IJNU Original Article

Int J Nephrol Urol, 2010; 2(4): 532-536

Increased Pro-BNP Secretion in Hypertensive Patients

Massimino Senatore[1*], Giovanni Carlo Gallo[1], Michele Buemi[2], Renzo Bonofiglio[3]

[1]Department of Nephrology and Dialysis, Hospital "L. Pasteur", San Marco Argentano (Cs), Italy

[2]Department of Nephrology, Messina University, Messina, Italy

[3]Department of Nephrology, Dialysis and Transplantation, Cosenza Hospital, Cosenza, Italy

Abstract

Background and Aims: The precursor of the Brain Natriuretic Peptide (pro-BNP) represents a biological marker whose behavior in stress condition can reveal the beginning of a condition of chronic heart failure in patients at risk. The objective of our work was to evaluate the behavior of pro-BNP after hydrosaline overload on a sample of hypertensive patients.

Methods: The authors have evaluated the incretory stimulation of brain natriuretic peptide in a group of 13 patients with arterial hypertension. All of the individuals underwent a hydrosaline overload 20% of plasmatic value. Blood samples for pro-BNP determination were obtained from the antebrachial vein at time 0, 2nd hour, 4th hour, 7th hour and 10th hour. The same procedure was applied upon a control group of healthy individuals. The study was repeated after 7 months in 18 hypertensive patients. All of the individuals underwent a hydrosaline overload 25% of plasmatic value. Statistics were calculated with intra-group and intergroup analysis.

Results: The results obtained showed an increase in the secretion of pro-BNP which became important after 4 hours from the first examination in the group of hypertnsive patients. No modifications were observed in healthy group. In the second phase of the study, the results become more statistically significant than in the first part of the study. The most interesting result is the difference in secretion of pro-BNP between the hypertension group and control group which occurs earlier in respect to the first part of the study. Moreover, there is an increased production of pro-BNP between the patients with hypertension non-dippers in respect to the dippers.

Conclusions: The authors hypothesized that the increase of secretion of pro-BNP during arterial hypertension could be considered as a compensatory phenomenom linked to intolerance toward hydrosaline overload and if so, it can be due to a molecular pathology of the renal tubule and/or to a molecular pathology of the competent cells of cardiac muscle. This phenomenom seems particularly to be evidenced in non-dipping hypertension category of patients in which the cardiovascular risk is very high. Our study contributes to confirm that dynamic tests are more useful tools than static tests in exploring the organ reserve function.

Keywords: Hypertension, Pro-Brain Natriuretic Peptide, Cardiovascular Risk

Introduction

The need to protect the health of individuals is a very important concern of the scientific world. Research tries to analyze early signs of homeostatic

**Correspondence:*
Massimino Senatore, MD
Piazza dei Bruzi, 587100 Cosenza, Italy
Tel: 0984510233/245
Fax: 0984939661
Email: senatorem@yahoo.com
Received: 15 Apr 2010
Revised: 3 May 2010
Accepted: 18 May 2010

In this context the static or basal determination of biomarkers of diseases has showed a limited value. We think that it is very important to create new protocols which could better consider the metabolic processes in dynamic and/or in stress condition.It is possible to assimilate a dynamic test into an organ functional reserve evaluation test.Usually, dynamic test is loading test, which is based on delta increase of basal parameters.

We wondered if this reasoning is valid for a good prevention of cardiovascular risk (CVR), especially if it follows arterial hypertension and if it would help us to know better the neuroendocrine mechanisms which accompany the hypertensive disease.

The analysis in basal conditions of secretions of natriuretic peptides (NPs) in various stages of CHF has been interesting (1-3). The diagnostic value of this measurement has its limits because it only confirms clinical signs of chronic heart failure (CHF) and helps in the differential diagnosis of pulmonary or cardiac dyspnea (4).

There have been discussions on the use of biochemical markers especially NPs, in persons at risk for developing CHF in the community.

We wonder if NPs are good neuroendocrine "markers" of conditions leading to CHF (5, 6) and if more information could be obtained from a dynamic evaluation of neurohormonal secretion. The precursor of the Brain Natriuretic Peptide (proBNP) is the hormone which has been chosen for the performing this research.

The Brain Natriuretic Peptide, originally isolated from the brain of pigs, is synthesized in ventricular cardiomyocytes in response to ventricular pressure or volume stress (7). The physiological effects of BNP are stronger than the effects of the atrial natriuretic peptide (8). Its clearance is much more rapid (8) and the normal vascular and kidney responses to BNP are conserved in patients undergoing therapy (9). Screening of general populations with pro-BNP holds promise for the detection of significant underlying cardiac and functional abnormalities, as well as for the early detection of the propensity to develop future cardiovascular events. Few studies available in literature show only static values of pro-BNP and in situations of hemodynamic compensation.

The objective of our work was to evaluate the behaviour of pro-BNP after hydrosaline overload on a sample of hypertensive patients, simulating a situation of stress on the cardiovascular system of patients at risk.

Materials and Methods

We divided the study into two phases separated by a seven months interval which was necessary to analyze the behavior of pro-BNP after two different amounts of hydrosaline overload. The study was performed in the Operative Unit of San Marco Hospital between January and July 2009.

Phase 1

Thirteen patients with hypertension (average age 51.2 ± 4.4 years old) were tested. They had hypertension for over 3 years (Table 1). None of these patients had a heart attack. All of the patients were treated with a hypotensive therapy with one pharmaceutical agent. The patients were advised to avoid changing their eating habits or therapy for 15 days before testing. EKG and echocardiograms were performed upon all of the patients before the study. Only 4 patients had a modest left ventricular hypertrophy (evaluated as a width of the diastolic septum of 11-14 mm and the posterior wall between 11 and 14 mm). All of the patients had normal functioning of the left ventricle and normal dimension of every atrium. Thirteen healthy individuals (average age 44.9 ± 6.3 years) were placed into the study as a control group. The average of the cardiac mass did not differ between the two groups. All of the individuals underwent a hydrosaline overload infusion calculated as 20 % of plasmatic volume administered over a 120 min

period.

Blood samples for pro-BNP determination were obtained from the antebrachial vein at time 0, 2nd, 4th, 7th and 10th hour. All patients were kept in supine position for the whole time of the study. All specimens were frozen to -20°C and tested simultaneusly.

Phase 2

After seven months the analysis was repeated on a second group of 18 patients (average age 54.2 ± 3.4 years) whose characteristics were the same as the patients of the first phase (Table 1).

The patients were treated with a hypotensive therapy with one pharmaceutical agent.

Table 1. Patients chracteristics (mean ± SEM)

Variable	Phase I			Phase II		
	H. pts.	Control group	P	H. pts.	Control group	P
Male/female	7/4	5/5	n.s	10/6	5/5	n.s
Age, years	51.2 ± 4.4	44.9 ± 6.3	n.s	54.2 ± 3.4	46.1 ± 5.3	n.s
Body mass index, kg/m²	25.3 ± 5	25.69 ± 3.52	n.s	25.4 ± 5	25.6 ± 3.5	n.s
Duration of hypertension, months	18 ± 5			20 ± 5		
PAS, mmHg	143 ± 17	122 ± 5	0.05	145 ± 11	125 ± 7	0.05
PAD, mmHg	89 ± 6	79 ± 4	n.s	80 ± 6	75 ± 3	n.s
Serum creatinine, mg/dl	0.9 ± 0.2	0.9 ± 0.1	n.s	0.9 ± 0.3	0.9 ± 0.2	n.s
Left ventricular ejection fraction, %	62 ± 4	62 ± 3	n.s	65 ± 3	63 ± 2	n.s
Left ventric. shortening fraction,%	35 ± 3	34 ± 3	n.s	35 ± 8	34 ± 9	n.s
Left atrial size, mm	30 ± 5	31 ± 6	n.s	32 ± 4	31 ± 8	n.s

H. Pts, hypertensive patients

None of the patients had a heart attach. Ten healthy patients were used as the control group. The average size of the heart did not differ between the two groups. The ecocardiogram resulted in 5 patients with a modest left ventricular hypertrophy. This second group of patients underwent the same protocol as the first group. The hydrosaline overload was increased to 25% of plasma volume.

The blood pressure of the patients was monitored continuously during both test periods with holter device. Either clinical events or hypertensive crises related to saline overload was registered.

The results were evaluated accordig to dipping or no-dipping conditions. Pro-BNP determination was performed by RIA using a Roche Elecsys 1010 (10). The comparison between the groups was done by Student's t Test for paired and unpaired data. Statistical data was analyzed by the SPSS Windows programm (version 9.0; Chicago, Ill., USA). The protocol of this research was approved by the Ethical Commission of the Hospital and all the patients gave their written consent to partecipate in this study.

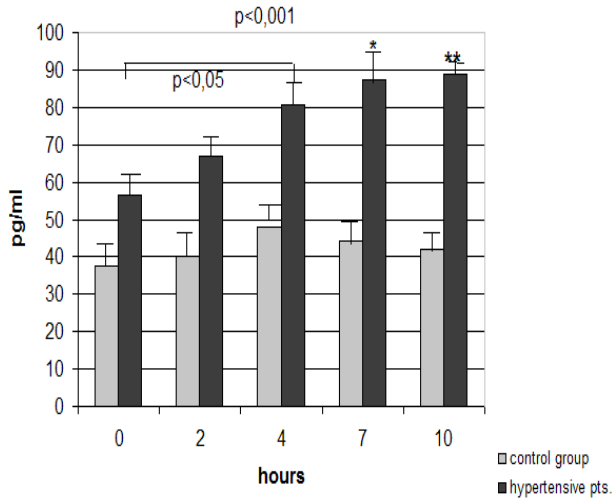
Results

In the first phase (20% plasmatic value hydrosaline overload), we registered a significant difference of the pro-BNP values in patients with hypertension vs healthy controls from the seventh hour ($p<0.05$ at the 7th hour and $p<0.03$ at the 10th hour) ahead (Fig.1). Furthermore, a hypertensive intragroup analysis Moreover, there is an increased production of pro-

shows an important statistical difference between time 0 and, respectively, 4th ($p<0.05$), 7th ($p<0.03$) and the 10th hour ($p<0.001$).

In the second phase (25% hydrosaline overload) the intragroup results were confirmed. Moreover, the statistical significance beetwen normal subjects and hypertesive patients was anticipated to the 4th hour ($p<0.05$) of observation (Fig. 2).

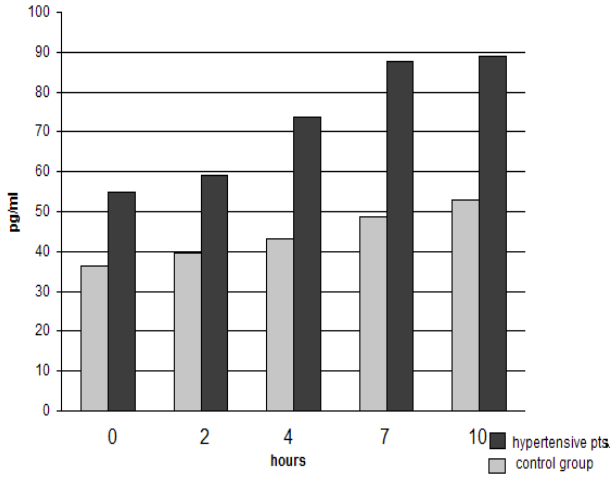
Figure 1. Plasma pro-BNP concentrations (mean ±SEM)



*p< 0.05 vs. control group of the same time

**p<0.03 vs. control group of the same time

Figure 2. Plasma pro-BNP concentrations (part II) (mean ± SEM)



*p< 0.05 vs. control group of the same time

**p< 0.001 vs. control group of the same time

Moreover, there is an increased production of pro-BNP between the patients with non dippers hypertension ($p<0.002$) in respect to the dippers (Fig. 3). Even in this case, the average cardiac size did not vary between the two groups.

Discussion

The increase in concentration of NPs during CHF and the positive correlation between this concentration and the degree of CHF stimulated the use of NP determination tests (11, 12).The determination of pro-BNP is a very reliable analytic method and it is easy to perform (13).

The test confirms the clinical diagnosis of CHF and it can evaluate the seriousness. It is also useful for the stratification of risk in patients with acute coronary syndrome and congestive heart failure (14). This data makes the test useful only with greater values of cut-off and it helps in excluding a clinical diagnosis of CHF (15).On the contrary, no differences exist in basal determination of pro BNP either in healthy status or in clinical events predisposing to CHF as the advanced grades of hypertension.

In the present study we have tried to verify if a pro-BNP dynamic analysis could add new elements to anticipate the clinical signs of CHF.Our research have demontrated that, after an exogenous stimulus (idrosaline overload), there is a higher pro-BNP secretion in hypertensive patients than in normal group and this phenomenom seems particularly to be evidenced in non-dipping hypertension, category of patients in which the cardiovascular risk is very high. However, we don't assert that this difference may be used to discriminate a normal from a pathological condition.

Conclusions

We hypothesized that any increase of secretion of NPs during arterial hypertension could be considered

as a compensatory phenomenom linked to intolerance toward hydrosaline overload and if so, it can be due to a molecular pathology of the renal tubule and/or to a molecular pathology of the competent cells of cardiac muscle. But we are not able to state that the diversity on increatory behavior is primitively linked to a sodium sensibility of the hypertensive state or if it is secondary to cardiac stimuli.

Our study contributes to confirm that the dynamic tests are more useful tools than static in exploring the organ reserve function.

Conflict of Interest

None declared.

References

1. Senatore M, Sapio C, Di Somma A, Caporale G, Russo A, Gallo GC. Does an endocrinal phase of chronic heart failure exist? Clin Nephrol. 2005;63:413-4.
2. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med. 2002;347:161-7.
3. McDonagh TA, Robb SD, Murdoch DR, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet. 1998;351:9-13.
4. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Head-to-head comparison of the diagnostic utility of BNP and NT proBNP in symptomatic and asymptomatic structural heart disease. Clin Chim Acta. 2004;341:41-8.
5. Olsen MH, Wachtell K, Tuxen C, et al. N-Terminal Pro-Brain Natriuretic Peptide Predicts Cardiovascular Events in Hypertension: A LIFE Substudy. JACC. 2003;41:6:Abstract:1133.
6. Olsen MH, Hansen TW, Christensen MK, et al. N-terminal pro-brain natriuretic peptide, but not high sensitivity C-reactive protein, improves cardiovascular risk prediction in the general population. Eur Heart J. 2007;28:1374-81.
7. Kinnunen P, Vuolteenaho O, Ruskoaho H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: effect of stretching. Endocrinology. 1993;132:1961-70.
8. Pidgeon GB, Richards AM, Nicholis MG, Espiner EA, Yandle TG, Frampton C. Differing metabolism and bioactivity of atrial and brain natriuretic peptides in essential hypertension. Hypertension 1996; 27:906-13.
9. Marcus LS, Hart D, Packer M, et al. Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure: a double-blind, placebo-controlled, randomized crossover trial. Circulation. 1996;94:3184-9.
10. Prontera C, Emdin M, Zucchelli GC, Ripoli A, Passino C, Clerico A. Analytical performance and diagnostic accuracy of a fully-automated electrochemiluminescent assay for the N-terminal fragment of the pro-peptide of brain natriuretic peptide in patients with cardiomyopathy: comparison with immunoradiometric assay methods for brain natriuretic peptide and atrial netriuretic peptide. Clin Chem Lab Med. 2004;42:37-44.
11. Pfister R, Scholz M, Wielckens K, Erdmann E, Schneider CA. Use of NT-proBNP in routine testing and comparison to BNP. Eur J Heart Fail. 2004;6:289-93.
12. Seino Y, Ogawa A, Yamashita T, et al. Application of NT–proBNP and BNP measurements in cardiac rate: a more discerning marker for the detection and evaluation of heart failure. Eur J Heart Fail. 2004;6:295-300.
13. Fonseca C, Sarmento PM, Minez A, et al. Comparative value of BNP and NT-proBNP in diagnosis of heart failure. Rev Port Cardiol. 2004;23:979-91.
14. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet. 2000;355:1126-30.
15. Al-Barjas M, Nair D, Ayrton P, Morris R, Davar J. How can the role of N terminal pro B Natriuretic Peptide be optimized in heart failure screening? A prospective observational comparative study. Eur Heart J Fail. 2004;3:51.