

ORIGINAL ARTICLE

EFFECT OF DEMOGRAPHIC AND CLINICAL VARIABLES ON NT-proBNP

Sofia Amjad¹, Sobia Hassan², Amna Faruqi³

¹Associate Professor of Physiology, Ziauddin University, Karachi, Pakistan

²Assistant Professor of Pathology, Altamash Institute of Dental Medicine,

³Assistant Professor of Physiology, Islamabad Medical & Dental College.

ABSTRACT

Background: A number of demographic and clinical variables have an effect on NT-proBNP, which has been used as a serological marker for evaluating cardiovascular disease. This study was done to evaluate the effect of these confounding variables on NT-proBNP.

Methods: A cross-sectional study was performed on 50 Coronary artery bypass grafting (CABG) patients. Data of demographic and clinical variables was obtained from the patients. Samples of serum and pericardial fluid were collected and NT-proBNP levels were assessed in all the samples by an electrochemiluminescence immunoassay. Transformation of NT-proBNP values into log was done. The effect of all the variables on pericardial fluid and serum levels of log NT-proBNP was statistically calculated.

Result: In this study NT-proBNP was found to be increased significantly with age (p-value of 0.01 and 0.02). Males constituted 86 % of our sample and NT-proBNP was insignificantly higher in men than women (p =0.227 and 0.245). There was also no significant difference between the mean NT-proBNP levels in hypertensives and diabetics.

Conclusion: Age is the confounding variable which has significant effect on NT-proBNP concentrations while other demographic and clinical variables did not show a significant effect. Therefore, a minute adjustment should be made for the independent effects of age.

KEYWORDS: Pro-brain natriuretic peptide, Coronary Artery Bypass Grafting, Heart failure, hypertension, Diabetes Mellitus

Corresponding Author

Sofia Amjad,

Associate Professor of Physiology

Ziauddin University

Email: drsofiaamjad@gmail.com

INTRODUCTION

Natriuretic peptides have been used as diagnostic markers in heart failure (HF)¹. Amino-terminal pro-brain natriuretic peptide (NT-proBNP) being a more stable serological marker, has been more significant for evaluating cardiovascular disease². NT-proBNP has been used in a number of studies, as a prognostic marker of heart failure, acute coronary syndromes, stable coronary artery disease, and stroke³. A number of demographic and clinical variables have shown an effect on peptide concentrations of natriuretic peptides in plasma. Parallel changes have been seen in NT-proBNP with

age, Left ventricular ejection failure (LVEF), and Left ventricular (LV) diameter in chronic and symptomatic HF⁴. The increase in concentrations of natriuretic peptides with age may be due to an increase in the release or a decrease in the clearance of NT-proBNP⁴. The changes in left ventricular compliance and decreased cardiac diastolic function may be the other reasons for increase in natriuretic peptides with age^{5,6}. The direct association of NT-proBNP with age has been used for improving diagnostic sensitivity for younger patients⁵.

Januzzi *et al* have also studied the relationship between gender and NT-proBNP levels. NT-proBNP

levels have been found to be high in older female subjects compared to age-matched male subjects. This may be due to a higher prevalence of diastolic abnormalities and reductions in Glomerular Filtration rate (GFR)⁵. This has also been observed that a positive association of female gender is related to estrogen status, as high BNP levels have been seen in women using Hormone replacement therapy (HRT)⁷. Differences in endothelin and angiotensin-converting enzyme activity have also been demonstrated due to effect of HRT⁷.

Association of hypertension with elevated levels of NT-proBNP has also been reported. Hypertensive patients even with normal heart geometry have a slightly elevated natriuretic peptide level. If hypertension is associated with left ventricular hypertrophy, natriuretic peptide level is further increased⁶. The increase in systolic pressure causes an increase in ventricular wall stiffness causing increase in ventricular muscle and increased concentrations of natriuretic peptides⁶. This correlation is strongest with concentric hypertrophy, which is in particular linked to increased morbidity and mortality⁸.

Many studies have stated that pericardial fluid levels of natriuretic peptides are higher than plasma because of more closely related pericardial fluid with left ventricle than serum^{9,10}. Hence, analysis of pericardial fluid NTproBNP along with serum may provide more information about the ventricular function because a number of factors affect the natriuretic peptide levels in serum.

This study was designed to identify potentially confounding variables for the analysis of the plasma and pericardial fluid concentration of NT-proBNP, which might guide in better diagnostic performance of the marker. The objective of this study is to measure the effect of demographic and clinical variables on both pericardial and serum NTproBNP in patients undergoing coronary artery bypass grafting (CABG).

METHODS

A cross sectional study was done. Approval was taken from ethics committee on human research of Ziauddin University, Karachi. A total of 50 CABG patients were taken. All patients gave written informed consent. All the data about age, gender, hypertension and diabetes mellitus was collected from the patients. Echocardiography was done to measure the ejection fraction (EF). Both pericardial fluid and blood samples were collected during CABG in evacuated plastic tubes. Both the samples were centrifuged at 3500g for 10 min at 4 °C immediately after collection, and were stored at -80 °C. NT-proBNP (cobas e pro-BNP electrochemiluminescence immunoassay (Roche Diagnostics, Man-

heim, Germany cat #04842464 190) was measured in both the samples.

Data entry and statistical analysis was performed using SPSS version 17.0 (Chicago, IL). Ratio (Male: Female) was calculated for gender distribution. Descriptive statistics were used. Mean and standard deviation was calculated for continuous response variables and frequencies and percentages were calculated for presenting categorical variables. Univariate analysis for comparison was done by employing unpaired t-test. Log transformation of serum and pericardial NT-proBNP levels was done because of the large variation in the level of cardiac peptides in both serum and pericardial fluid. P-value less than 0.05 were considered as significant.

RESULT

Fifty patients taken in this study were divided into two groups depending upon the age: group 1 with age from 45 to 55 years, and group 2 with ages ranging from 56 to 65 years.

NT-proBNP levels of serum in the two age groups were 2.10 ± 0.64 pg/ml and 2.56 ± 0.60 pg/ml (p-value = 0.01 for difference). Regarding pericardial fluid, NT-proBNP levels between the two age groups, were 2.70 ± 0.46 pg/ml and 3.07 ± 0.68 pg/ml (p-value = 0.02 for difference) (**table -1**).

Effect of gender was also analyzed on serum and pericardial NTproBNP. (**table-1**) There were 43 males and 7 females. The serum values of NT-proBNP in males and females were 2.47 ± 0.65 pg/ml and 2.15 ± 0.56 pg/ml (p-value = 0.227 for difference). The pericardial fluid values of NT-proBNP in males and females were 3.0 ± 0.6 pg/ml and 2.69 ± 0.48 pg/ml (p-value = 0.245 for difference). No significant difference was seen.

Out of 50 patients, 46 were hypertensive while only 4 were non hypertensive. The NTproBNP level in serum of hypertensives was 2.508 ± 0.66 pg/ml and in non-hypertensives was 2.13 ± 0.49 pg/ml with a p-value of 0.09 as shown in table 3. Pericardial fluid value of NT-proBNP in hypertensives was 3.04 ± 0.66 pg/ml and in non-hypertensives was 2.68 ± 0.50 pg/ml with a p-value of 0.11. Therefore, this factor has an effect on peptide levels but is not significant.

Regarding status of diabetes, there were 26 diabetics and 24 non-diabetics. Serum NT-proBNP level in diabetic and non-diabetics was 2.49 ± 0.66 pg/ml and 2.35 ± 0.62 pg/ml (p-value of 0.47 for difference). Pericardial NT-proBNP value for diabetics and non-diabetics was 2.97 ± 0.71 pg/ml and 2.94 ± 0.57 pg/ml (p-value of 0.86 for difference). (**Table -1**)

Table-1: Effect of Age, gender, hypertension and diabetes on serum and pericardial NT-pro-BNP

Effect of Age on serum and pericardial NT-pro-BNP		
VARIABLES	Log serum NT- proBNP (pg/ml)	Log pericardial NT- ProBNP (pg/ml)
Age group 45-55 years (n=35)	2.10±0.64	2.70±0.46
Age group 56-65 years (n=35)	2.56±0.60	3.07±0.68
P- value	0.01	0.02
Effect of gender on serum and pericardial NT-pro-BNP		
Men(n=43) Mean ± S.D	2.47±0.65	3.0±0.66
Women(n=43) Mean ± S.D	2.15±0.56	2.69±0.48
P- value	0.227	0.245
Effect of hypertension on serum and pericardial NT-pro-BNP		
Hypertensive (n=39) Mean ± S.D	2.508±0.66	3.04±0.66
Non Hypertensive (n=11) Mean ± S.D	2.13±0.49	2.68±0.50
P- value	0.09	0.11
Effect of diabetes on serum and pericardial NT-pro-BNP		
Diabetes (n=26) Mean ± S.D	2.49±0.66	2.97±0.71
Non Diabetes (n=24) Mean ± S.D	2.35±0.62	2.94±0.57
P- value	0.47	0.86

DISCUSSION

Studies have reported that plasma concentrations of NT-proBNP were significantly higher in women than in men, and the mean concentration of plasma NT-proBNP almost doubled per age decade regardless of sex¹. In this study concentration of NT-proBNP in serum and pericardial fluid was higher in males than in females. This may be due to the fact that in our study, females patients were fewer in number.. However, regarding age, there is significant correlation of age with both serum and pericardial fluid NT-proBNP levels. This association has previously been reported in normal subjects, which may be due to increased myocardial mass, chamber specific alterations in gene expression,

and a reduction in the renal clearance of natriuretic peptides with aging¹¹⁻¹³.

The secretion of NT-proBNP levels is increased in type² diabetes with cardiovascular disease as compared to normal subjects. There are several possible mechanisms for the rise in NT-proBNP levels in diabetes. It may be due to high prevalence of diastolic dysfunction, atherosclerotic changes in coronary arteries, increased collagen content in heart and decreased myocardial relaxation. However the present study has not shown such an effect of diabetes on NT-proBNP levels. It may be due to shorter duration of diabetes and better glycaemic control¹⁴.

Previous studies have been reported that plasma NT-proBNP levels are higher in patients with high blood pressure compared to those with normal blood pressure¹⁵. This may be due to the fact that high blood pressure leads to LV hypertrophy and as a result of this increased wall stress of LV occurs¹⁶. But this study has not shown significant effect of hypertension on NT-proBNP levels which may be due to good control of blood pressure. In future, better designed prospective studies are necessary to investigate the effect of demographic and clinical variables on NT-proBNP levels and their bearing on mortality risk.

CONCLUSION

Demographic and clinical variables did not show a significant effect on NT-proBNP concentrations both in plasma and pericardial fluid, except, for age. In conclusion, individuals with elevated NT-proBNP concentrations appeared to be independently associated with an increased risk for cardiac diseases. A small adjustment should, however, be made for the independent effects of age.

REFERENCES

1. Raymond I, Groenning B, Hildebrandt Py, Nilsson J, Baumann M, Trawinski J, et al. The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population. *Heart*. 2003;89(7):745-51.
2. Geng Z, Huang L, Song M, Song Y. N-terminal pro-brain natriuretic peptide and cardiovascular or all-cause mortality in the general population: A meta-analysis. *Scientific Reports*. 2017;7.
3. Wei G, Yaqi R, Ningfu W, Xuwei H. N-terminal prohormone B-type natriuretic peptide and cardiovascular risk in stable coronary artery disease: a meta-analysis of nine prospective studies. 2012;e92-8
4. Masson S, Latini R, Anand IS, Vago T, Angelici L, Barlera S, et al. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clinical chemistry*. 2006;52(8):1528-38.
5. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients. *European heart journal*. 2006;27(3):330-7.
6. Zhu W-H, Chen L-Y, Dai H-L, Chen J-H, Chen Y, Fang L-Z. Correlation between B type natriuretic peptide and metabolic risk factors. *Archives of medical science: AMS*. 2016;12(2):334-40.
7. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC. Plasma brain natriuretic peptide concentration: impact of age and gender. *Journal of the American College of Cardiology*. 2002;40(5):976-82.
8. Nishikimi T, Yoshihara F, Morimoto A, Ishikawa K, Ishimitsu T, Saito Y, et al. Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. *Hypertension*. 1996;28(1):22-30.
9. Watanabe M, Kawaguchi S, Nakahara H, Hachimaru T. The roles of natriuretic peptides in pericardial fluid in patients with heart failure. *Clinical cardiology*. 2009;32(3):159-63.
10. Amjad S, Sami SA, Basir MN, Hameed K, Fujita M, Ahmad HR. Pericardial fluid and serum biomarkers equally predict ventricular dysfunction. *Asian Cardiovascular and Thoracic Annals*. 2013;21(2):160-5.
11. Sayama H, Nakamura Y, Saito N, Kinoshita M. Why is the concentration of plasma brain natriuretic peptide in elderly inpatients greater than normal? *Coronary artery disease*. 1999;10(7):537-40.
12. Raizada V, Thakore K, Luo W, McGuire P. Cardiac chamber-specific alterations of ANP and BNP expression with advancing age and with systemic hypertension. *Molecular and cellular biochemistry*. 2001;216(1-2):137-40.
13. Giannessi D, Andreassi M, Del Ry S, Clerico A, Colombo M, Dini N. Possibility of age regulation of the natriuretic peptide C-receptor in human platelets. *Journal of endocrinological investigation*. 2001;24(1):8-16.
14. Sahu A, Gupta T, Kavishwar A, Sarkar PD, Singh R. Diagnostic Role of NT Pro BNP in Diabetes Type 2 Patients Associated with Cardiovascular Disease Risk, A Study from Central India. *Journal of Medicine*. 2010;11(1):33-8.
15. Rivera M, Taléns-Visconti R, Salvador A, Bertomeu V, Miró V, de Burgos FG, et al. NT-proBNP levels and hypertension. Their importance in the diagnosis of heart failure. *Revista Española de Cardiología (English Edition)*. 2004;57(5):396-402.
16. Mancina G, Kjeldsen SE, Zappe DH, Holzhauser B, Hua TA, Zanchetti A, et al. Cardiovascular outcomes at different on-treatment blood pressures in the hypertensive patients of the VALUE trial. *European heart journal*. 2016;37(12):955-64.