NT-proBNP Levels and Hypertension. Their Importance in the Diagnosis of Heart Failure

Miguel Rivera,[a] Raquel Taléns-Visconti,[a] Antonio Salvador,[b] Vicente Bertomeu,[c] Vicente Miró,[d] Fernando García de Burgos,[e] Vicente Climent,[f] Raquel Cortés,[a] Rafael Payá,[g] José L. Pérez-Boscá,[g] Luis Mainar,[h] Alejandro Jordán,[e] Francisco Sogorb,[f] Juan Cosín,[a] Vicente Mora,[b] José L. Diago, and Francisco Marín[f] for Dysfunction Group VI of the Community of Valencia.

[a]Servicio de Cardiología, Centro de Investigación Hospital La Fe, Valencia, Spain.
[b]Servicio de Cardiología, Hospital Dr Peset, Valencia, Spain. [c]Servicio de Cardiología, Hospital San Juan, Alicante, Spain. [d]Servicio de Cardiología, Hospital La Fe, Valencia, Spain.
[e]Servicio de Cardiología, Hospital de Elche, Alicante, Spain. [f]Servicio de Cardiología, Hospital General, Alicante, Spain. [g]Servicio de Cardiología, Hospital General, Valencia, Spain. [h]Servicio de Cardiología, Hospital Requena, Valencia, Spain. [i]Servicio de Cardiología, Hospital General, Castellón, Spain.

Introduction. N-terminal pro-brain natriuretic peptide (NT-proBNP) is useful in the diagnosis of heart failure. We compared NT-proBNP levels in patients with and without a diagnosis of arterial hypertension.

Patients and method. Participants were recruited from a random sample of 999 inhabitants from the Community of Valencia (eastern Spain). Of these patients, 432 said they suffered from dyspnea and were referred to their hospital (10 hospitals involved), where blood samples were taken, an echo-Doppler study was performed, and the patients completed a questionnaire. Of the 432 participants with dyspnea, 215 gave informed consent for their inclusion in the study, and 202 completed the study. Hypertension was diagnosed in 72 participants and 130 were normotensive.

Results. For the whole population, NT-proBNP, expressed as the median and range, was 88 (0-2586) pg/mL. When we compared hypertensive with normotensive participants, we found higher NT-proBNP levels in the former group: median 123, range 0-2184 pg/mL, versus median 77, range 0-2586 pg/mL ($P<.01$). When we excluded subjects with systolic left ventricular dysfunction, we found higher levels in participants with hypertension: 119 (0-2184 pg/mL) vs 72 (0-997 pg/mL) ($P<.01$). When we also excluded subjects with diastolic dysfunction, we found (median 85, range 0-430 pg/mL) and (median 66, range 0-997 pg/mL), respectively (p = NS).

Conclusion. In a population study of subjects with dyspnea, hypertensive patients have higher NT-proBNP levels than subjects with normal blood pressure. This difference disappeared when patients with diastolic dysfunction were excluded from the analysis. Hypertension can thus be a confounding factor that potentially decreases the specificity of NT-proBNP levels for the diagnosis of heart failure. These findings should be taken into account when conducting clinical and epidemiological studies in which patients with both heart failure and hypertension are included.

Key words: *NT-proBNP. Hypertension. Heart failure.*

Full English text available at: www.revespcardiol.org

Hipertensión y valores de NT-proBNP. Su importancia en el diagnóstico de insuficiencia cardíaca

Introducción. El propéptido natriurético cerebral N-terminal (NT-proBNP) es útil en el diagnóstico de insuficiencia cardíaca. Hemos comparado los valores de NT-proBNP en sujetos con y sin diagnóstico de hipertensión arterial.

Pacientes y método. Los sujetos estudiados se obtuvieron de una muestra aleatoria de 999 habitantes de la Comunidad Valenciana. Del total, 432 declararon presentar disnea y fueron remitidos a su hospital de referencia (10 hospitales en el estudio), donde se les realizó una toma de sangre y un estudio eco-Doppler y completaron un cuestionario específico. De los 432 sujetos, 215 dieron su consentimiento informado para su inclusión en el estudio, que se completó en 202 pacientes. Se diagnosticó hipertensión en 72 sujetos y 130 fueron normotensos.

Resultados. Para la toda población, el NT-proBNP, expresado como mediana y rango, fue de 88 (0-2.586) pg/ml. Cuando comparamos a los sujetos hipertensos

---

ABBREVIATIONS

NT-proBNP: N-terminal pro-brain natriuretic peptide.
PANES: the Prevalence of Angina in Spain study (Estudio Prevalencia de Angina de Pecho en España).
LV: left ventricle.
Vp: mitral valve flow propagation velocity.
EF: ejection fraction.
E/A: E to A wave ratio of transmitral flow-rate.

---

con los normotensos, encontramos valores mayores de NT-proBNP en los hipertensos (123 [0-2.184] frente a 77 [0-2.586] pg/ml; p < 0,01). Cuando excluimos a los sujetos con disfunción sistólica del ventrículo izquierdo, encontramos valores superiores en aquellos con hipertensión (119 [0-2.184] frente a 72 [0-997] pg/ml; p < 0,01). Cuando además excluimos a los sujetos con disfunción diastólica encontramos 85 (0-430) y 66 (0-997) pg/ml, respectivamente (p = NS).

Conclusión. En un estudio poblacional de sujetos con disnea, los pacientes hipertensos tienen valores más elevados de NT-proBNP. Esta diferencia desaparece al excluir a los pacientes con disfunción diastólica. La hipertensión podría ser un factor de confusión que disminuya la especificidad del NT-proBNP para el diagnóstico de la insuficiencia cardíaca. Estos hallazgos deberían considerarse al llevar a cabo estudios clínicos y epidemiológicos en los que coexistan pacientes con insuficiencia cardíaca e hipertensión.

Palabras clave: *NT-proBNP. Hipertensión. Insuficiencia cardíaca.*

INTRODUCTION

Heart failure is a common cause of hospitalization and death in the developed world. Improving the diagnosis and care of patients with this syndrome could have a great impact on its associated mortality and health costs. Against this background, knowing the plasma concentrations of certain natriuretic peptides might be very useful in the diagnosis of heart failure.[1]

The endocrine function of the heart was confirmed over 20 years ago with the discovery of atrial natriuretic peptide (ANP). This eventually led to the description of a family of peptides involved in cardiovascular homeostasis (the natriuretic peptide family) whose members are of similar structure but different genetic origin. These peptides promote natriuresis and diuresis, act as vasodilators and have antimitogenic effects on cardiovascular tissues.[2] Two members of this family, ANP and brain natriuretic peptide (BNP), are secreted by the heart mainly in response to the stretching of the myocardium induced by volume overload or in response to hypertrophy.[3] The endocrinologically active C-terminal peptides—ANP and BNP—and their N-terminal prohormone fragments can be found in the plasma.

Natriuretic peptides are also useful as independent markers in risk stratification. Increased blood levels of these peptides have been recorded in congestive heart disease and acute myocardial infarction (AMI), suggesting they play a role in the pathophysiology of these conditions.[4-6]

High blood pressure affects more than half of elderly people, and prevalence continues to increase with age.[7] High blood pressure is associated with an increased risk of developing congestive heart disease, and patients with hypertrophy of the left ventricle or chronic heart failure have a much greater risk of dying.[8] High blood pressure also increases the risk of suffering a cerebrovascular accident, coronary artery disease, terminal renal disease and death.[7] The majority of people know it is important to monitor their blood pressure, but few do so. The morbidity and mortality associated with the problem therefore remain high. The recommendations of the Seventh Report of the Joint National Committee for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure, and of the WHO-International Society of Hypertension,[9] provide the most recent guidelines to family doctors for the control of high blood pressure, as well as information on its prevention, detection, assessment and treatment. Similar information is provided regarding its associated morbidity.

Increased plasma concentrations of N-terminal brain natriuretic peptide (NT-proBNP) are associated with increased wall stress, and high blood pressure is a common cause of the latter in the left ventricle (LV).[10] The present study examines plasma concentrations of NT-proBNP in patients with and without a diagnosis of heart failure, in an attempt to evaluate the influence of high blood pressure. The study population was selected from patients with dyspnea, given their high probability of suffering heart failure, in order to evaluate the use of NT-proBNP in the diagnosis of this syndrome in the general population.

PATIENTS AND METHODS

Population Studied

Patients were recruited from the PANES[11] study database (*Prevalencia de Angina de Pecho en España*— The Prevalence of Angina in Spain study). Those selected—all with dyspnea—came from the Valencia

Community (eastern Spain: Provinces of Castellón, Valencia, and Alicante). A total of 999 patients in the database lived in this region, of whom 432 declared suffering some degree of dyspnea (after receiving a detailed verbal explanation of the symptoms). All 432 patients were originally referred to their respective hospitals (a total of 10 were involved in the study), of these 215 agreed to enter the study. All underwent blood extraction, an echo-Doppler study, and completed a specific questionnaire that asked whether they had ever been diagnosed with high blood pressure[9] and what type of medication they had been prescribed. The blood pressure of every patient was also taken (for use in later calculations); those who met the diagnostic criteria for high blood pressure were considered hypertensive.

The study protocol was approved by the appropriate revision boards or the ethics committees of each center. The study was performed in accordance with the clinical practice guidelines and ethical standards regarding experiments on human beings established by the Declaration of Helsinki. All patients gave their written, informed consent to take part. At the end of the study, complete data were available for 202 patients.

The main cardiological diseases diagnosed were ischemic heart disease (n=31), valve disease (n=7), dilated cardiomyopathy (n=3), and congenital heart disease (n=1). Seventy two patients were diagnosed with hypertension and were treated (58% with angiotensin converting enzyme inhibitors, 42% with calcium antagonists, 32% with diuretics, and 11% with beta-blockers). Of these patients, 63.7% received monotherapy, 33.4% received 2 medications, and 2.9% received 3. In addition, the functional class of all patients was determined according to the criteria of the New York Heart Association (NYHA) (Table 1). Thirty one patients were found to have diabetes mellitus, and 37 were diagnosed with other diseases. Of the 202 patients who completed the study, 73 were obese (body mass index >30 kg/m^2).

Analysis of NT-proBNP Levels

Blood samples (in EDTA) were extracted by venipuncture after patients had lain in a supine position for at least 30 min. Samples were separated into their component fractions by centrifugation in Eppendorf tubes before transport to the laboratory for analysis. The concentration of NT-proBNP in EDTA-plasma was determined in duplicate (and blind) by *in vitro* immunoenzymatic analysis using an ELISA kit (Roche Diagnostics);[12] the results are expressed in pg/mL (measurement range 0-2069 pg/mL).

Echocardiographic Study

This part of the study was performed using a number of standard echocardiography systems (those available at the 10 hospitals taking part). All were equipped with 2.5 MHz transducers. The images and the Doppler traces were recorded on video tape for centralized analysis (blind to the results of other tests).

All two-dimensional images, the Doppler spectrum and color Doppler, were analyzed using a computerized system (EcoDat; Software Medicina S.A.). Mean values for each Doppler variable were calculated for 4 cardiac cycles in each patient.

The mitral valve flow propagation velocity (Vp) was determined as previously described,[13] using the value of 45 cm/s as a cut-off point for the diagnosis

TABLE 1. **Patient Clinical and Analytical Characteristics***

	Diagnosed With Hypertension (n=72)	Not Diagnosed With Hypertension (n=130)	P
Age, years	68±8	64±9	<.05
Male/female	28/44	61/69	NS
SBP, mm Hg	155±24	134±18	<.001
HR, beats/min	75±16	72±11	NS
NYHA functional class			
I	22 (31%)	69 (53%)	
II	39 (54%)	47 (36%)	
III	11 (15%)	14 (11%)	
LV mass index, g/m^2	127±45	105±47	<.01
Creatinine, mg/dL	1.1±0.9	0.9±0.2	<.05
Hematocrit, %	43±5	43±5	NS
NT-proBNP, pg/mL	123 (0-2184)	77 (0-2586)	<.01

*HR indicates heart rate; NYHA, New York Heart Association; SBP, systolic blood pressure; LV, left ventricle. Results are expressed as means ± SD or number of patients. NT-proBNP values are expressed as median plus range.

TABLE 2. **Echocardiographic Characteristics of Patients With an Ejection Fraction of >50%***

	Vp<45 cm/s (n=34)	Vp>45 cm/s (n=132)	P
E, cm/s	55±14	61±15	<.05
E/A	0.79±0.14	0.87±0.19	<.05
EF	64±6	66±5	<.05
LV mass index, g/m²	132±75	106±36	<.01

*A indicates maximum late transmitral flow rate; E, maximum early transmitral flow rate; EF, ejection fraction; LV, left ventricle; Vp, mitral valve flow propagation velocity. Results are expressed as means ±SD.

of diastolic dysfunction. The A and E waves of the transmitral flow-rate were measured by pulsed Doppler , and the E/A ratio was calculated. The area-length method was used to calculate the ejection fraction (EF) (100 ([end diastolic volume-end systolic volume]/end diastolic volume). The cut-off point for systolic dysfunction was taken as 50%.[14] Left ventricular mass was determined as previously described.[15]

The intraobserver and interobserver variability for Vp was 7.2±8.0% and 8.0±8.0% respectively (the absolute difference divided by the mean value of all measurements).

Statistical Analysis

Results are expressed as means ± standard deviation (SD), except those for NT-proBNP (non-symmetrical distribution) which are expressed as the median plus the range. Two groups of patients were distinguished: those with and those without a diagnosis of high blood pressure. The Student t test for independent samples was used to compare continuous, normally distributed variables. The Fisher exact test was used to compare qualitative independent variables. The Mann-Whitney U test was used to compare the NT-proBNP values of the hypertensive and non-hypertensive patients.

When patients with systolic—and later, diastolic—dysfunction were excluded, the Mann-Whitney U test was again used to compare the NT-proBNP levels of the hypertensive and non-hypertensive patients.

All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS/PC) v10.1, (SPSS Inc. Chicago, Illinois). Significance was set at $P<.05$.

RESULTS

For the population as a whole, the mean values for NT-proBNP, Vp, EF and the LV mass index were 88 (0-2586) pg/mL, 60±19 cm/s, 63±8%, and 112±47 g/m² respectively.

The distribution of patients with a diagnosis of some

heart problem across the hypertensive and non-hypertensive groups was: ischemic heart disease—hypertensive 48%, non-hypertensive 52%—, valve disease —hypertensive 43%, non-hypertensive 57%—, dilated cardiomyopathy—hypertensive 33%, non-hypertensive 67%—; 1 patient with high blood pressure was diagnosed with congenital heart disease. According to the clinical and echocardiographic studies, 50% of the patients had dyspnea of non-cardiac origin.

Patients with a diagnosis of high blood pressure (n=72, Vp=58±19 cm/s, EF=64±9%, LV mass index=127±45 g/m²) were found to have higher NT-proBNP levels than those with normal blood pressure (n=130, Vp=61±9 cm/s, EF=63±8%, LV mass index=105±47 g/m²): 123 [0-2184] pg/mL compared to 77 [0-2586] pg/mL; $P<.01$; Table 1).

When patients with left ventricular systolic dysfunction were excluded (EF<50%) (see Table 2 for the echocardiographic traces of patients with EF>50%), and the hypertensive and non-hypertensive patients compared (hypertensive patients: n=65, Vp=59±19 cm/s; non-hypertensive patients n=114, Vp=63±19 cm/s), those with high blood pressure were again found to have higher NT-proBNP levels (119 [0-2184] compared to 72 [0-997] pg/mL in non-hypertensive patients; $P<.01$). When patients with signs of left ventricular diastolic dysfunction (Vp<45 cm/s) were also excluded from the analysis, the NT-proBNP level of the 44 hypertensive patients remaining was 85 (0-430) pg/mL compared to 66 (0-997) pg/mL in the 86 remaining non-hypertensive patients (P=NS).

The comparison of NT-proBNP levels between hypertensive and non-hypertensive patients with respect to etiological group showed that those with no cardiological diagnosis but with high blood pressure (n=52) had higher plasma NT-proBNP levels than those with normal blood pressure (n=108) (34 [0-568] pg/mL compared to 19 [0-289] pg/mL; $P<.01$). When patients with systolic dysfunction were excluded, those with high blood pressure (n=48) had higher NT-proBNP levels than did patients with normal blood pressure (n=99) (33 [0-586] pg/mL compared to 19 [0-289] pg/mL; $P<.01$). When patients

with a Vp of <45 cm/s were also excluded, the difference disappeared.

In patients with valve disease (n=7), hypertensive patients were found to have a mean NT-proBNP level of 228 (125-316) pg/m, whereas those with normal blood pressure had 50 (28-84) pg/mL (*P*<.05). When patients with an EF<50% were excluded, those with high blood pressure were found to have higher NT-proBNP levels (228 [125-316] compared to 49 [28-55] pg/mL in non-hypertensive patients; *P*<.05). When patients with both systolic and diastolic dysfunctions were removed from the analysis, no significant differences were found between hypertensive and non-hypertensive patients.

In patients with ischemic heart disease (n=31), no significant differences were seen in NT-proBNP levels between those who were hypertensive and those who were not.

The small number of patients with dilated cardiomyopathy (n=3) meant no such comparisons could be made.

DISCUSSION

The natriuretic peptide system becomes most active when there is ventricular dysfunction. Recently it has been confirmed that, of all the neurohormones studied, the cardiac natriuretic peptides are the best predictors of morbidity and mortality in AMI patients (when measured in the subacute phase), and in patients with chronic heart failure.[2,16] These peptides have an excellent negative predictive power, particularly in high risk patients. An increase in BNP values is sufficient to justify further tests.[2] In addition, the natriuretic peptides are useful in the control of therapy and for monitoring the course of disease in patients with heart failure. They can also be employed in risk stratification with respect to heart failure and myocardial infarction.[2,17] High plasma levels of NT-proBNP are also associated with increased wall stress (which is directly related to ventricular pressure) —and high blood pressure is a common cause of increased left ventricular wall stress.[10] High blood pressure affects more than half of all elderly people and its prevalence continues to increase with age.[7] Since heart failure and hypertension frequently coexist, this study examined the plasma concentrations of NT-proBNP in a population with dyspnea; those with and without a diagnosis of high blood pressure were compared given the clinical and epidemiological importance of any potential findings.

The results show that plasma NT-proBNP levels are higher in patients with high blood pressure compared to those with no such diagnosis. The distribution of patients with heart disease between the hypertensive and non-hypertensive patient groups was similar. Since systolic dysfunction is associated with

increased NT-proBNP levels,[18] these patients were excluded in the second phase of analysis, and it was found that hypertensive patients still showed high levels of the peptide. In a third step, those patients with diastolic dysfunction (another potential cause of high NT-proBNP levels—see Lubian et al[19]) were excluded from the analysis.[13] Lubian et al[19] found increased NT-proBNP levels in patients with diastolic dysfunction but normal systolic function, but differences between hypertensive and non-hypertensive patients disappeared. This shows that, in the present hypertensive patients, the levels of the peptide increased because of changes in diastolic function. In other words, NT-proBNP levels in patients with dyspnea and high blood pressure probably increase because of diastolic dysfunction.[20,21]

Many Doppler indices are used to describe diastolic dysfunction, but the present work took a Vp of 45 cm/s as the cut-off point for diastolic dysfunction (as described by García et al[13]). Unlike other indices, the Vp is a well-known Doppler variable associated with left ventricular diastolic dysfunction.[22] Furthermore, the Vp reflects changes in relaxation, distensibility and rigidity, and its fluctuations are simultaneous with changes in other variables (Table 2). In addition, in the present work, Vp results were found to be very reproducible.

With respect to EF, the 50% level was used as a cut-off point for systolic dysfunction: the literature shows a value of <50% is normally used in populational studies.[14] Although the mean EF recorded was acceptable, it should be remembered that only about 50% of patients had dyspnea of cardiac origin, and it was not possible to confirm the declarations of the remaining patients when specific tests (NYHA) were performed. Furthermore, although in clinical practice EF is used as an absolute value (despite the fact that in the diagnosis of left ventricular systolic dysfunction a cut-off point has to be selected), there is no doubt that it is a relative value for each heart and that small reductions in a patient's EF (compared to earlier readings) can be interpreted as systolic dysfunction. In a general population of elderly patients (such as those of the present study), changes in systolic and diastolic function can both occur. This might lead to changes in the severity of symptoms without this being reflected in resting EF readings.[23]

The equipment used to record the NT-proBNP levels was first generation, and the results showed a wide range from 0-2586 pg/mL. The lower limit of detection may not have been sufficiently sensitive—thus the readings of 0 pg/mL. Nonetheless, these results show that the values are in coherence with the well validated Doppler indices and the statistical analysis supports the conclusions inferred from the results. The values of a range that superimpose one group on another in the general population would not exist when dealing

with an individual patient.

For non-hypertensive patients with an EF>50 and a Vp of >45 cm/s, the NT-proBNP values ranged from 0-997 pg/mL—a higher value than might be expected. This could be due to mitral or aortic regurgitation in some patients who still have good ventricular function, but who show increased left ventricular volume.[24,25]

Ideally, the statistical analysis used would have been two-way ANOVA, in which the effect of the presence or absence of high blood pressure on the appearance of systolic or diastolic dysfunction would have been examined.[26] In optimum conditions, the results obtained would have been more powerful. However, since the distribution was not normal, two-way ANOVA was impossible, and the procedure described above was selected.

In conclusion, this work shows that, in a general population, hypertensive subjects have higher NT-proBNP levels than those with normal blood pressure. This difference is maintained when patients with systolic dysfunction are removed from the analysis. However, when those with signs of both systolic and diastolic dysfunction are removed, no significant differences are seen between hypertensive and non-hypertensive patients. The fact that NT-proBNP levels were higher in the hypertensive population with dyspnea (largely due to changes in diastolic function) could introduce confusion that might reduce the specificity of NT-proBNP in the diagnosis of heart failure. These findings should be taken into consideration in clinical and epidemiological studies in which there are patients with heart failure and high blood pressure. The present study could serve as a basis for the use of NT-proBNP levels in the control of treatment and monitoring of patients with high blood pressure.

REFERENCES

1. Remme WJ, Swedberg K. Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527-60.
2. Mair J, Hammerer-Lercher A, Puschendorf B. The impact of cardiac natriuretic peptide determination on the diagnosis and management of heart failure. Clin Chem Lab Med 2001; 39:571-88.
3. Groenning BA, Nilsson JC, Sondergaard L, Pedersen F, Trawinski J, Baumann M, et al. Detection of left ventricular enlargement and impaired systolic function with plasma N-terminal pro brain natriuretic peptide concentrations. Am Heart J 2002;143:923-9.
4. Cho Y, Somer BG, Amatya A. Natriuretic peptides and their therapeutic potential. Heart Dis 1999;1:305-28.
5. Cosín Aguilar J, Hernándiz Martínez A, Díez Gil JL, Capdevila Carbonell C, Salvador Sanz A, Diago Torrent JL, et al. Valor del nivel de NTproBNP en población adulta extrahospitalaria. Rev Esp Cardiol 2003;56:236-44.
6. Osca J, Quesada A, Arnau MA, Osa A, Hervás I, Almenar L, et al. Péptido cerebral natriurético. Valor diagnóstico en la insuficiencia cardíaca. Rev Esp Cardiol 2002;55:7-15.
7. Basile J. Hypertension in the elderly: a review of the importance of systolic blood pressure elevation. J Clin Hypertens (Greenwich) 2002;4:108-19.
8. Zoccali C, Mallamaci F, Tripepi G. Hypertension as a cardiovascular risk factor in end-stage renal failure. Curr Hypertens Rep 2002;4:381-6.
9. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. J Hypertens 1999;17:151-83.
10. Pries AR, Secomb TW. Structural adaptation of microvascular networks and development of hypertension. Microcirculation 2002;9:305-14.
11. Cosin J, Asin E, Marrugat J, Elosua R, Aros F, De los Reyes M, et al. Prevalence of angina pectoris in Spain. PANES Study group. Eur J Epidemiol 1999;15:323-30.
12. Karl J, Borgya A, Gallusser A, Huber E, Krueger K, Rollinger W, et al. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. Scand J Clin Lab Invest Suppl 1999;230:177-81.
13. García MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol 1998;32:865-75.
14. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. JAMA 2002;288: 1252-9.
15. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450-8.
16. Krishnaswamy P, Lubien E, Clopton P, Koon J, Kazanegra R, Wanner E, et al. Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction. Am J Med 2001;111:274-9.
17. De Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med 2001;345:1014-21.
18. Campbell DJ, Mitchelhill KI, Schlicht SM, Booth RJ. Plasma amino-terminal pro-brain natriuretic peptide: a novel approach to the diagnosis of cardiac dysfunction. J Card Fail 2000;6:130-9.
19. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. Circulation 2002;105:595-601.
20. Pieske B, Herrmann-Lingen C, Von Lewinski D, Sander J, Schenker W, Wiesenthal T, et al. NT-pro brain natriuretic peptide as marker for severity and prognosis of left ventricular dysfunction [abstract]. Circulation 2002;106:683.
21. Dahlof B, Zanchetti A, Diez J, Nicholls MG, Yu CM, Barrios V, et al, for the REGAAL Study Investigators. Effects of losartan and atenolol on left ventricular mass and neurohormonal profile in patients with essential hypertension and left ventricular hypertrophy. J Hypertens 2002;20:1855-64.
22. Cohen GI, Pietrolungo JF, Thomas JD, Klein AL. A practical guide to assessment of ventricular diastolic function using Doppler echocardiography. J Am Coll Cardiol 1996;27:1753-60.
23. Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with «isolated» diastolic heart failure and diastolic dysfunction. Circulation 2002;105: 1195-201.
24. Brookes CI, Kemp MW, Hooper J, Oldershaw PJ, Moat NE. Plasma brain natriuretic peptide concentrations in patients with

chronic mitral regurgitation. J Heart Valve Dis 1997;6:608-12.
25. Gerber IL, Stewart RAH, French R, Legget ME, Greaves SC, Sutton TM, et al. Natriuretic peptides are elevated in aortic regurgitation but correlate poorly with disease severity. J Am Coll Cardiol 2002;350B:4094.

26. Kleinbaum DG, Kupper LL, Muller KE. Applied regression analysis and other multivariable methods. 2nd ed. Boston: PWS-Kent, 1988; p. 417-57.