
RVI (mm/m²)	Patients	10.73	10.56	4.59–19.02	2.30	<0.95
	Controls	10.76	10.72	5.76–14.68	2.21	
LVEDVI (ml/m²)	Patients	88.87	79.3	38.69–184.19	37.30	<0.0004
	Controls	61.04	64.34	34.13–86.56	12.82	
LVESVI (ml/m²)	Patients	60.18	50.09	24.77–136.09	28.93	<0.0000
	Controls	23.31	24.48	13.16–34.22	5.70	
EF (%)	Patients	33.43	35.68	12.64–40.32	6.52	<0.0000
	Controls	61.96	61.68	57.14–68.52	3.53	
LVMI (g/m²)	Patients	155.68	138.51	67.64–347.59	51.08	<0.0000
	Controls	98.92	99.45	66.41–127.88	15.64	

*Student's *t*-test – two groups (unpaired). LAI MM = left atrium index MM; LAI 2D = left atrium index 2D; RAI 2D = right atrium index 2D; LVEDDI = left ventricular end diastolic diameter index; LVESDI = left ventricular end systolic diameter index; SF = shortening fraction; RVI = right ventricle index; LVEDVI = left ventricular end diastolic volume index; LVESVI = left ventricular end systolic volume index; EF = ejection fraction; LVMI = left ventricular mass index

≥25%. The deceleration time (DT) of E wave was in the majority of the cases higher than 130 msec.

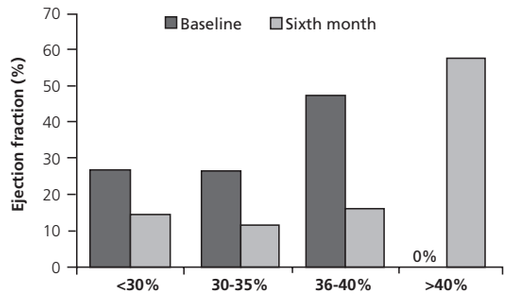
Pulmonary artery systolic pressure (PASP) values were higher (mean 37.65 mmHg) in the patient sample.

The LVM index (LVMI) showed values at baseline that ranged from reference values to moderate rises, but the relative wall thickness (RWT) was lower than 0.45. This sample of 68 patients (34 irbesartan and 34 captopril) is thus divided into two groups. For the same RWT <0.45, one group had a normal LVMI and the other group an increased LVMI. The latter group displayed a pattern of eccentric hypertrophy. Within the group under study, 45 patients (66.17%) showed eccentric left ventricular hypertrophy at baseline.

Echocardiographic LVEF improved throughout the six months of treatment, with an improvement from the lower values (<30%) to better stages, while a number of patients reached values higher than 40% (Figure 3). The increase of LVEF between baseline and month six in both drugs reached statistical significance.

After analysing the difference at month six between the irbesartan and captopril groups, EF was significantly higher in the irbesartan group.

Figure 3 Echocardiogram – patients' sample – ejection fraction baseline versus sixth month



Shortening fraction (SF) increased significantly between baseline and month six in both treatment groups. After analysing the difference at month six between the irbesartan and the captopril groups, SF was significantly higher in the irbesartan group.

Radionuclide ventriculography of equilibrium

Relating to the RNVE parameters within the sample of patients and in the controls, end diastolic and end systolic left ventricular volumes were higher and LVEF was lower in the patients than in the controls. These differences were significantly different, either in absolute values or with correction for BSA (Table 3).

In both treatment groups, there was an improvement in EF by RNVE, assessed at the third month; there was a change from the groups with lower EF, even <30%, to sets with progressively higher EF. An increased number of patients attained values above 40%. Although there wasn't an exact overlap of the EF obtained through RNVE and echocardiography, the findings were essentially the same.

The RNVE LVEDV and the LVESV decreased between the basal phase and the third month, the change reaching statistical significance in the irbesartan group. The EF increased significantly between the baseline and the third month in both treatment groups.

Laboratory parameters

Mean laboratory values of BNP, ANP, norepinephrine, aldosterone, and creatinine were significantly higher in patients than in controls at baseline (Table 4).

ANP and BNP values tended to be higher in the more severe NYHA functional classes; this trend continued to the third month of follow-up, but was lost at the sixth month.

BNP and ANP showed a positive correlation with CTI at baseline (Figure 4).

Table 3 Radionuclide ventriculography of equilibrium (RNVE) – baseline versus controls (related to body surface area)

	Patients=68 Controls=26	Mean	Median	Range	SD	p-value*
LVEDVI ml/m²	Patients	111.30	96.32	36.74–266.51	48.02	<0.0000
	Controls	63.53	66.49	38.04–80.73	12.13	
LVESVI ml/m²	Patients	78.99	63.91	26.08–231.92	42.91	<0.000
	Controls	24.31	24.75	11.74–33.64	5.36	
EF%	Patients	31.45	33.72	12.92–40.46	7.81	<0.0000
	Controls	61.85	61.44	55.72–70	3.43	

*Student's *t*-test – two groups (unpaired). LVEDVI = left ventricular end diastolic volume index; LVESVI = left ventricular end systolic volume index; EF = ejection fraction; SD = standard deviation

Table 4 Baseline laboratory parameters, patients versus controls

	Patients (n=68) Controls (n=26)	Mean	Median	Range	SD	p-value*
Ang II (pmol/L)	Patients	5.72	2.10	0.30–41	9.75	<0.075
	Controls	2.26	2.05	0.30–5.20	1.53	
ANP (pmol/L)	Patients	30.32	20.10	0.70–123.20	25.97	<0.0004
	Controls	11.18	8.9	2.6–32.8	7.92	
BNP (pmol/L)	Patients	44.78	23.25	1.6–233	54.36	<0.0007
	Controls	7.12	3.60	0.5–37.2	8.28	
Plasma renin activity (ng/ml/h)	Patients	0.75	0.35	0.03–6.5	1.08	<0.18
	Controls	0.46	0.40	0.07–1.3	0.34	
Aldosterone (ng/dL)	Patients	10.26	6.8	1–32	8.11	<0.0085
	Controls	5.8	5.4	0.8–15.80	3.69	
Norepinephrine (pg/ml)	Patients	432.15	369	118–2091	288.41	<0.0000
	Controls	164.75	157.5	107–264	41.88	
Creatinine (mg/dL)	Patients	1.12	1.10	0.70–1.6	0.21	<0.0000
	Controls	0.93	0.90	0.70–1.30	0.15	

*Student's *t*-test – two groups (unpaired). Ang II = angiotensin II; ANP = A-type natriuretic peptide; BNP = B-type natriuretic peptide; SD = standard deviation

Figure 4 Cardiothoracic index (CTI) versus B-type natriuretic peptide (BNP) at baseline

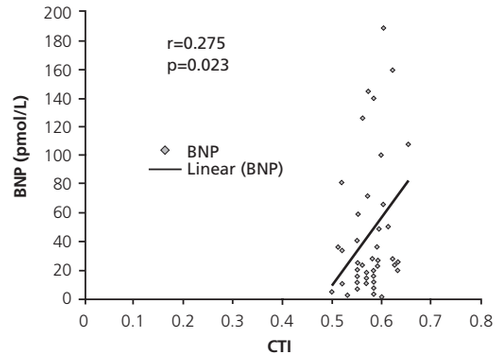
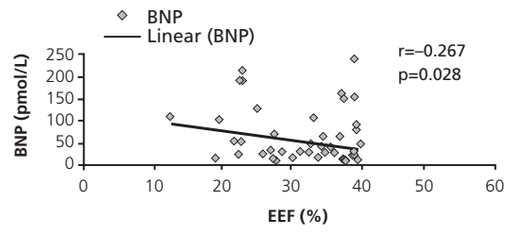


Figure 5 Echocardiographic ejection fraction (EEF) versus B-type natriuretic peptide (BNP) at baseline



In our study, BNP was positively correlated with NYHA functional class at baseline (r=0.247; p=0.042) and inversely correlated with echocardiographic EF (r=–0.267; p=0.028) (Figure 5). ANP also showed a negative correlation with echocardiographic EF (r=–0.272; p=0.025).

There was an inverse correlation between ANP and EF by RNVE at baseline.

ANP and BNP at baseline were also correlated (r=0.812; p=0.000).

ANP decreased significantly between baseline and the sixth month in the irbesartan group, and was also significantly lower at six months.

ANP decreased by 8.19 pmol/L throughout the six months in the irbesartan group (p=0.02) and decreased 0.89 pmol/L in the captopril group (p=0.85). At month six, ANP was 16.49 pmol/L lower in the irbesartan group than in the captopril group (p=0.002).

BNP also decreased significantly between baseline and the sixth month in the irbesartan group, and was significantly lower in the irbesartan group then in captopril group at six months (Table 5).

BNP decreased by 24.18 pmol/L throughout the six months in the irbesartan group (p=0.03) and increased by 1.61 pmol/L in the captopril group (p=0.84). BNP was 28.23 pmol/L lower in the irbesartan group than in the captopril group (p=0.001) at six months.

Ang II could only be determined during the basal phase. The values were higher in the patient group, which is in accordance with the fact that plasma levels of Ang II tend to be higher in patients with CHF. However, the differences were not of statistical significance.

There was no significant difference in creatinine levels at baseline between the two treatment groups; the same was shown at the sixth month (p=0.36). The mean value of creatinine was 1.14 mg/dL in the irbesartan group and 1.10 mg/dL in the captopril group (p=0.40) at baseline. At the sixth month, the mean value of creatinine was 1.18 mg/dL in the irbesartan group and 1.13 mg/dL in the captopril group (p=0.36).

Between the baseline and the sixth month, the mean value of creatinine increased slightly, though within the reference values, in both irbesartan and captopril groups.

The trend towards higher values of ANP and BNP in correlation with NYHA classes held out at the third month of the follow-up, but was lost at the sixth month, within the two groups.

ANP decreased significantly between baseline and the sixth month in the irbesartan group. Following the analysis of the difference in the sixth months between the irbesartan and captopril groups, ANP was significantly lower in the irbesartan group.

Table 5 Laboratory parameters – irbesartan versus captopril – baseline versus sixth month

	Irbesartan=34 Captopril=34	Baseline Mean	Median	Range	DP	p-value*	Sixth month Mean	Median	Range	SD	p-value*
ANP (pmol/L)	Irbesartan	25.73	18.5	0.7–81.7	20.83	0.15	17.53	14.35	3.8–67.10	12.77	<0.004
	Captopril	34.91	21.35	3.9–123.2	29.87		34.02	21.15	5.3–119.4	29.69	
BNP (pmol/L)	Irbesartan	43.56	20.85	1.6–233	59.37	0.85	19.38	13.40	1.10–130.1	23.29	<0.006
	Captopril	46.01	23.8	2.9–188.5	49.72		47.61	28.35	1.2–220.5	52.54	
Plasma renin activity (ng/ml/h)	Irbesartan	0.72	0.30	0.03–5.40	1.05	0.85	2.19	0.85	0.07–19	4.15	<0.14
	Captopril	0.77	0.40	0.10–6.5	1.12		1.07	0.5	0.16–6.5	1.42	
Aldosterone (ng/dL)	Irbesartan	10.74	6.45	1.9–30.5	8.77	0.63	11.75	5.35	0.5–85.3	15.96	<0.50
	Captopril	9.77	7.25	1–32	7.5		9.58	6.55	0.8–47	9.36	
Norepinephrine (pg/ml)	Irbesartan	389.89	368	118–853	180.2	0.23	291.46	264.5	107–737	154.66	<0.84
	Captopril	474.42	373	123.2–2091	364.32		298.82	238	129–690	140.76	

*Student's *t*-test – two groups (unpaired). ANP = A-type natriuretic peptide; BNP = B-type natriuretic peptide; SD = standard deviation

ANP decreased by 8.19 pmol/L throughout the six months in the irbesartan group (p=0.02) and by 0.89 pmol/L in the captopril group (p=0.85). At the sixth month, ANP was 16.49 pmol/L lower in the irbesartan group than in the captopril group (p=0.002).

BNP decreased significantly between baseline and the sixth month in the irbesartan group, and was also significantly lower at the sixth month in this group (see Table 5).

BNP decreased by 24.18 pmol/L throughout the six months in the irbesartan group (p=0.03) and increased by 1.61 pmol/L in the captopril group (p=0.84). BNP was 28.23 pmol/L lower in the irbesartan group than in the captopril one (p=0.001) at the sixth month.

Holter

In the study of 24-hour ECG Holter, monitoring, there was a much higher frequency of premature ventricular contractions (PVC) in the patients (47.5±120.8) than in the controls (0.73±1.51) (p=0.05). Ventricular tachycardia (VT) was only observed in the patient group (15 cases); this was not sustained and was mostly monomorphous and of short duration. Of the 23 patients who developed episodes of non-sustained VT in the basal phase or in the third month, five (21.7%) had confirmed ischaemic heart disease.

There were no significant differences in the frequency of PVC or VT between the captopril and irbesartan groups.

Adverse effects

There were three cases (8.82%) of dry cough in the captopril group, all in male patients. One case (2.94%) of epigastric pain was also registered in the captopril group. These situations did not require discontinuation of the treatment.

Discussion

It should be stressed that, although many of the study patients had a previous history of hypertension, the majority of the patients were normotensive at the time of enrolment, presumably because of the progression of CHF. High blood pressure is one of the most prevalent causes of CHF according to the Framingham studies, followed by ischaemic heart disease.

A marked improvement of NYHA class from III and IV to class II was observed in the 68 patients between baseline and month six. This outcome can be ascribed to the benefit of the medication, which also led to a reduced number of hospital admissions throughout the six months of the study.

In both the Evaluation of Losartan in The Elderly (ELITE) and the Evaluation of Losartan in The Elderly II (ELITE II) studies,[1] no significant differences were observed in the number of hospitalisations for CHF between the losartan group and the captopril one. In the ELITE study, hospital admissions were 5.7% in both groups.

The inverse correlation between the CTI and the EF measured by echo and RNVE that was found in our sample is consistent with other studies, in which increasing CTI is inversely correlated with LVEF.[2] The CTI was also found to be a prognostic marker of mortality in some studies.[3,4] The remarkable progress that was noticed in echocardiographic LVEF is likely to be done to the study medication.

LVEDD, LVESD and LVSF, determined by M mode echocardiography in the 68 patients, can be regarded as prognostic markers in CHF.[5-7]

The high values of PASP were consistent with the presence of CHF, which is associated with an increase in this parameter.[8-10] ASP has been shown to be a marker of mortality in CHF.[11,12]

The high number of patients with EF ≥20% and with a DT higher than 130 msec at baseline might have contributed to the reduced morbidity rate throughout the six months of observation. Even though we were dealing with severely altered functional parameters, they do not represent the group with the worst prognosis of this disease.

As already mentioned, much higher values of LVEDV and LVESV and much lower values of the LVEF in the sample of patients in relation to the controls were observed. In the literature, there is evidence that EF by RNVE is an independent predictive marker of mortality.[8,13-18] The low EF in the 68 patients is consistent with a poor prognosis.

The improvement of the LVEF through the three months that was noticed by RNVE is a prognostic harbinger, which goes along with an improvement of the condition of the patients.

The statistically significant higher values of the BNP, ANP, NE, and aldosterone at baseline between the patients and the controls support the presumption that these results have diagnostic value. In other studies, these parameters are related to the diagnosis of CHF, particularly in patients not treated with drugs which interfere with the neurohumoral system. They are also likely to be associated with the severity and the prognosis of CHF in large samples. Nevertheless, it should not be overlooked that these markers can be misleading in individual patients.[19,20]

The majority of the studies concerning the neuroendocrine response in CHF are carried out in patients treated with diuretics, digitalis and even ACE-Is. This was also the case in our study; although it doubtless effects the mechanisms under study, for ethical reasons such drug treatment can not be avoided.

In our study, BNP showed an inverse correlation with EF by echo and a positive correlation with NYHA functional classes. ANP also showed a negative correlation with EF by echo and RNVE that goes along with the evaluation of the severity of CHF.

An increase in BNP and ANP has been positively correlated with LV systolic dysfunction. The baseline negative correlation verified between the echocardiographic EF and the ANP and the BNP can help us estimate the extent of the EF by lab determination. BNP, in particular, will give complementary information with clinical and functional value. The diagnosis of CHF by means of lab tests

can therefore be envisaged.[21] Hara *et al*.[22] found an inverse correlation between ANP concentrations and EF and a direct correlation between ANP and the severity of CHF.

The positive correlation that was found at baseline between BNP and NYHA class must be stressed. This factor can contribute towards the diagnosis and evaluation of the severity of CHF.

Both BNP and ANP have been investigated in asymptomatic LV dysfunction as well as in CHF; they are likely to be useful for the clinical screening of patients because of their high negative predictive value.[21,23]

BNP and ANP are progressively released into the blood stream in the transition from asymptomatic LV dysfunction to established CHF,[24] and their plasma values seem to be diagnostic markers.[25] In some studies, high values of BNP and other natriuretic peptides[26] allowed the diagnosis of patients at greater risk of morbidity and mortality.[8,27-31] This is a likely consequence of the cardiac burden and reflect the severity of the clinical situation in advanced stages of LV dysfunction.[28]

In patients with CHF, plasma NE levels are increased;[32-36] the prognostic deterioration is directly correlated with activation of the sympathetic nervous system.[37] NE values can be far higher in patients with severe symptoms,[34,35,38] although NE concentrations in individual cases are poorly related with the severity of LV dysfunction.[35,38,39] In cases of asymptomatic LV dysfunction, baseline values of NE can occasionally be similar to the values of healthy controls.[40] Although NE has been shown to be a prognostic marker in many studies.[2,27,41-43] this is not an unanimous finding.[44] In the study of Cohn *et al*.,[42] plasma NE levels were highly predictive of mortality. However, BNP[45] and ET-1[46] are found to be better prognostic markers for CHF than NE.

Throughout the six months, a decrease in ANP in the patient group was observed. In some studies,[47] a decrease in the ANP levels can be seen as a marker of clinical improvement.

Recently, groups of investigators have suggested that BNP measurements can be useful as a guide for therapy titration in ambulatory CHF patients.[47-50]

In the CONSENSUS study,[27] a positive correlation was found between ANP and plasma NE levels. In other studies, plasma BNP, ANP and N-terminal ANP (N-ANP) concentrations also seem to be inversely correlated with the LVEF.[51]

The statistically significant higher baseline values of serum creatinine in the patient group can be explained by the presence of LVSD.

BNP was positively correlated with ANP in our study. This fact may allow for a better interpretation of the clinical situation of CHF.

Notwithstanding the stimulation of natriuretic peptides in the patient group, serum aldosterone was markedly higher than in the controls, which could be due to both stimulation of aldosterone itself and to the interaction of substances which inhibit its secretion.

Taking into account the existing correlations between BNP, ANP and CTI and the correlations between this latter parameter and the echocardiographic and the RNVE main parameters, it can be concluded that the chest X-ray may usefully contribute toward the diagnosis of CHF and the evaluation of its severity.

In the irbesartan group, there was a statistically significant reduction of ANP, BNP, and NE during the treatment period, suggesting that monitoring of these parameters may be useful in the assessment of patient progress.

No cases of first dose hypotension were observed. The small number of adverse effects throughout the six months are in accordance with the low rate of adverse effects normally associated with the study drugs.

There were no deaths in the patient group during the follow-up period, which is likely to be attributed to the effective treatment of CHF and the intensive follow-up. However, the small number of patients and the short duration of follow-up are not sufficient to carry out a formal evaluation.

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