

Biological Markers and Guided Therapy, Vol. 2, 2015, no. 1, 13 - 23  
HIKARI Ltd, [www.m-hikari.com](http://www.m-hikari.com)  
<http://dx.doi.org/10.12988/bmgt.2015.5101>

**The BNP Gene Polymorphism as a Regulator of  
Brain Natriuretic Peptide Plasma Level in  
Men with Uncomplicated Essential  
Hypertension and Left Ventricular Hypertrophy**

**Iuliia P. Pashkova**

Vinnytsia National Pirogov Memorial Medical University  
Department of Internal Medicine of the Medical Faculty №2  
Pirogov str., 56, Vinnytsia, postcode UA-21018, Ukraine

Address for correspondence:  
Postcode UA-21020, Ukraine, Vinnytsia, L.Ukrainka Str., 65/2

**Vadym M. Zhebel**

Vinnytsia National Pirogov Memorial Medical University  
Department of Internal Medicine of the Medical Faculty №2  
Pirogov str., 56, Vinnytsia, Postcode UA-21018, Ukraine

Address for correspondence:  
Professor of Internal Medicine of the Medical Faculty №2 of  
Vinnytsia National Pirogov Memorial Medical University  
Vinnytsia, V. Porik str., 35/19, Postcode UA-21030, Ukraine

**Hanna O. Palahniuk**

Vinnytsia National Pirogov Memorial Medical University  
Department of Internal Medicine of the Medical Faculty №2  
Pirogov str., 56, Vinnytsia, postcode UA-21018, Ukraine

Address for correspondence:  
Vinnytsia, Skaletskyy str. 38A/30, Postcode UA-21000, Ukraine

**Olena O. Sakovych**

Vinnitsia National Pirogov Memorial Medical University  
Department of Internal Medicine of the Medical Faculty №2  
Pirogov str., 56, Vinnitsia, postcode UA-21018, Ukraine

Address for correspondence:  
Vinnitsia, 40th Anniversary of the Victory str., 50/144  
Postcode UA-21036, Ukraine

**Olga L. Starzhynska**

Vinnitsia National Pirogov Memorial Medical University  
Department of Internal Medicine of the Medical Faculty №2  
Pirogov str., 56, Vinnitsia, postcode UA-21018, Ukraine

Address for correspondence:  
Vinnitsia, Sverdlov St. 184/56, Postcode UA-21018, Ukraine

**Alla F. Gumenyuk**

Vinnitsia National Pirogov Memorial Medical University  
Department of Internal Medicine of the Medical Faculty №2  
Pirogov str., 56, Vinnitsia, postcode UA-21018, Ukraine

Address for correspondence:  
Vinnitsia, V. Porik 14/40, Postcode UA-21000, Ukraine

**Olexandr I. Datsyuk**

Vinnitsia National Pirogov Memorial Medical University  
Department of Surgery №1, course of Anesthesiology and Intensive Care  
Pirogov str., 56, Vinnitsia, postcode UA-21018, Ukraine

Address for correspondence:  
Vinnitsia, Agrarian St. 8, Postcode UA-21019, Ukraine

**Natalia V. Zhebel**

Vinnitsia National Pirogov Memorial Medical University  
Department of Internal Medicine of the Medical Faculty №2  
Pirogov str., 56, Vinnitsia, postcode UA-21018, Ukraine

Address for correspondence:  
Vinnitsia, V. Porik str., 35/19, Postcode UA-21030, Ukraine

Copyright © 2015 Iuliia P. Pashkova et al. This article is distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

### Abstract

**Aim:** The BNP biomarker application optimization for myocardial dysfunction diagnosis in men citizens of Podillia region in Ukraine with uncomplicated essential hypertension and left ventricular hypertrophy by determining the plasma levels in patients with different BNP gene variants.

**Methods.** We examined 141 men, age 40 – 60 years, who live in Podillia region. Among them 62 men were diagnosed uncomplicated EH with left ventricular hypertrophy (stages 1 and 2) and CHF I-II classes according to NYHA Classification. 79 healthy men were included into the control group. The patients with uncomplicated EH and the healthy men were representative by age. The BNP (T-381C) gene polymorphism was determined by PCR, and the level of BNP plasma concentrations was established by ELISA.

**Results.** In both healthy men and patients with uncomplicated EH with LVH, residents of Podillia region, age 40-60 years, dominates the T381C genotype and the C allele of the BNP gene. It was found that any inherited variant of the BNP gene was not associated with the risk of developing uncomplicated EH with LVH in men residents of Podillia region. However, carriers of the C381C genotype and the C allele of the BNP gene have significantly higher levels of BNP in plasma in both healthy men and patients with uncomplicated EH and LVH, residents of Podillia region, age 40-60 years. There are calculated levels of BNP that can be used for screening of large groups of people for early diagnosis of uncomplicated EH with LVH: BNP boundary level  $\geq 82,41$  pg/ml ables to diagnose uncomplicated EH with LVH in male carriers of the C allele heterozygote carriers of the genotypes T381C and C381C of the BNP gene; BNP boundary level  $\geq 45,34$  pg/ml ables to diagnose uncomplicated EH with LVH in male homozygote carriers of the T381T genotype of the BNP gene.

**Keywords:** essential hypertension, gene polymorphism of the brain natriuretic peptide, plasma concentration of the brain natriuretic peptide

### Introduction

In 1988 T. Sudoh, working in H. Matsuo research group, presented a peptide similar to the atrial natriuretic peptide (ANP) which was isolated from the brain of guinea pigs and called brain natriuretic peptide (BNP) [18]. Further studies showed convincingly that the main source of BNP were myocardium cells. It was demonstrated that BNP had an important pathophysiological importance in the diagnosis of heart failure (HF), risk stratification and monitoring chronic heart failure (CHF) treatment effectiveness. It is known that synthesis of BNP depends directly on left ventricle (LV) volume distension and preload pressure and is a sensitive and specific indicator of left ventricular dysfunction [3-5,8,14,17,19].

According to the recommendations of the European Association of Cardiology (ESC, 2012) and the American College of Cardiology/American Heart Association (ACC/AHA, 2013) there were proposed boundary levels of BNP to exclude the diagnosis of acute heart failure (BNP <100 pg/ml) and CHF (BNP <35 pg/ml) and also to evaluate the CHF treatment effectiveness [12]. The employees of the Department of Internal Medicine of the Medical Faculty №2 VNPMMU have calculated the boundary level of BNP which is 50 pg/ml for screening diagnosis of isolated diastolic dysfunction of the heart when systolic function is saved [20].

According to the global human genome data (The "Human Genome" European Community 2013) there were found 29 genic loci which are involved in the regulation of blood pressure (BP). The research of single nucleotide polymorphisms (SNPs) which also contribute to the regulation of blood pressure (the BNP gene is being considered among them as well) is still in progress. Currently the most significant BNP gene polymorphism is defined and studied. It is the physiological substitution of thymine to cytosine at the position of 381 (T-381C) also known as (SNP rs198389) which participates in the development of essential hypertension (EH) [2, 5, 7, 11, 13, 15-16]. However, the data about the plasma level of BNP in different variants of the BNP gene polymorphism in patients with uncomplicated EH with left ventricular hypertrophy (LVH) is not numerical and has not been studied in the Ukrainian population yet at all.

The aim of the study is the BNP biomarker application optimization for myocardial dysfunction diagnosis in men residents of Podillia region in Ukraine with uncomplicated essential hypertension and left ventricular hypertrophy by determining the plasma concentration levels in carriers of different BNP gene variants.

## **Methods**

The study involved 141 middle-aged male residents in Podillia region. Among them 62 men from the main group were diagnosed uncomplicated EH with LVH (stages 1 and 2), with saved systolic function and CHF I-II classes according to NYHA Classification, whose average age was  $49,19 \pm 0,66$  years and 79 healthy men whose age ( $49,01 \pm 0,73$  years) did not differ from patients with uncomplicated EH with LVH and made the control group ( $p > 0,05$ ). The diagnosis of EH was established on the basis of the patients' complaints, anamnesis, physical examination, laboratory and instrumental methods of investigation according to the guideline of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) in 2013 [6].

Systolic function of left ventricle was assessed in terms of ejection fraction (EF). Systolic function was considered saved when EF was over 45%. All patients during the examination were treated at Vinnytsia regional specialized dispensary of radiation protection of the Ministry of Health of Ukraine and Military Medical

Center of the Central Region of Air Force of Ukraine and were observed from December 2013 to July 2014.

Exclusion criteria of the study were: secondary hypertension, renal and liver dysfunction, coronary heart disease the onset of which was before EH, endocrine, hematological, neoplastic and autoimmune disorders, patients with EH complications: myocardial infarction, acute cerebrovascular accident. Genotyping of the BNP gene was conducted using polymerase chain reaction after isolation of genomic DNA from white blood cells of venous blood. This study was carried out jointly with the Research Institute of the genetic and immunological bases of pathology and pharmacokinetics "Ukrainian Medical Stomatological Academy" (Poltava, the head is prof. I.P. Kaidashev). The BNP concentration in plasma was determined by using ELISA method on enzyme-linked immunosorbent analyzer "Numareader single» (Germany) at 450 nm and differential filter 630 nm. To determine the BNP plasma concentration a standard set of the firm «Peninsula laboratories Inc.» (USA) was used.

The mathematical processing was performed on a personal computer using a standard statistical package STATISTICA 6,0. There were checking distribution of genes polymorphisms frequencies in the population according to Hardy-Weinberg equilibrium law using a calculator gene expert to calculate the number of statistical parameters in the study "case-control" which using SNP (State Scientific Center of the Russian Federation "HosNYY genetics", *gen-exp.ru*). Boundary BNP level determined by the method proposed by M.U. Antamonov in collaboration with V.M. Zhebel, O.O. Sakovych, G.V. Wilczynskyy, O.O. Singh [1,9,21].

## Results

It was established that in the male control group the frequency of the genotype T381T of the BNP gene was 18,9% (n=15), the genotype T381C - 49,37% (n=39) and the genotype C381C - 31,65% (n=25) ( $p_{CC-TT} > 0.05$ ;  $p_{TC-CC} > 0.05$ ;  $p_{TC-TT} \leq 0,05$ ). The frequency of the T allele in male from the control group was 43.67%, the C allele - 56.33% ( $p < 0.05$ ).

It was investigated that in patients from the main group dominated the C allele and the genotype T381C, but there were no significant differences in carriage of the genotype variants of the BNP gene compared with those in the control group ( $p > 0,05$ ) (Figure 1).

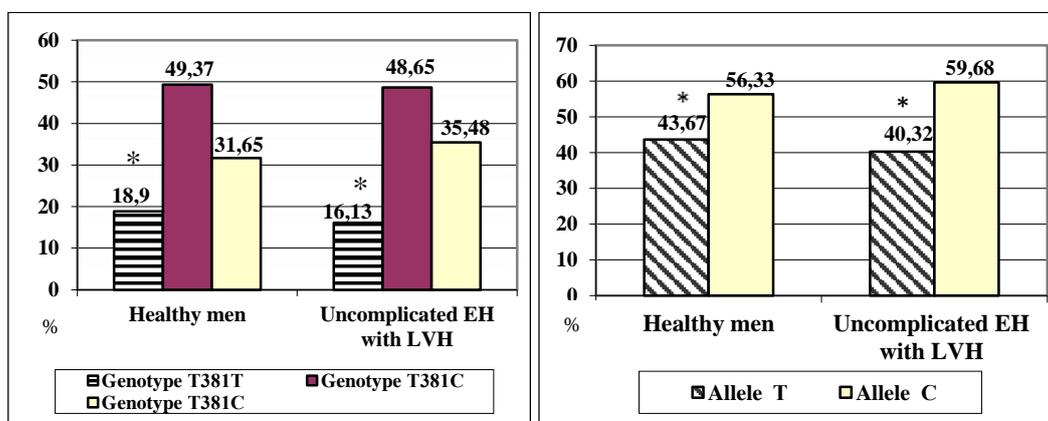


Fig. 1 The distribution of the BNP gene genotypes frequencies and alleles in men citizens of Podillia region in the healthy patients and the patients with uncomplicated EH and LVH (%)

Note: The difference is significant ( $p \leq 0,05$ ) when compared to: \* - the T381C genotype/the C allele within each group.

The odds ratio was calculated to assess the risk of development of uncomplicated EH with LVH in carriers of different BNP genotypes in men citizens of Podillia region, age 40-60 years. It was established that inherited the BNP gene variant was not associated with the risk of development of uncomplicated EH (for genotypes general model for imitation is not significant  $\chi^2=2,18$ ;  $p=0,14$ ; odds ratio OR <1; alleles multiplicative model for imitation is not significant  $\chi^2=2,23$ ,  $p=0,33$ ; odds ratio OR <1) after calculating the number of statistical parameters using the calculator gene expert.

The plasma BNP level in the control group was  $21,74 \pm 0,50$  pg/ml. In patients with uncomplicated EH and LVH average concentration of plasma BNP was  $77,40 \pm 2,85$  pg/ml and was significantly higher than in the control group ( $p < 0,0001$ ).

The next step was to determine the BNP plasma levels in men with uncomplicated EH and LVH with different stages of arterial hypertension (AH). It was determined that there was not significant difference in BNP plasma concentrations in different stages of hypertension in patients with uncomplicated EH and LVH ( $p > 0,05$ ) (Table 1).

Table 1  
Plasma brain natriuretic peptide levels in men with uncomplicated EH and LVH and different stages of hypertension (M $\pm$ m)

Stages of hypertension	Uncomplicated EH with LVH
1. 1 stage	78,52 $\pm$ 5,22
2. 2 stage	78,38 $\pm$ 4,22
3. 3 stage	73,89 $\pm$ 6,07
$p > 0,05$	$p_{2-1}$ ; $p_{3-1}$ ; $p_{3-2}$

It was interesting to find the difference in concentrations BNP concentrations in carriers of various variants of the BNP gene. It was established a significant difference in concentrations BNP plasma concentrations between carriers of the genotypes T381T, T381C and C381C of the BNP gene both in the control group and in the patients with uncomplicated EH and LVH ( $p < 0,0001$ ). The highest concentration of BNP was found in homozygote carriers of the genotype C381C of the BNP gene and the lowest level was found in homozygote carriers of the genotype T381T of the BNP gene ( $p < 0,0001$ ) and that means that the presence of the C allele in the genotype of the BNP gene is associated with a higher plasma concentration of the peptide (Table 2).

Table 2  
Plasma brain natriuretic peptide levels in the healthy men and in the patients with uncomplicated EH and LVH with different genotypes of the BNP gene ( $M \pm m$ )

Genotypes of the BNP gene	1. Healthy men	2. Uncomplicated EH with LVH	$p < 0,0001$
T381T	15,95 $\pm$ 0,89	48,16 $\pm$ 0,63	$p_{2-1}$
T381C	22,42 $\pm$ 0,21	90,89 $\pm$ 0,77	$p_{2-1}$
C381C	29,62 $\pm$ 0,44	101,28 $\pm$ 0,90	$p_{2-1}$
p	$p_{TC-TT} < 0,0001$ ; $p_{CC-TT} < 0,0001$ ; $p_{CC-TC} < 0,0001$	$p_{TC-TT} < 0,0001$ ; $p_{CC-TT} < 0,0001$ ; $p_{CC-TC} < 0,01$	

The BNP plasma levels was determined in the healthy men and in the patients with uncomplicated EH and LVH in carriers of different alleles of the BNP gene. It was found that in the healthy men there was not significant difference in the BNP plasma levels in carriers of different alleles of the BNP gene ( $p_{T-C} > 0,05$ ). In the patients with uncomplicated EH and LVH was significantly greater level of BNP in carriers of the C allele of the BNP gene ( $p_{T-C} < 0,0001$ ). However, the BNP plasma concentration in men with EH who are carriers of the C allele and the T allele of the BNP gene were significantly higher than in the same allele carriers in the control group (Table 3).

Table 3  
Plasma brain natriuretic peptide levels in the healthy men and in the patients with uncomplicated EH and LVH in carriers of different alleles of the BNP gene ( $M \pm m$ )

Alleles of the BNP gene	1. Healthy men	2. Uncomplicated EH with LVH	$p < 0,0001$
C	29,62 $\pm$ 0,44	101,28 $\pm$ 0,90	$p_{2-1}$
T	19,89 $\pm$ 0,50	72,81 $\pm$ 3,00	$p_{2-1}$
p	$p_{T-C} > 0,05$	$p_{T-C} < 0,0001$	

There were established BNP levels for screening diagnosis of uncomplicated EH with LVH in men citizens of Podillia region in Ukraine that can be applied during examining of large groups of people to identify persons who require to be conducted full examination including ultrasound of the heart and indentify the presence of EH:

- The BNP level  $\geq 47,22$  pg/ml (sensitivity - 95%, specificity – 82,2% correctness – 89,23%, false negative answer - 5%, false positive answer – 11,82%) can diagnose uncomplicated EH with LVH in males.

However, the BNP plasma concentration can be influenced by genetics. The results indicated that the presence of the C allele in the genotype of the BNP gene is associated with higher plasma concentrations of peptide so it was decided to calculate the BNP boundary levels for the C allele carriers - carriers of the heterozygote genotype T381C and carriers of the homozygote genotype T381T:

- The BNP level  $\geq 82,41$  pg/ml (sensitivity - 92%, specificity – 84,7% correctness – 84,14%, false negative answer - 4%, false positive answer - 9,56%) can diagnose uncomplicated EH with LVH in males the C allele carriers and the heterozygote T381C, C381C of the BNP gene;

- The BNP level  $\geq 45,34$  pg/ml (sensitivity - 91%, specificity – 84,3% correctness – 96,1%, false negative answer - 0%, false positive answer – 5,26%) can diagnose uncomplicated EH with LVH in males with the homozygote genotype T381T of the BNP gene.

## Discussion

It was determined that in both healthy men inhabitants of Podillia region and in patients with uncomplicated EH and LVH dominates the C allele and the genotype T381C of the BNP gene. At the same time the C381C genotype reveals more frequently in the Americans, the Russians and the Germans. The T381T genotype is more common among Russian citizens. The frequencies of polymorphic genotypes of the BNP gene did not differ significantly in patients from different populations [2,7,10].

No significant differences were revealed in the BNP plasma levels in men with uncomplicated EH and LVH with different stages of hypertension. Different plasma peptide concentrations in patients with different genotypes of the BNP gene might cause some discussion. As noted above, the patients with uncomplicated EH and LVH have significantly higher peptide levels for all variants of genotypes of the BNP gene than the healthy men. Thus, the studies of L.C. Costello-Boerrigter et al. (2011), A. Meirhaeghe et al. (2007) and R. Pfister et al. (2011) found that inherited genotypes of the BNP gene with the presence of the C allele - T381C and C381C is associated with high plasma concentration of peptide in patients with uncomplicated EH and LVH [7,13,15]. E.N. Berezikova (2013) investigated the BNP gene polymorphism in patients of both sexes with CHF where it was shown that in healthy individuals of Russian population with the genotype C381C plasma levels of N-terminal prohormone of brain natriuretic peptide was significantly higher than in carriers of the genotype T381T [2]. BNP

plasma concentrations in carriers of the C allele and the genotype - C381C and T381C were significantly higher than in carriers of the genotype T381T among the control group and the patients with uncomplicated EH and LVH which corresponded to literature data. This may require further in-depth research of genetic influence on the BNP plasma concentrations, along with other factors, which could require revision of normative BNP levels in healthy subjects and as pathological marker where BNP has diagnostic value.

## Conclusions

1. The T381C genotype and the C allele of the BNP gene dominate among the healthy men and the patients with uncomplicated EH and LVH, residents of Podillia region, age 40-60 years.
2. The BNP gene variant is not associated with the risk of development of uncomplicated EH with LVH in men inhabitants of Podillia region in Ukraine.
3. The carriers of the genotypes C381C and T381C and the C allele of the BNP gene have significantly higher plasma levels of the aforementioned peptide among the control group and in the patients with uncomplicated EH and LVH.
4. There were estimated BNP boundary levels that can be used for screening of large contingents of people for early diagnosis of uncomplicated EH with LVH for the C allele and the heterozygote T381C and C381C carriers and homozygote carriers of the genotype T381T of the BNP gene.

**Acknowledgements.** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. We thank all patients for their participation in the investigation, and the doctors, nurses, and administrative staff of the Vinnytsia Regional Specialized Radiation Protection Dispensary and Military Medical Center of the Central Region of the Air Forces of Ukraine (Vinnytsia, Ukraine) that assisted with the study.

**Ethical principles.** All the patients have given their written informed consent for participation in the study.

**Conflict of Interest:** The authors declare no conflict of interest.

## References

- [1] M.Y. Antomonov, The calculation of boundary (critical) levels of acting accounting factors for different types of data obtained in hygienic research, *Health of Settlements*, **43** (2004), 573-579.
- [2] E.N. Berezikova, S.D. Mayanskaya, L.A. Garayev, S.N. Shilov, Gene polymorphism of brain natriuretic peptide in patients with chronic heart failure, *Kazan Journal of Medicine*, (2013), no. 4, 433-438.

- [3] A. Berezin, Utility of Biomarkers in Contemporary Management of Chronic Heart Failure, *Annals of Clinical and Laboratory Research, iMedPub Journals*, **3** (2015), no. 2, 16-28.
- [4] A. Bhardwaj, S.U. Rehman, A.A. Mohammed, et al., Quality of life and chronic heart failure therapy guided by natriuretic peptides: results from the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study, *American Heart Journal*, **164** (2012), no. 5, 793-799.  
<http://dx.doi.org/10.1016/j.ahj.2012.08.015>
- [5] O. Blonar, V. Zhebel, The level of B-natriuretic peptide in patients with obesity, *Materials of the Canadian Cardiovascular Congress*, **14** (2012), 40.
- [6] G.M. Chairperson, R.F. Chairperson, K. Narkiewicz, et al., 2013 ESH/ESC Guidelines for the management of arterial hypertension, *Journal of Hypertension*, **31** (2013), no. 7, 1281-1357. <http://dx.doi.org/10.1097/01.hjh.0000431740.32696.cc>
- [7] L.C. Costello-Boerrigter, G. Boerrigter, S. Ameenuddin, et al., The Effect of the Brain-Type Natriuretic Peptide Single-Nucleotide Polymorphism rs198389 on Test Characteristics of Common Assays, *Mayo Clinic Proceedings*, **86** (2011), no. 3, 210-218. <http://dx.doi.org/10.4065/mcp.2010.0708>
- [8] A. Hammerer-Lercher, P. Collinson, M.P. Dieijen-Visser, et al., Do laboratories follow heart failure recommendation and guidelines and did we improve? The CARDiac MARKer Guideline Uptake in Europe (CARMAGUE), *Clinical Chemistry and Laboratory Medicine*, **51** (2013), no. 6, 1301-1306.  
<http://dx.doi.org/10.1515/cclm-2012-0510>
- [9] V.I. Juncker, S.G. Grigorev, *Mathematical - Statistical Data Processing of Medical Research*, St. Petersburg: MMA, 2002, 266.
- [10] M. Lajer, L. Tarnow, A. Jorsal, et al., Polymorphisms in the B-type natriuretic peptide (BNP) gene are associated with NT-proBNP levels but not with diabetic nephropathy or mortality in type 1 diabetic patients, *Nephrol. Dial. Transplant.*, **22** (2007), no. 1, 3235-3239. <http://dx.doi.org/10.1093/ndt/gfm360>
- [11] D.E. Lanfear, J.M. Stolker, S. Marsh, et al., Genetic variation in the B-type natriuretic peptide pathway affects BNP levels, *Cardiovascular Drugs and Therapy*, **21** (2007), no.1, 55– 62. <http://dx.doi.org/10.1007/s10557-007-6007-5>
- [12] J.J.V. McMurray, S. Adamopoulos, S.D. Anker, et al., ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012, *European Heart Journal*, **33** (2012), no. 14, 1787-1847.  
<http://dx.doi.org/10.1093/eurheartj/ehs104>
- [13] A. Meirhaeghe, M.S. Sandhu, M.I. Carthy, Association between the T-381C polymorphism of the brain natriuretic peptide gene and risk of type 2 diabetes in

human populations, *Human Molecular Genetics*, **16** (2007), no. 11, 1343-1350.  
<http://dx.doi.org/10.1093/hmg/ddm084>

[14] S.R. Motiwala, J.L. Januzzi Jr., The role of natriuretic peptides as biomarkers for guiding the management of chronic heart failure, *Journal of Clinical Pharmacy and Therapeutics*, **93** (2013), no. 1, 57-67.  
<http://dx.doi.org/10.1038/clpt.2012.187>

[15] R. Pfister, S. Sharp, R. Luben, et al., Mendelian Randomization Study of B-Type Natriuretic Peptide and Type 2 Diabetes: Evidence of Causal Association from Population Studies, *PLoS Medicine*, **8** (2011), no. 10, 1-11.  
<http://dx.doi.org/10.1371/journal.pmed.1001112>

[16] R. Poręba, K. Początek, P. Gać, et al., SNP rs198389 (T-381 C) polymorphism in the B-type natriuretic peptide gene promoter in patients with atherosclerotic renovascular hypertension, *Polskie Archiwum Medycyny Wewnętrznej*, **119** (2009), no. 4, 219 -224.

[17] O. Sakovych, V. Zhebel, A. Gumenyuk, et al., Plasma levels of vascular natriuretic peptide in women with essential hypertension, *Heart Failure*, 60152 (2014), 1492.

[18] T. Sudoh, K. Kangawa, N. Minamino, et al., C-type natriuretic peptide: a new member of natriuretic peptide family identified in porcine brain, *Biochemical and Biophysical Research Communications*, **168** (1990), no. 2, 863-870.  
[http://dx.doi.org/10.1016/0006-291x\(90\)92401-k](http://dx.doi.org/10.1016/0006-291x(90)92401-k)

[19] V.A. Vizir, A.E. Berezin, The value of the activation of natriuretic peptides in heart failure from the perspective of opportunities to the real need, *Ukrainian Medical Journal*, **4** (2004), no. 42, 70-77.

[20] V. Zhebel, O. Starzhynska, U. Hefter, Polymorphism of the angiotensin II receptor gene in hypertensive patients of different stages as a factor of influence on the structure and function of the myocardium, *Ukrainian Journal of Cardiology*, Materials of the international forum "Cardiology yesterday, today and tomorrow", **3** (2006), 54-58.

[21] V. Zhebel, O. Sakovych, G. Wilczynskyy, O. Singh, Ukraine Patent 67486, the IPC G01N 33/48 (2006.01), Method of diagnosis of chronic heart failure in women of postmenopausal age with hypertension, the applicant and the owner the Vinnitsa National Piragov Memorial Medical University. - №u201108789, appl. 07/12/11, publ. 27.02.12, Bulletin of №4.

**Received: October 1, 2015; Published: October 28, 2015**