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Is There A Correlation Between Left Atrium Diameter and NT-ProBNP Levels in Resistant Hypertension?

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Abstract

Objectives: Resistant hypertension (RHT) defines uncontrolled blood pressure despite appropriate treatment and identifies a high-risk population, which may benefit from different diagnostic and therapeutic approaches. This study has investigated the relationship between left atrial diameter (LAD) and N- terminal pro- brain type natriuretic peptide (NT-proBNP) levels in true RHT patients with sinus rhythm.

Materials and Methods: The outpatient data of Kemalpaşa State Hospital's cardiology clinic has been reviewed retrospectively. The patients with RHT are included but patients with secondary hypertension, pseudo-RHT, atrial fibrillation and left ventricle ejection fraction <50% are excluded from analysis. Age and gender specific cut-off levels have been used for NT-proBNP.

Results: Among 74 true RHT patients, 48 were female. The mean age was 61.9±11.2 years. Mean LAD was 40.9±4.0 mm and mean NT-proBNP was 330.3±394.9 pg/mL. Larger LAD was correlated to higher levels of NT-proBNP (r=0.451, p<0.001). Even after controlling for age, gender, heart rate, systolic and diastolic blood pressures, partial correlation was continued between LAD and NT-proBNP (r=0.234, d.f=67, p<0,05).

Conclusion: The current study showed that larger LAD is related to higher levels of NT-proBNP in RHT, which may allow us to use simple echocardiographic parameter to diagnose high-risk patients and hypervolemia instead of NT-proBNP, an expensive biomarker. Because of single-center results and limited number of patients, further studies are needed.

Keywords: Resistant hypertension, NT-proBNP, left atrial diameter

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Introduction

Resistant hypertension (RHT) is defined as failure to achieve blood pressure goals under recommended treatment strategy in adherent patients. RHT definition requires that the recommended treatment strategy contains appropriate lifestyle and optimal or best tolerated doses of at least three drugs with the condition that at least one being diuretic[1]. While the underlying mechanism of RHT is poorly understood, it is known that the patients with RHT are at higher risk of target organ damage and cardiovascular events[2].

Left atrial (LA) enlargement is a common finding in hypertension and considered closely related to the diastolic dysfunction of left ventricle. LA enlargement is also crucial in atrial fibrillation (AF), which carries high risk for stroke and mortality[3]. According to the Framingham study, a 5 mm increase in LA diameter (LAD) led to a 39% increase in the AF-incidence[4].

Natriuretic peptides involve volume homeostasis and cardiac remodeling and excite attention for risk stratification in various clinical scenarios. According to Framingham Offspring Study, brain natriuretic peptide (BNP) level above 80th percentile was associated with increased risk for major cardiovascular events, including heart failure and mortality[5]. Masugata et al. reported that as an echocardiographic parameter, LAD correlates best with BNP in well-treated hypertensive patients[6]. Such as BNP, N-terminal pro brain natriuretic peptide (NT-proBNP) is also a predictor of mortality in hypertension and in secondary prevention. It is shown that NT-proBNP correlates with left ventricular mass index[7].

In the present study, we aimed to investigate the correlation between LAD and NT-proBNP in RHT population and searched for the answer if LAD, a basic echocardiographic parameter, could be used instead of NT-proBNP, an expensive biomarker, to identify the highest risk patients in the high-risk population of RHT.

Materials and Methods

The outpatient data of Kemalpaşa State Hospital is screened retrospectively through the hospital communication system (HCS), Probel. System records, which contain data about patient demographics, laboratory and imaging records, prescription and adherence information of patients, who applied to the cardiology outpatient clinic between January and September 2015, are reviewed. Data of 1057 hypertensive patients older than 18 years in both genders is screened retrospectively. RHT is defined as 1) lack of blood pressure (BP) control despite three drugs, one diuretic or 2) need for more than three drugs (four or more) to control BP in adherent patient, in whom secondary hypertension (HT) and white-coat HT are excluded. To avoid any misevaluation, patients with moderate to severe valvular disease, systolic heart failure as left ventricle ejection fraction (LVEF) <50% and AF are excluded. Also patients with a creatine level of >1.5 mg/dL are excluded because this level of creatine is considered as a manifestation of chronic kidney disease. After applying all the criteria, 74 patients with RHT on sinus rhythm are included to analyze.

All data is collected through the HCS according to the International statistical classification of diseases and related health problems. Patient's demographics, such as age, gender, patient's complaint at application, accompanying illness, systolic and diastolic BP in the office is obtained from the patient's application page. For ECG and echocardiographic parameters such as LVEF, left ventricle hypertrophy (LVH), left ventricle diastolic dysfunction (LVDD), LAD and diameter of ascendant aorta, imaging studies are used. Blood and urine biochemistry, fasting glucose, renal and liver function tests, lipid panel, thyroid function tests, NT-proBNP, microalbuminuria, are collected from laboratory studies. Medication and adherence are controlled through the www.medeczane.gov.tr, if the patients refilling their pills appropriately.

NT-proBNP measurement is made with Cobas® system and the Elecsys proBNP II assay; Roche Diagnostics GmbH. Reference ranges for NT-proBNP are defined

according to prospectus information in 97.5th percentile, which differ with age and gender. Reference values are given in the Table 1.

Statistical Analysis

In the statistical analysis, all continuous measures are expressed as mean ± standart deviation. Frequencies and percentages are reported for categorical variables. Statistical analyses are performed with the IBM SPSS Statistics 22 software package. Associations between variables are tested by Pearson's correlation (Pearson's coefficient of correlation "r"). A p value <0.05 is considered statistically significant.

Compliance with ethical standards

The present study is designed as a retrospective archive screening study. For this study, no external funding is received. All authors declare no conflict of interest. Ethic approval for the study is obtained from the Clinical Research Ethical Board of Ege University School of Medicine on 22.11.2016 with the number 16-10.1/3. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

After screening outpatient data and applying the inclusion criteria, 74 patients are defined as true RHT on sinus rhythm. Exercise intolerance and fatigue were the most frequent complaints according to the application reports. Among 74 patients, 48 (64.9%) were female and 26 (35.1%) were male. The mean age was 61.76±11.27 years. All the 74 patients were receiving adequate doses of a renin-angiotensin system blocker, either angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, plus a diuretic. The third pill was a beta-blocker in 21 patients and a calcium antagonist in 12 patients. The remaining 41 patients needed more than three drugs. Type 2 diabetes mellitus was present in 25 patients. None of the diabetic patients were taking high doses of glitazones, which is known as a specific factor for hypervolemia, and only two patients were receiving intensive insulin treatment.

Mean systolic and diastolic blood pressures were 172.55±20.21 and 93.31±13.74 mmHg. Patient's imaging studies are reviewed for echocardiographic parameters. All the 74 RHT patients had LVH and LVDD. LVEF, ascendant aorta width and LAD were 57.36±2.89%, 35.41±3.73 mm and 40.96±4.09 respectively. The mean NT-proBNP level was 330.30±394.96 pg/mL. All the remaining demographics are given in the Table 2.

Table 1. Age and gender specific cut-off levels of NT-proBNP

Age	NT-proBNP for male	NT-proBNP for female
18-44 years	<85.8 pg/mL	<130 pg/mL
45-54 years	<125 pg/mL	<249 pg/mL
55-64 years	<210 pg/mL	<287 pg/mL
65-74 years	<376 pg/mL	<301 pg/mL
>75 years	<486 pg/mL	<738 pg/mL

NT-proBNP: N-terminal pro b-type natriuretic peptide,
Reference ranges for NT-proBNP are defined according to prospectus information in 97.5th percentile, which differ with age and gender

Table 2. Demographics for RHT patients on sinus rhythm

RHT patients on sinus rhythm (n=74, 48 female and 26 male)	
Age (years)	61.76±11.27
Heart rate (bpm)	72.74±11.87
Systolic BP (mmHg)	172.55±20.21
Diastolic BP (mmHg)	93.31±13.74
NT-proBNP (pg/mL)	330.30±394.96
LAD (mm)	40.96±4.09
LVEF (%)	57.36±2.89
Ascendant Aorta (mm)	35.41±3.73
Fasting glucose (mg/dL)	120.31±44.31
Urea (mg/dL)	35.54±13.10
Creatinin (mg/dL)	0.96±0.21
Potassium (mmol/L)	4.34±0.46
Low dansity lipoprotein (mg/dL)	114.37±36.94
Trigliseride (mg/dL)	165.19±70.84
C-reactive protein (mg/dL)	5.06±4.91

RHT: Resistant hypertension, BP: Blood pressure, LAD: Left anterior diameter, LVEF: Left ventricular ejection fraction
Demographics are given as arithmetic mean ± standart deviation

After group demographics, the relationship between LAD and NT-proBNP is investigated and Pearson's correlation analysis is performed (Table 3). Between LAD and NT-proBNP, a pairwise correlation (r=0.451, p<0.001) is found. After controlling for age, gender, heart rate, systolic and diastolic BP, a partial correlation (r=0.234, d.f=67, p=0.049) is still remained. The correlation between age and NT-proBNP is already known. Therefore cut-off values based on NT-proBNP are qualified by age. Also in the present study, this relationship is well observed. There was a pairwise correlation between age and NT-proBNP (r=0.670, p<0.001) and the correlation still remained after controlling for gender, heart rate, systolic and diastolic BP (r=0.590, d.f=67, p<0.001). At last, the correlation between LAD and age is investigated. At first glance, there was a pairwise correlation between LAD and age (r=0.469, p<0.001) but after controlling for gender, heart rate, NT-proBNP, systolic and diastolic BP, the partial correlation is disappeared (r=0.175, d.f=67, p=0.151). This suggests that the correlation between LAD and NT-proBNP is not a spurious relationship driven by age, gender, heart rate or blood pressure.

Discussion

RHT defines a specific population among hypertensive patients. True RHT prevalence is considered less than 10% of all-treated hypertensive patients, but RHT patients carry a higher risk for hypertension mediated organ damage, chronic kidney disease and early cardiovascular events[1]. Daugherty et al. demonstrated that RHT is associated with an increased risk of adverse cardiovascular outcomes, even after multivariable adjustment[8]. It is very important to make the risk stratification for identifying the highest risk patients who may benefit from specific diagnostic and therapeutic approaches. Gaddam et al. reported patients with RHT have higher levels of natriuretic peptide levels compared to controls[2], but there is evidence that not all the RHT patients have high levels of NT-proBNP[9], which leads to the question if NT-proBNP may be used in risk stratification beyond its volume-overload meaning also in the RHT population. Apart from its role in the diagnosis of heart failure, NT-proBNP is related to cardiac remodeling and is a predictor of mortality in hypertension[7], so it has become even more popular in detecting the high-risk patients for cardiovascular conditions. There are several studies, which confirmed the relationship between NT-proBNP and LAD in hypertensive patients[3,6,10]. Recently, Courand et al. has demonstrated that NT-proBNP mirrors the damaging effects of high BP on target organs in hypertensive patients and NT-proBNP level increases with the increasing number of target organs involved[7]. Because of the number of true RHT patients are relatively low, RHT patients are not studied widely in this condition. The present study has investigated if LAD, a simple echocardiographic parameter, is correlated with NT-proBNP, an integrative marker of high clinical interest. When established further this relationship can be used to predict high risk patients among the adherent RHT patients on the appropriate therapy. There was a significant pairwise correlation between LAD and NT-proBNP (r=0.451, p<0.001) in the RHT group and the partial correlation still remained statistically significant after controlling for other risk factors like age, gender, heart rate, systolic and diastolic BP, which are known for interference. This study suggests that LAD and NT-proBNP correlate positively, so larger LAD is related to higher NT-proBNP levels, even after controlling for other interacting factors. This finding may be used to predict the patients with high NT-proBNP levels, which

Table 3. Pairwise and partial correlations between NT-proBNP, LAD and age

		LAD (mm)	Age
NT-proBNP	Pairwise	0.451 (p<0.001)	0.670 (p<0.001)
	Partial	0.234, (p=0.049)[a]	0.590 (p<0.001)[b]
LAD (mm)	Pairwise	-	0.469 (p<0.001)
	Partial	-	0.175 (p=0.151)[c]

NT-proBNP: N-terminal pro b-type natriuretic peptide, LAD: Left atrial diameter
Pairwise correlation coefficients are Pearson's r
[a]Controlling for Age, Gender, HR, SBP, DBP
[b]Controlling for LA, Gender, HR, SBP, DBP
[c]Controlling for BNP, Gender, HR, SBP, DBP

is an indicator for high cardiovascular and mortality risk, by using LAD. There was also a pairwise correlation between age and NT-proBNP (r=0.670, p<0.001) and even after controlling all other related factors, a powerful and significant correlation (r=0.590, d.f=67, p<0.001) remain, which is very important in the studies involve NT-proBNP to take age specific cut-off levels instead of common cut-off's to avoid misevaluation. Another interesting finding of this study is the relation between LAD and age. While a powerful pairwise correlation between LAD and age was detected consistent with some previous studies[11,12], the correlation disappears after controlling for other effecting factors, such as gender, NT-proBNP, heart rate, systolic and diastolic BP. This finding is consistent with the findings of some more recent studies that normal ageing does not increase LA size[3].

Limitations of the study

The most important limitation of the study is its retrospective single-center design. The sample size is another important limiting factor. Because of the low prevalence of true RHT, despite of retrospective screening data of 1057 hypertensive patients only 74 true RHT patients on sinus rhythm were identified. A larger dataset with perhaps data from multiple centers can allow for more advanced tests. This study used office-based BP measurement, but ambulatory BP measurement could be more accurate. Also medications and treatment adherence are controlled through the health insurance system, but there is always a chance that some patients have refilled their prescriptions and not taken pills regularly. Despite these limitations, these study presents analyses performed on the real-world patient data and can help inform practitioners about their diagnostic and treatment decisions.

Conclusion

The present study suggests, in RHT patients, larger LADs are related to higher levels of NT-proBNP and the correlation is still consistent even after controlling other factors, which may influence this relation. This may allow us to use a simple echocardiographic parameter to predict not only the volume status of the patient but also identify the high-risk patients.

Ethics

Ethics Committee Approval: Ethic approval for the study is obtained from the Clinical Research Ethical Board of Ege University School of Medicine on 22.11.2016 with the number 16-10.1/3.

Informed Consent: Informed consent was not obtained due to the study is retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.İ.T., Concept: E.İ.T., Design: E.İ.T., Data Collection or Processing: E.İ.T., E.Ş., Analysis or Interpretation: E.İ.T., E.Ş., Literature Search: E.İ.T., Writing: E.İ.T., E.Ş.

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References

1. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal 2018;39:3021-3104.
2. Gaddam KK, Nishizaka MK, Pratt-Ubunama MN, et al. Resistant hypertension characterized by increased aldosterone levels and persistent intravascular volume expansion. Arch Intern Med 2008;168:1159-64.
3. Chen Y, Sato H, Watanabe N, et al. Factors influencing left atrial volume in treated hypertension. Journal of Cardiology 2012;60:133-8.
4. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 1994;271:840-4.
5. Phelan D, Watson C, Martos R, et al. Modest elevation in BNP in asymptomatic hypertensive patients reflect sub-clinical cardiac remodeling, inflammation and extracellular matrix changes. Plos One 2012;7:e49259.
6. Masugata H, Senda S, Murao K, et al. Association between echocardiographic parameters and brain natriuretic peptide levels in treated hypertensive patients. Clin Exp Hypertens 2011;33:187-91.

7. Courand PY, Harbaoui B, Bècle C, Mouly-Bertin C, Lantelme P. Plasma NT-proBNP mirrors the deleterious cardiovascular and renal continuum in hypertension. Eur J Prev Cardiol 2017;24:452-9.

8. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation 2012;125:1635-42.

9. Turkoglu EL, Kircicegi Cıcekdag EC. Resistant hypertension in elderly: a clinical manifestation of heart failure with preserved ejection fraction? Retrospective single-center analysis. Clinical and Experimental Hypertension 2018.

10. Lantelme P, Laurent S, Besnard C, et al. Arterial stiffness is associated with left atrial size in hypertensive patients. Arch Cardiovasc Dis 2008;101:35-40.

11. Nikitin NP, Witte KK, Thackray SD, Goodge LJ, Clark AL, Cleland JG. Effect of age and sex on left atrial morphology and function. Eur J Echocardiogr 2003;4:36-42.

12. De Castro S, Caselli S, Di Angelantonio E, Del Colle S, Mirabelli F, Marcantonio A, Puccio D, Santini D, Pandian NG. Relation of the left atrial maximal volume measured by real-time 3D echocardiography to demographic, clinical, and Doppler variables. Am J Cardiol 2008;101:1347-52.