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ORIGINAL ARTICLE

NT-pro BNP versus E/E' Ratio after ECG Treadmill Test in Asymptomatic Hypertensive Patients with Exercise-Induced Diastolic Dysfunction

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ABSTRACT

Left ventricle dysfunction is the link between the heart morphological changes and the overt heart failure. Hypertension is one of the main cardio-vascular conditions which can lead to development of left ventricle failure. The study was conducted at outpatient Clinic – Medlife, Memorial Hospital. It intended to compare NT-pro BNP and the ratio E/E' as markers of diastolic dysfunction in hypertensive patients and normal ejection fraction (EF) and no signs or symptoms of heart failure. Both indexes proved to reflect independently diastolic dysfunction in symptomatic patients with different cardiac diseases but not in asymptomatic hypertensive patients. It was a single-center observational study recruiting 40 participants (20 F 52-70 age, and 20 M 56-67 age). Natriuretic peptides are widely accepted as biomarkers in heart failure with reduced ejection fraction. NT-pro BNP proved to be a very good means of diagnosing exercise-related left ventricular dysfunction (LVD) showing that it could unveil a subclinical LVD, especially in patient with myocardial remodeling. The main goal of this study was to compare the values of NT-pro BNP and E/E'. We have found no correlation between NT-pro BNP and E/E', both pre-exercise and post-exercise, demonstrating that the later was not a reliable means of diagnosing LVD at effort in aymptomatic hypertensive patients.

Keywords: hypertension; left ventricle 'diastolic dysfunction; NT-pro BNP; E/E'.

REZUMAT

Disfuncția de ventricul stâng constituie anomalia fiziopatologică incipientă care face trecerea de la modificările morfopatologice la dezvoltarea insuficienței cardiace manifeste. Hipertensiunea este una din afecțiunile cardio-vasculare frecvente care poate conduce la insuficiență cardiac. Acest studiu a fost efectuat în Clinica Medlife – Memorial Hospital. Studiul și-a propus să compare NT-pro BNP și raportul E/E'ca markeri ai disfuncției diastolice la pacienții hipertensivi cu FE normală și fără semne sau simptome de insuficiență cardiacă. Atât E/E'cât și NT-pro BNP au demonstrat utilitatea în diagnosticarea disfuncției diastolice în studii separate și la pacienți simptomatici ca diferite afecțiuni cardiace, dar nu și la pacienții hipertensivi asimptomatici. Este un studiu observațional unicentru în care au fost incluși 40 de participanți (20 F 52-70 de ani, 22 B 56-67 de ani). S-a demonstrat că NT-pro BNP este un foarte bun mijloc pentru diagnosticul disfuncției diastolice a ventriculului stâng induse de efort, în special la pacienții hipertensivi cu remodelare miocardică1. În studiul nostru nu s-a găsit nicio corelație între NT-pro BNP și E/E, atât pre-efort cât și post-efort, demonstrând că raportul E/E'nu este o metodă utilă pentru diagnosticul disfuncției diastolice a ventriculului stâng la pacienții hipertensivi asimptomatici.

Cuvinte cheie: hipertensiune, disfuncție diastolică ventricul stâng, NT-pro BNP, E/E'.

INTRODUCTION

Cardio-vascular diseases remain the main cause of mortality and morbidity in the developed countries despite the newest treatments. In dealing with this problem the main goal is to diagnose them as early as possible and treat them accordingly, in order to prevent the progression to heart failure[1,2].

Hypertension if left untreated will inevitably lead to left ventricular failure. Through structural changes which affect the myocardium it initially brings about left ventricular dysfunction and finally overt heart failure develops[1,2].

N-terminal pro-brain natriuretic peptide (NT-pro BNP) emerged as the most useful biomarker for dia-

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gnosing acute heart failure, for guided-treatment and fallow-up of the patients with overt heart failure[3-6].

The level of NT-pro BNP at rest was also used as a possible biomarker for estimating the exercise capacity in healthy volunteers or in patients with heart failure[7].

On the other hand, NT-pro BNP levels at effort was used as a marker of exercise-induced increase in filling pressures in many clinical settings, to either diagnose diastolic dysfunction or the degree of the severity of heart failure. It was reported in patients with old myocardial infarction[8], in patients with severe valvular diseases[9], in patients with heart failure[10] dilated cardiomyopathy and mitral stenosis[11]. In a meta-analyzes of 51 studies encompassing different heart diseases, Remmelzwaal Sh. and co. concluded that the natriuretic peptides are a reasonable tool for diagnostic of diastolic dysfunction and HFpEF, but is better to be used as a rule out criteria[12]. Even in the normal subjects, either trained athletes or non-trained volunteers, the relation between secretion of NT-pro BNP and effort was studied and reported with a direct positive relationship[13-15].

So a direct positive relationship between the levels of NT-pro BNP and filling pressures at exercise was clearly proved in many studies but all were done in patients with symptomatic heart failure[16].

Another way of diagnosing non-invasively the diastolic dysfunction is echocardiography. The E/E' ratio has been studied extensively at rest and proved to be a reliable index so that it was included in the guidelines for diagnosing diastolic dysfunction[17] as an important piece of information in the algorithm for estimation of filling pressures. It has even been compared with PCWP measured in catheterization laboratory and proved to be a reliable method for estimation non-invasively the filling pressures in patients with dyspnea[18] or heart diseases[19] but not in asymptomatic hypertensive patients.

The correlation between invasively measured PCWP on one hand with NT-pro BNP and E/E' ratio on the other hand at exercise, was proven in a study by C. Tschope[20]. The study was done in patients with heart failure though and in spite of an excellent negative predictive value found a low sensitivity for NT-pro BNP.

As regards the hypertensive patients, the direct positive relationship between NT-pro BNP on the one hand and pulmonary artery pressure together with PCWP measured invasively during exercise on the other hand, was proven but mainly in symptomatic hypertensive patients[20,21].

In an recent study Paun and co (in Press), demonstrated that NT-pro BNP was a very good means of diagnosing exercise-induced diastolic dysfunction especially in hypertensive patients with left ventricular remodeling (LVH) and normal EF[22].

In this study we intended to see if E/E' can accurately predicts the diastolic dysfunction by non-invasively identifying those asymptomatic hypertensive patients whom develop increase filling pressure at exercise. Consequently, we analyzed the figures of E/E' against the levels of NT-pro BNP at rest and after the ECG treadmill test in these category of patients.

OBJECTIVES

In the natural history of heart failure LVD is firstly seen with exertion, when patients start to complain of dyspnea or fatigue, and only later it manifests even at rest.

In this study we intended to see if E/E' can accurately predicts the LV diastolic dysfunction in asymptomatic hypertensive patients who develop increased filling pressure at exercise. Whereas NT-pro BNP proved to have a direct positive relationship with PAPs and PCWP at exercise in several clinical settings including in hypertensive patients, especially by invasive measurements, the studies which looked at E/E' ratio as an index of diastolic dysfunction at exercise presented discordant or elusive conclusions.

Nevertheless, both indexes showed independently in some studies a correlation with exercise-induced diastolic dysfunction, but mainly in symptomatic patients, regardless the heart disease.

Consequently, we consider NT-pro BNP levels the reference method against which the echocardiographic E/E' ratio was analyzed, both at rest and after the ECG treadmill test.

METHODS

This is a single-center observational study which was conducted at the outpatients in Medlife Memorial Hospital.

The authors randomly included hypertensive patients regardless what stage their BP was at the time when diagnose was made, as long as it had been controlled for the past 3 months previously, according to their home recordings.

The excluding criteria were: AF and conduction abnormalities, moderate-severe valvulopathies, cardi-

Table 1. Participants' data

	Peak BP	BNP-1	BNP-2	BNP-3	Mass index (gr/mp)	E/E' preefort	E/E' postfort
Group I 23 pts	177 - 225 Mean=201 Std=14	95 – 325 Mean=168.43 Std=57.14	113 –387 Mean=244.13 Std=82.34	107-484 Men=272.08 Std=118.39	70 – 88 Mean=79.21 Std=5,63	5,4 – 16 Mean=9.81 Std=2.60	5,7-17 Mean=11.00 Std=3.32
Group II 17 pts	178 – 224 Mean=201 Std=14.6	26-190 Mean=76.48 Std=48.83	25-200 Mean=85.64 Std=49.23	39-140 Mean=85.84 Std=35.30	51-68 Mean=59.05 Std=4.42	5-13.3 Mean=8.81 Std=2.53	2-14 Mean=8.81 Std=2.79

omyopathies and known ischemic heart disease. Also, there were excluded patients with advanced renal disease (stage >II), lung diseases or hepatic diseases. Likewise, all patients who could not finished the exercise ECG test or showed ischemic abnormalities and abnormal hypertensive response during the test, were excluded too.

Initially, there were observed 57 participants in the pre-run period. After considering the including and excluding criteria there were only 40 subjects left (20 F 52-70 age, and 20 M 56-67 age). They were included in 2 different groups: Group 1 for the hypertensive patients with LVH (23 patients, 13 F, mean age 63,5years) and Group 2 for the hypertensive patients without LVH (17 patients, 7 F, mean age 60 years) (Table 1).

We defined the LVH and LVD according to the *European Society of Cardiology* guidelines[8,23].

All participants had a rest ECG done, an exercise ECG test done and an echocardiography at rest and after exercise. The echocardiography measurements were done according the European Society of Cardiology guidelines[24]. We measured the E/E' ratio before and within 60 seconds after the treadmill test was completed, as an average of septal and lateral readings. The exercise ECG test was done according to Bruce protocol[25]. We measured the levels of NT-pro BNP 3 times: before the treadmill test (BNP-1), immediately after the test (BNP-2) and 24 hours after the test (BNP-3) (Table 1).

STATISTICS

We analyzed the distribution of data through the Kolmogorov-Smirnov test and showed a normal distribution. This way, we could use the t-test for paired data, for two independent means.

Firstly, in order to see whether or not the values of NT-pro BNP after exercise are statistically different from those measured at rest, we compared the values of NT-pro BNP before and after effort within the two groups separately. We considered the Ho hypothesis that there was no difference between the 2 types of values of NT-pro BNP (before and after the exercise) at an alpha value of <0.05. In other words, we compared BNP-1 with BNP-2 and BNP-1 with BNP-3 in each group (Table 2). We analyzed separately the concentrations of NT-pro BNP seen in males from those seen in females. In Group 1 the statistics showed p<0.05 in men and women too, whereas in Group 2 the p>0.05, for both, men and women.

Then, we cross-compared the values of NT-pro BNP between the two groups of patients. The p values were < 0.00001 (Table 3).

Secondly, we looked to see if there is any correlation between the levels of NT-pro BNP and the E/E' ratio, and between LVH and both indexes. We used the Pearson correlation test.

Due to the fact that the LV mass index has different values for men and women, we divided the patients from both Groups into two subgroups according to the gender. We chose to use the maximum values for NT-pro BNP after effort, regardless the time of measuring (immediately after the test or 24h after the test),

Table 2. Statistics for BNP comparison within each Group (p values)

Female/Male	BNP-1 vs BNP-2	BNP-1 vs BNP-3
Group 1	0.00004 / 0.0298	0.00018 / 0.0273
Group 2	0.472 / 0.218	0.406 / 0.148

Table 3. Cross-comparing the BNPs (LVH vs no LVH)

Group 1 vs Group 2	BNP-1	BNP-2	BNP-3
BNP-1	P<00001		
BNP-2		p<.00001	
BNP-3			p<.00001

Tabel 4: Statistics results for correlation

		BNP-1 vs E/E'rest	BNPmax vs E/E'postex	LVH vs BNPmax	LVH vs E/E'postex
Group 1	F	R=0.02 p=0.93	R=0.18 p=0.53	R=0.69 p=0.008	R=0.44 p=0.13
	M	R=0.35 p=0.31	R=0.36 p=0.30	R=0.76 P=0.009	R=33 p=0.34
Group 2	F	R=0.03 p=0.938	R=-0.54 p=0.20	R=0.08 p=0.85	R=--0.10 p=0.82
	M	R=-0.003 p=0.998	R=0.68 p=0.27	R=-0.38 p=0.27	R=0.002 p=0.994

The results are shown as Pearson R correlation factor and as p value indicating the statistical significance. (Table 4).

The only high correlation with statistically significance was seen in both men and women, in Group 1, and only for the relationship between the maximum value of NT-pro BNP and LVH. (Figure 1 and 2) All other statistics showed no or weak correlations with no statistical significance.

DISCUSSION

Heart failure with either reduced or preserved ejection fraction, is the main cause of hospital admissions related to cardio-vascular diseases in the developed countries[8]. On the other hand, hypertension which is the most frequent cardio-vascular disease, if left untreated, can lead to heart failure[1,2,23]. Over the past decades, several highly efficient antihypertensive drugs have been approved. In spite of that, many hypertensive patients finally develop LVD and then overt heart failure[24].

There are several means to evaluate left ventricle function after exercise, like catheterization and echocardiography. Each has its own advantages, but most importantly some disadvantages.

The E/E' ratio was validated in several studies and provided by the Guidelines as a useful index for evaluating left ventricle filling pressures, but in symptomatic patients and only at rest[25].

Oleg F. Sharifov and co, in an excellent meta-analysis found no sufficient evidence to support the use of E/E' for assessing the changes of left ventricle filling pressure after exercise[26].

Nonetheless, measuring the levels of NT-pro BNP in blood is non-invasive, objective, more precise, being operator and patient independent. It was proved invasively to correlate very well with PCWP and PAPs during exercise in different heart diseases[13-15]. It was also demonstrated by N Paun and co. to be an excellent means for detecting left ventricular dysfunction after exercise, especially in asymptomatic hypertensive patients with LVH[27].

The authors of this study wanted to see if the changes of E/E' ratio after exercise fallow the changes of concentrations of NT-pro BNP, in hypertensive patients with preserved ejection fraction and no symptoms of heart failure, neither at rest nor at effort.

We measured two values of NT-pro BNP after exercise: BNP-2 which reflects the deposits of BNP within the cytoplasm of myocites, ready to be relea-

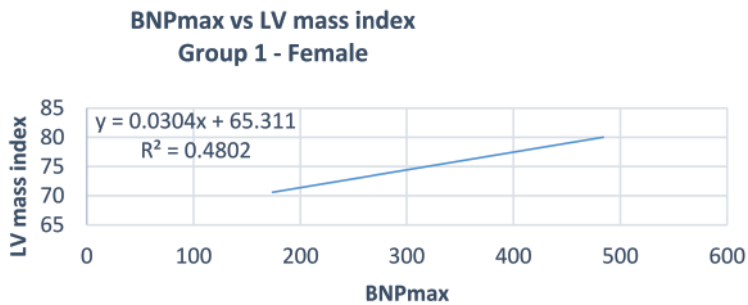

Figure 1.

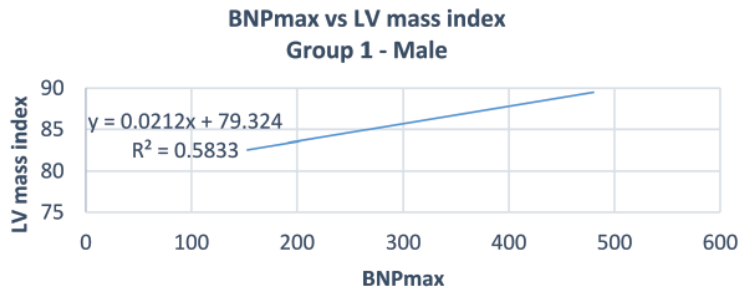

Figure 2.

sed whenever myocardial wall stress increases; BNP-3 which reflects the de novo synthesis of BNP in myocites triggered by increase of the LV myocardial wall stress[28,29]. We noticed that in some patients the highest increase of NT-pro BNP was immediately after the exercise (BNP-2), while in the others was latter, that is 24 hours after exercise (BNP-3). That is why we decided to use the highest BNP figures after the exercise (BNP-max) in some calculations.

The values of E/E' at rest were within normal limits, with the exception of 3 patients in Group 1 and only 2 patients in Group 2. After exercise all patients from both groups had normal E/E', suggesting no high filling pressures. The figures showed a very high variability though.

When we looked at NT-pro BNP figures, before and after exercise, the results were opposite in the two groups. While in Group 2, patients without LVH, the figures after exercise were not statistically different from those before exercise, in Group 1, patients with LVH, there was a statistically significant exercise-related increase in NT-pro BNP (Table 2). Thus, whereas in Group 1 the results were concordant, in Group 2 they showed discordant statistically significance.

Accordingly, we can consider that NT-pro BNP could identify an increase in wall-stress in hypertensive patients with LVH after effort whereas E/E' could not. The peak exercise blood pressure could not account for the differences between the 2 groups as there was no statistically difference between them (Table 1).

Subsequently, we analyzed the correlation between the two methods. In both groups there was no statistically relevant correlation between them, neither before, nor after exercise (Tab 4). So, in hypertensive patients without LVH both methods showed concordant results: there was no exercise-induced diastolic dysfunction, both in females and in males. The lack of correlation between the two methods seen in hypertensive patients with LVH, on the other hand, strengthened the observation that they might have different sensibilities in identifying diastolic dysfunction in this category of patients.

These results lead us to another analyze in order to see which of the two methods better reflects the reality. We compared the figures of LV mass index with both parameters. Once again, while post exercise E/E' ration did not correlate, NT-pro BNP after exercise showed a high significant correlation with LVH for both males and females. (Tab 4, Chart 1 and 2). The higher the left ventricle mass the higher the concentration of NT-pro BNP.

This way we identified a group of population at high risk for developing left ventricle dysfunction, namely the asymptomatic hypertensive patients with increased myocardial mass.

It allowed us to consider the two groups of subjects included in our study as being two different populations, not only statistically but clinically too.

With the data from our study and many other studies alike, the question of why the post exercise E/E' ratio has showed so different results has been raised.

We have taken into consideration 2 type of explanations. Firstly, there are the technical factors. The E' is a highly angle-dependent measurement, using the position of the probe on the patient's chest as a reference point. At peak exercise and even immediately after exercise both, the patient's wall chest and the rapidly-beating heart move vigorously, so that it is very difficult to keep track of one in report to the other. This can also cause the deterioration of the quality of the images (increased signal noise, fusion of E' wave with isorelaxation period wave and fusion of E with A and E' and A' waves). At the same time, E' is influenced by the underlying pathology thus errors can occur whenever one or the average of 2 measu-

rements are extrapolated to the entire ventricle. This is particularly true in patients with asymmetrical LV hypertrophy or ischemia and in those with excessive cardiac translation (hyper dynamic ventricle). In the MYDISE study, the cornerstone of the tissue Doppler imaging, the author concluded that the diastolic velocities of the myocardium had a weak reproducibility[30]. Another factor would be the timing of measurements. We measured the E/E' ratio after the exercise, when the filling pressures and wall stress may have been decreased. In this situation, E/E' may only express the abnormalities during the recovering period, which are less intense than those during the peak exercise. Whereas the NT-pro BNP levels measure the maximum changes brought about by the peak exercise.

Then come the physiological factors. The mitral valve inflow tract E velocity is preload dependent making it vulnerable to patient's hydration status, which changes during and after exercise through intense sweating. The E' velocity is also afterload dependent and consequently it should be interpreted in conjunction with the patient's changes in the afterload at the moment of measurement. We advance the hypothesis that the E/E' ratio may be less sensitive in identifying small increases in LV filling pressures following the first morphological changes in the LV myocardium when compared with NT-pro BNP[31]. This happens in the early stage of diastolic dysfunction. It may require a minimum threshold of increased filling pressure to modify the E/E' ratio.

CONCLUSION

Based on the findings of our study we can conclude that the hypertensive patients despite the fact that they have a preserved EF and no signs of heart failure, can develop asymptomatic exercise-related diastolic dysfunction. But not all of them, only those with LVH. On the other hand, we demonstrated that the left ventricular mass is an important factor which controls the secretion of natriuretic peptides through the elevated myocardial wall stress induced by the stiffness of the LV cavity.

NT-pro BNP has proved to be a more sensitive method in unveiling this phenomenon as compared to E/E' ratio.

STUDY LIMITATIONS

The findings from our study may be statistically significant but we need larger studies to confirm them and see if they are clinically relevant too.

FUTURE PERSPECTIVES

The hypertensive patients with left ventricular hypertrophy are at higher risk for developing left ventricular dysfunction, and as a consequence they must be closer follow-up and more intensively treated with medication. This way we can treat them earlier and more efficiently with clear benefit in terms of developing overt heart failure and adverse CV events[32,33].

Measuring NT-pro BNP after ECG treadmill test in asymptomatic hypertensive patients can emerge as a new tool useful to refine the diagnosis of the LV diastolic dysfunction even from the early stage of the disease, when other measurements may not be sensitive enough. It could lead to reclassify the hypertensive patients from class A to class B heart failure.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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