# The left atrial phasic functions and the relationship with plasma N-terminal pro-B-type natriuretic peptide levels and symptomatic states in patients with hypertrophic cardiomyopathy

*Kamil Tülüce, Selcen Yakar Tülüce[1], Oğuz Yavuzgil, Elnur İsayev, Murat Bilgin, Filiz Akyıldız Akçay[1], Sanem Nalbantgil, Filiz Özerkan*

Department of Cardiology, Faculty of Medicine, Ege University; İzmir-*Turkey*
[1]Clinic of Cardiology, Atatürk Training and Research Hospital; İzmir-*Turkey*

## ABSTRACT

**Objective:** We aimed to evaluate left atrium (LA) phasic functions and relation with N-terminal pro-B- type natriuretic peptide (NT-proBNP) levels and symptomatic states of the patients with hypertrophic cardiomyopathy (HCM).

**Methods:** Left atrial volume was calculated at end-systole (Vmax), end-diastole and pre-atrial contraction by echocardiography in 75 patients with HCM and 75 control subjects. Left atrial ejection fraction (LAEF), expansion index (LAEI), active emptying volume index (LAAEVI) and fraction (LAAEFr), passive emptying volume index (LAPEVI) and fraction (LAPEFr) were calculated. NT-proBNP levels were measured.

**Results:** Left atrial active emptying volume (LAAEV) positively correlated with Vmax (r=0.343, p=0.003) up to a point, but then reached a plateau with larger LA volumes in HCM group. The LAAEFr was the only variable which was similiar between asymptomatic patients and controls, but was significantly decreased in symptomatic patients (p<0.05). NT-proBNP was correlated with LAEF (r=-0.32, p=0.005), LAEI (r=-0387, p=0.001), and LAAEFr (r=-0.25, p=0.035) but not related with LAPEFr (p=0.4). In receiver operating characteristic curve analysis an NT-proBNP cut-off value of 1415 pg/mL identified reduced LAEF with 87% specificity and 59% sensitivity [AUC=0.77 (95% CI: 0.65-0.89), p=0.004], a cut-off value of 820 pg/mL predicted impaired LAEI with 81% specificity ve 67% sensitivity [AUC=0.78 (95% CI: 0.66-0.9), p<0.001]; while a cut-off value of 1320 pg/mL predicted impaired LAAEFr with 76% specificity and 67% sensitivity [AUC=0.79 (95% CI: 0.68-0.91), p=0.02].

**Conclusion:** In HCM, LA phasic functions alter according to the Frank-Starling mechanism indicating occurrence of a secondary atrial myopathy. Impairment of LA booster pump function seems to be associated with appearance of symptoms and NT-proBNP levels predict the deterioration of LA reservoir and pump functions in HCM population. *(Anadolu Kardiyol Derg 2014; 14: 719-27)*

**Key words:** hypertrophic cardiomyopathy, atrial phasic functions, natriuretic peptide, diagnostic accuracy, sensitivity, specificity

## Introduction

Hypertrophic cardiomyopathy (HCM) is associated with unexplained hypertrophy of the left ventricle (LV), myocardial disarray and interstitial fibrosis (1). These pathologies lead to stiffness of the LV wall, which results in the elevation of the LV filling pressure. Because the left atrium (LA) immediately responds to changes in the LV end-diastolic pressure, LA enlargement is common in HCM (2). Resting left ventricular outflow tract (LVOT) gradient, LV wall thickness and elevated LV filling pressure have been suggested as potential contributors to LA enlargement (3). Left atrial volumetric remodeling reflects the severity and duration of the LV filling pressure elevation and has been shown to be a predictor of functional capacity (2). Left atrial volumetric changes affect phasic functions (2). The course of LA phasic functions in HCM has been attributed to the presence of the Frank-Starling mechanism in the LA (3). Assessment of phasic LA functions has revealed that a mild to moderate increase in LA volume causes an increase in LA contractility; however, a further increase in LA preload does not enhance the LA pump function, but rather leads to functional failure of the LA (3).

B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were shown to be elevated in conditions with high LV filling pressure, such as those observed in patients with HCM (4). High plasma NT-proBNP levels were correlated with impaired functional capacity, predicting mortality and morbidity in patients with HCM (5, 6). Several determinants of high plasma NT-proBNP levels have been demonstrated (7), but the

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**Address for Correspondence:** Dr. Kamil Tülüce, Ege Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 35100, İzmir-*Türkiye*
Phone: +90 232 390 40 01 Fax: +90 232 390 32 87 E-mail: kamiltuluce@gmail.com
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relationship with LA phasic functions has not been extensively evaluated in patients with HCM. Therefore, in this study we investigated the LA phasic functions in patients with HCM, and assessed the relationship with symptomatic state and plasma NT-proBNP levels.

## Methods

### Study population

We prospectively screened 93 consecutive patients fulfilling the diagnostic criteria for HCM. The diagnosis of HCM was made by 2-dimensional (2-D) echocardiographic findings if a hypertrophied (wall thickness ≥15 mm) and non-dilated LV chamber was present in the absence of any other cardiac or systemic disease that could also cause LV hypertrophy (1, 8). Excluded from this study were patients with severe epicardial coronary artery disease (≥70% stenosis of any major epicardial vessel (n=3), valvular stenosis (n=2), moderate to severe valvular regurgitation (except mitral regurgitation due to systolic anterior motion of the leaflet) (n=4), impaired systolic LV function (LVEF <55%) (n=2), detection of atrial fibrillation episodes on 24-hour Holter-ECG monitoring (n=4), and a history of invasive interventions to alleviate LVOT obstruction (n=3). The final study population consisted of 75 patients (48 men, 27 women) with HCM who were in normal sinus rhythm at the time of enrollment. Seventy-five volunteers (48 men, 27 women) with similar age and sex distributions and normal physical examination findings served as a control group. For all subjects aged 40 years or older, the presence of a normal coronary angiogram or <50% stenosis of any major epicardial vessel within 1 year before enrollment was necessary for inclusion. All participants gave written informed consent to participate in the study, which was approved by the hospital Ethic Committee.

### Echocardiography

Comprehensive echocardiographic evaluations including 2-D and M-mode were carried out by a Sonos 7500 ultrasound machine (Philips Medical Systems, Andover, MA, USA) equipped with 2.5 MHz transducer and recorded on VHS videotape. Two-dimensional parameters were measured according to the American Society of Echocardiography recommendations (9). Simultaneous electrocardiogram (ECG) recordings were done for all patients during the examination. Left atrial volumes (LAVs) were calculated in four- and two-chamber views by Simpson's rule. The endocardial border of the LA was manually traced to assess its area. The LA appendage and pulmonary veins were excluded from planimetry. The following LAVs were measured: the maximal volume ($V_{max}$) during left ventricular end-systole just before mitral valve opening, the minimal volume ($V_{min}$) just before mitral valve closure, and the LA volume before atrial contraction ($V_{preA}$) at the onset of the P wave on the simultaneously recorded ECG (10). In all subjects, LA volumes were indexed to body surface area (BSA) and LA volume index (LAVI) was calculated by indexing $V_{max}$ to BSA. Left atrial volumes were obtained as the mean of three consecutive beats. By using three LAVs, the LA phasic functions were evaluated and the following parameters were obtained, similar to previous studies (10-12):

1. LA ejection fraction (LAEF) defined as $(V_{max}-V_{min})/V_{max}\times100\%$)
2. LA expansion index (LAEI) defined as $(V_{max}-V_{min}) / V_{min}\times100\%$)
3. LA active emptying volume (LAAEV) defined as $(V_{preA}-V_{min})$
4. LA active emptying fraction (LAAEFr) defined as $(LAAEV/V_{preA}\times100\%)$
5. LA passive emptying volume (LAPEV) defined as $(V_{max}-V_{preA})$
6. LA passive emptying fraction (LAPEFr) defined as $(LAPEV/V_{max}\times100\%)$

Left atrial ejection fraction and expansion index were used for the assessment of the LA reservoir function, LAPEFr for the conduit function and LAAEFr for the booster pump function.

The peak LV outflow velocity was evaluated by continous wave (CW) Doppler in the apical five-chamber view using the modified Bernoulli equation. Mitral inflow velocities were studied using pulsed-wave (PW) Doppler after placing the sample volume at the leaflets' tips (13). The peak early (E-wave) and late (A-wave) velocities were measured. Both septal and lateral mitral annular velocities were obtained by tissue Doppler imaging (TDI). The average E′ velocity (E′av) was obtained from the septal and lateral annular E′ velocities and the ratio of the mitral inflow E velocity to average tissue Doppler velocity (E/E′av) was calculated for the prediction of LV filling pressure (14). Five to ten cardiac cycles were recorded during normal respiration for all pulsed Doppler samplings. Mitral regurgitation was graded qualitatively using the color flow jet area, jet density and contour using CW Doppler according to the guidelines (15).

### NT-proBNP measurements

Blood samples were obtained from each patient and control subject on the same day of his or her echocardiographic study. Blood samples were collected in Li-heparin tubes and centrifuged at 3000 rpm for 10 min. The plasma was extracted and stored at -25±6°C until the day of analysis. The NT-proBNP was measured by an enzyme-linked fluorescent assay (ELFA) method (VIDAS NT-proBNP, BioMérieux, France). The analytic range of the NT-proBNP assay spanned 20-25,000 pg/mL.

### Statistical analysis

All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean±standard deviation (SD). Categorical variables were analyzed using chi-square test. Shapiro-Wilk test was performed for testing normality. According to results of normality test; statistically significant differences between two groups of continuous variables were determined using the independent t-test and Mann-Whitney U test, as appropriate. The degree of association between variables was determined using Pearson's or Spearman's correlation analysis, as appropriate. Differences in continuous variables between multiple groups

were assessed using analysis of variance (ANOVA) with a posthoc Bonferroni correction. Differences between groups were considered statistically significant when the p value was <0.05. Logarithmic transformation of NT-proBNP levels was performed to reduce the effects of extreme values. Receiver operating characteristic curve (ROC) analysis was performed to identify patients with reduced LAEF, LAEI and LAAEFr defined by the mean value measured in control subjects 2-SD. Intra- and inter-observer reproducibility were evaluated by using Bland and Altman analysis (16) and intra-class correlation coefficient (ICC) for $V_{max}$, $V_{min}$ and $V_{preA}$. The measurements of 25 randomly selected patients with HCM were performed by two readers who were blinded to the patients' characteristics, and repeated within one month by one reader on videotapes.

## Results

### Study population

The clinical features of the HCM patients are summarized in Table 1. There were 63 (84%) patients with asymmetric septal hypertrophy, 8 (10.7%) with concentric hypertrophy, 3 (4%) with midventricular and 1 (1.3%) with apical HCM. Fifty-one (68%) patients were classified as New York Heart Association (NYHA) functional class I at the time of examination (Table 1). The demographic characteristics of patients and controls are listed in Table 2. There were no differences between two groups in terms of age, gender, body surface area and blood pressure measured at the time of enrollment. The median value of NT-proBNP was 663 pg/mL, while the median value in control subjects was 56.55 pg/mL (p<0.001). Comparisons of echocardiographic characteristics of the patient population and control subjects are shown in Table 3.

### Comparison of the left atrial volumes and related phasic functions

The LA phasic volume indices and related functions of the study population are summarized in Table 4. The LAVI was significantly higher in patients with HCM compared to the controls (Table 4). The LAEF and LAEI were significantly lower in the HCM group than in control subjects. No significant difference was detected between groups in terms of the LAAEFr and LAPEVI, but the LAPEFr was higher in controls than patients (33.01±10.1% versus 21.22±9.95%, p<0.001; Table 4).

The results of intra- and inter-observer variability showed good agreements for the $V_{max}$ [inter-observer variability mean difference 0.7, agreement -8.4, 9.8 mL, and ICC 0.90 (0.79-0.95); intra-observer variability mean difference 1.2, agreement -7.2, 9.5 mL, and ICC 0.91 (0.81-0.96)] the $V_{min}$ [inter-observer variability mean difference 0.2, agreement -4.9, 5.2 mL, and ICC 0.89 (0.77-0.95); intra-observer variability mean difference -0.5, agreement -4.9, 3.8 mL, and ICC 0.92 (0.83-0.96)] and the $V_{preA}$ [inter-observer variability mean difference -0.3, agreement -8.8, 8.3 mL, and ICC 0.89 (0.76-0.95); intra-observer variability mean difference 0.1, agreement -8.2, 8.4 mL, and ICC 0.90 (0.79-0.95)].

**Table 1. Clinical features of the HCM group**

| | n (%) |
|---|---|
| **Type of hypertrophy** | |
| ASH | 63 (84) |
| Concentric | 8 (10.7) |
| Midventricular | 3 (4) |
| Apical | 1 (1.3) |
| **Functional class (NYHA)** | |
| I | 51 (68) |
| II | 17 (22.7) |
| III | 7 (9.3) |
| IV | 0 (0) |
| **Mitral regurgitation** | |
| No | 11 (14.7) |
| Mild | 28 (37.3) |
| Moderate | 36 (48) |
| **Obstruction** | 42 (56) |

ASH - asymmetric septal hypertrophy; HCM - hypertrophic cardiomyopathy; NYHA - New York Heart Association

**Table 2. Baseline characteristics of the study population**

| | HCM group (n=75) | Control group (n=75) | *P* value |
|---|---|---|---|
| Age, years | 50.55±12.75 | 50.29±12.17 | 0.901 |
| Women/Men | 28/47 | 28/47 | 1.0 |
| Body surface area, $m^2$ | 1.87±0.22 | 1.91±0.19 | 0.189 |
| Systolic blood pressure, mm Hg | 123.1±15.6 | 126.9±16.5 | 0.147 |
| Diastolic blood pressure, mm Hg | 72.8±11.2 | 72.1±12.2 | 0.713 |

Continuous data are expressed as mean±SD and categorical data as numbers

**Table 3. Echocardiographic findings of the groups**

| | HCM group | Control group | *P* value |
|---|---|---|---|
| IVS thickness, cm | 2.04±0.45 | 0.95±0.12 | <0.001 |
| Posterior wall thickness, cm | 1.08±0.27 | 0.82±0.10 | <0.001 |
| LV mass index, $gr/m^2$ | 145.6±47.28 | 68.29±13.01 | <0.001 |
| Ejection fraction, % | 66.3±6.7 | 65.2±5.6 | 0.27 |
| **Diastolic parameters** | | | |
| E, cm/s | 72.1±20.7 | 72.6±13.9 | 0.83 |
| A, cm/s | 73.7±20.1 | 70.1±12.2 | 0.17 |
| E/A | 1.07±0.5 | 1.07±0.3 | 0.95 |
| E/E' septal annulus | 16.35±6.05 | 8.39±2.28 | <0.001 |
| E/E' lateral annulus | 11.95±5.82 | 6.68±2.28 | <0.001 |
| E/E' average | 13.27±5.12 | 7.34±2.05 | <0.001 |

Continuous data are expressed as mean±SD.
A - atrial (late) filling velocity; E - early filling velocity; E' - early diastolic tissue velocity; IVS - interventricular septum; LV - left ventricle

**Course of the left atrial reservoir and pump functions in the hypertrophic cardiomyopathy group**

In patients with HCM, the LAAEV was positively correlated with the LA end-diastolic volume ($V_{max}$) (r=0.343, p=0.003) up to a point, but then reached a plateau with larger end-diastolic LA volumes (Fig. 1A). The LAAEV increased in response to an increase in $V_{preA}$ (r=0.483, p<0.001; Fig. 1B).

To illustrate the relationship between the LA remodeling and phasic functions, the patient population was divided into four groups using LAVI values: group 1 (n=11) consisted of patients with LAVI <30 mL/m$^2$, group 2 (n=19) comprised patients with LAVI 30 to 40 mL/m$^2$, group 3 (n=31) contained patients with LAVI >40 to 60 mL/m$^2$ and group 4 (n=14) consisted of patients with LAVI > 60 mL/m$^2$.

**Table 4. Comparison of LA phasic functions between groups**

| | HCM group | Control group | *P* value |
|---|---|---|---|
| LAVI, mL/m$^2$ | 48.06±18.3 | 27.57±6.46 | <0.001 |
| LAEF, % | 53.49±11.76 | 61.66±8.27 | <0.001 |
| LAEI, % | 124.92±58.07 | 169.96±54 | <0.001 |
| $V_{preA}$I, mL/m$^2$ | 35.32±13.77 | 16.68±5.59 | <0.001 |
| LAAEVI, mL/m$^2$ | 13.13±5.56 | 7.2±2.99 | <0.001 |
| LAAEFr, % | 39.48±14.75 | 43.02±10.46 | 0.101 |
| LAPEVI, mL/m$^2$ | 9.57±6.16 | 8.09±3.48 | 0.08 |
| LAPEFr, % | 21.22±9.95 | 33.01±10.19 | <0.001 |

Continuous data are expressed as mean±SD
LAAEFr - left atrial active emptying fraction; LAAEVI - left atrial active emptying volume index; LAEI - left atrial expansion index; LAPEVI - left atrial passive emptying volume index; LAPEFr - left atrial passive emptying fraction; LAEF - left atrial ejection fraction; LAVI - left atrial volume index; VpreAI - LA volume index at the onset of P wave on ECG

The LAEF values were similar in groups 1 and 2 (p=1.0), but were significantly decreased in group 3 compared to group 2 (p=0.008) and group 4 compared to group 3 (p=0.05) (Fig. 2A). The LAAEFr did not differ between groups 1 and 2 (p=1.0), but was significantly decreased in group 3 compared to group 2 (p=0.008). No difference was detected between groups 3 and 4 (p=0.166; Fig. 2B).

**Relation between the left atrial volumetric remodeling and left ventricular filling pressure**

The average E/E′ ratio was positively correlated with the LAVI (r=0.297, p=0.01), $V_{max}$ (r=0.378, p=0.001), and $V_{preA}$ (r=0.302, p=0.009) and $V_{min}$ (r=0.450, p<0.001); and negatively correlated with the LAEF (r=-0.372, p=0.001), LAEI (r=-0.429, p<0.001) and LAAEFr (r=-0.328, p=0.005). No association was detected between the E/E′ ratio and LAPEFr (p=0.075).

**Relationship between the left atrial phasic functions and symptomatic state**

The LA phasic volume indices and functions were compared between symptomatic (n=24) and asymptomatic patients (n=51) (Table 5). The symptomatic patients had larger LAVI values (p=0.002) but lower LAEF (p=0.001) and LAAEFr (p=0.005) values, showing deterioration of the atrial reservoir and pump functions in symptomatic patients. The LAAEFr was not different between asymptomatic patients and controls, but was significantly decreased in symptomatic patients (Table 5).

**Clinical and echocardiographic determinants of plasma NT-proBNP levels**

Correlation analyses revealed that log NT-proBNP was significantly correlated with NYHA class (r=0.44, p<0.001) and average E/E′ ratio (r=0.27, p=0.02). The correlations between log

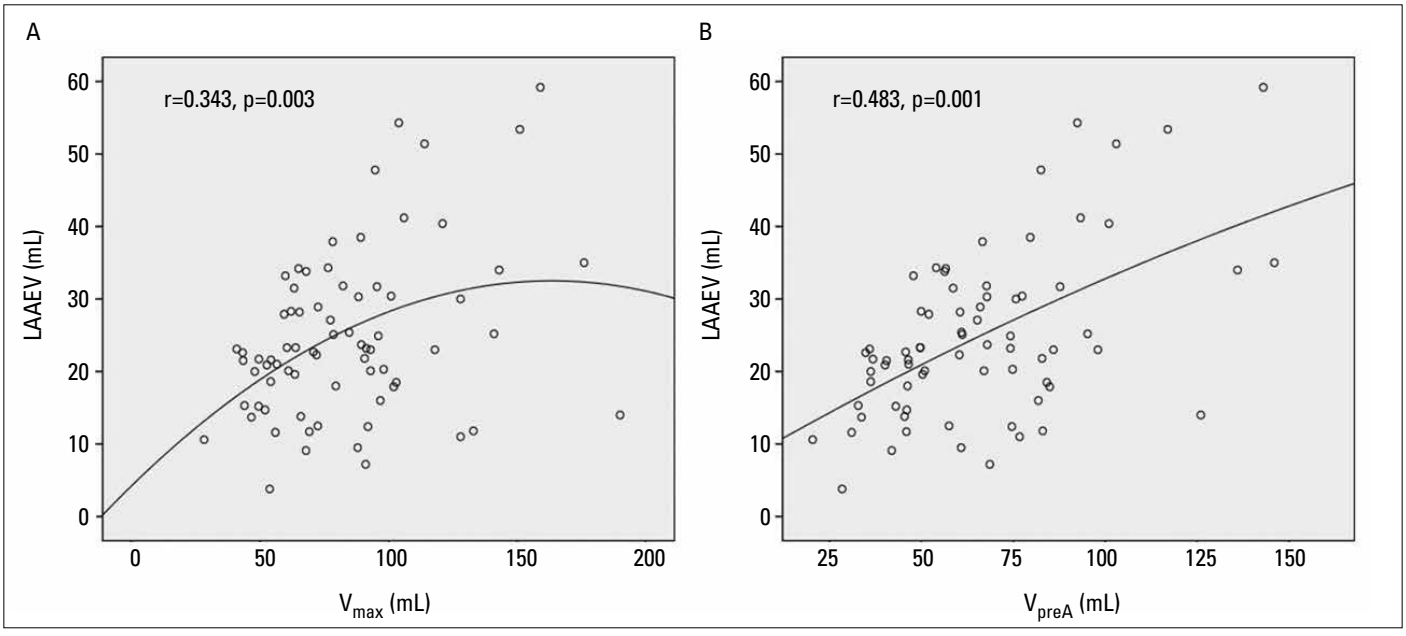


**Figure 1. A, B. Relation between (A) left atrial active emptying volume (LAAEV) and Vmax, (B) left atrial active emptying volume (LAAEV) and VpreA in patients with hypertrophic cardiomyopathy**

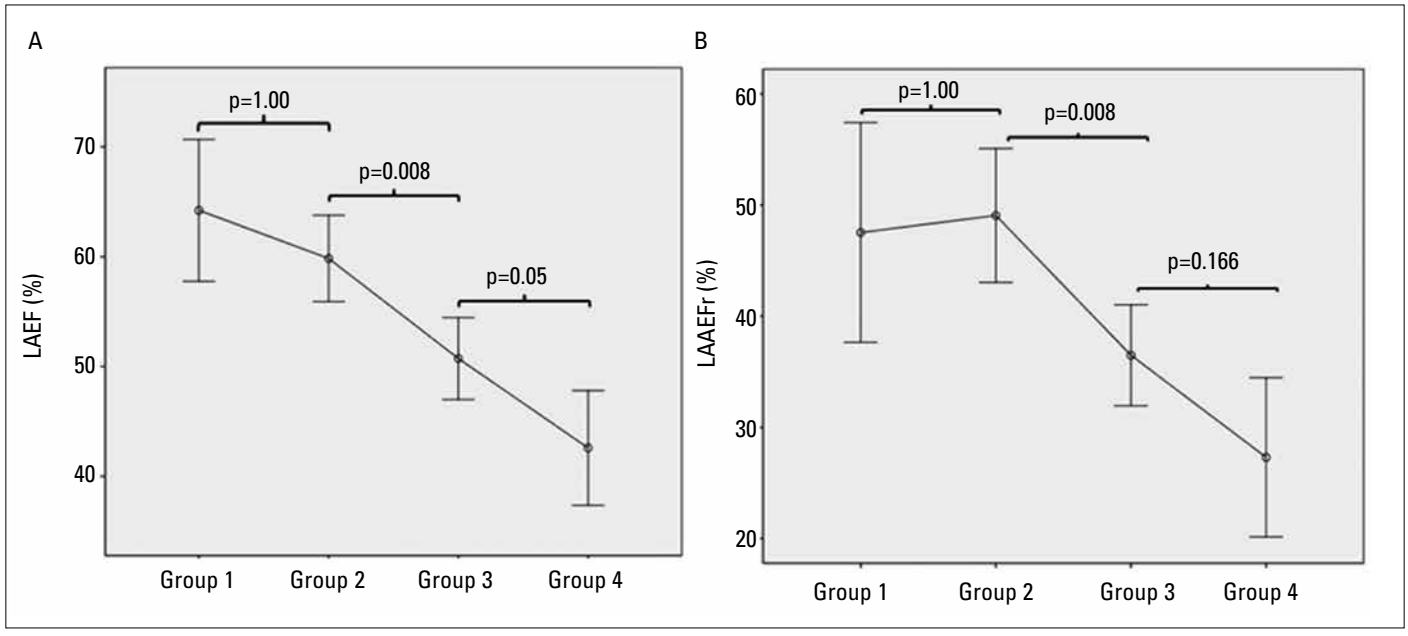


**Figure 2. A, B. (A) Left atrial ejection fraction (LAEF) and (B) left atrial active emptying fraction (LAAEFr) in different HCM groups**

**Table 5. Comparison of LA phasic functions between asymptomatic and symptomatic patients with HCM**

| | Controls (n=75) | Asymptomatic patients (n=51) | Symptomatic patients (n=24) | Overall *P* value |
|---|---|---|---|---|
| LAVI, mL/m$^2$ | 27.57±6.46 | 42.88±14.29* | 59.06±21.38*† | <0.001 |
| LAEF, % | 61.66±8.27 | 56.48±11.31* | 47.14±10.22*† | <0.001 |
| LAEI, % | 169.19±53.95 | 140.26±61.66* | 96±36.76*† | <0.001 |
| $V_{preA}$I, mL/m$^2$ | 16.66±5.63 | 31.45±11.66* | 43.14 ± 15.06*† | <0.001 |
| LAAEVI, mL/m$^2$ | 7.17±3 | 12.79±5.3* | 13.7±611* | <0.001 |
| LAAEFr, % | 43.02±10.46 | 42.71±14.37 | 32.47±13.3*† | 0.002 |
| LAPEVI, mL/m$^2$ | 8.06±3.5 | 8.96±5.22 | 10.93±7.7 | 0.06 |
| LAPEFr, % | 33.01±10.19 | 21.97±9.67* | 19.58±10.56* | <0.001 |

Continuous data are expressed as mean±SD
LAAEFr - left atrial active emptying fraction; LAAEVI - left atrial active emptying volume index; LAEF - left atrial ejection fraction; LAEI - left atrial expansion index; LAPEFr - left atrial passive emptying fraction; LAPEVI - left atrial passive emptying volume index; LAVI - left atrial volume index; $V_{preA}$I - LA volume index at the onset of P wave on ECG
*p<0.05 patients with HCM vs. controls. †p<0.05 symptomatic vs. asymptomatic patients with HCM

NT-proBNP and LAVI and the related phasic functions are presented in Figure 3. Significant negative correlations were found between log NT-proBNP and LAEF (r=-0.32, p=0.005), LAEI (r=-0.48, p<0.001) and LAAEFr (r=-0.25, p=0.035) (Fig. 3). Log NT-proBNP was not related with LAAEV (p=0.8), LAPEV (p=0.5) and LAPEFr (p=0.4). Positive correlations were detected between log NT-proBNP and $V_{min}$ (r=0.29, p=0.01), $V_{max}$ (r=0.24, p=0.04) and $V_{preA}$ (r=0.26, p=0.03).

### Plasma NT-proBNP level as a predictor of deterioration of left atrial reservoir and pump functions

According to ROC analysis, an NT-proBNP cut-off value of 1415 pg/mL corresponded to 87% specificity and 59% sensitivity [area under the curve (AUC)=0.77 (95% CI: 0.65-0.89), p=0.004, Fig. 4A] for the prediction of decreased LAEF, a cut-off value of 1320 pg/mL predicted reduced LAAEFr with 76% specificity and 67% sensitivity [AUC=0.79 (95% CI: 0.68-0.91), p=0.02; Figure 4B], whereas a cut-off value of 820 pg/mL predicted impaired LAEI with 81% specificity ve 67% sensitivity [AUC=0.78 (95% CI: 0.66-0.9), p<0.001; Fig. 4C].

## Discussion

In the present study, failure of LA phasic function was observed in response to larger LAVs in patients with HCM. Left atrial booster pump dysfunction is related to functional impairment in these patients. Plasma NT-proBNP levels predict deterioration of LA reservoir and booster pump functions in patients with HCM.

### Left atrial dysfunction in patients with hypertrophic cardiomyopathy

Left atrial remodeling is common in HCM. The possibility that intrinsic atrial myopathy contributes to LA remodeling in patients with HCM is controversial. We previously showed an involvement of the left atrial appendage (LAA) in the HCM disease spectrum leading to depressed LAA functions, independent of the presence and the degree of LV diastolic dysfunction (17), but have not studied the course of LA volumetric changes and functions. By extensively evaluating LA phasic functions in this study, we detected impaired reservoir and conduit functions but preserved booster pump functions in patients with HCM. Further analysis of patients with HCM showed that the LA pump and reservoir functions were preserved until the LAVI reached 40 mL/m$^2$, but greater increases in the LAVI resulted in deterioration of these functions. In our HCM cohort, LAAEV was posi-

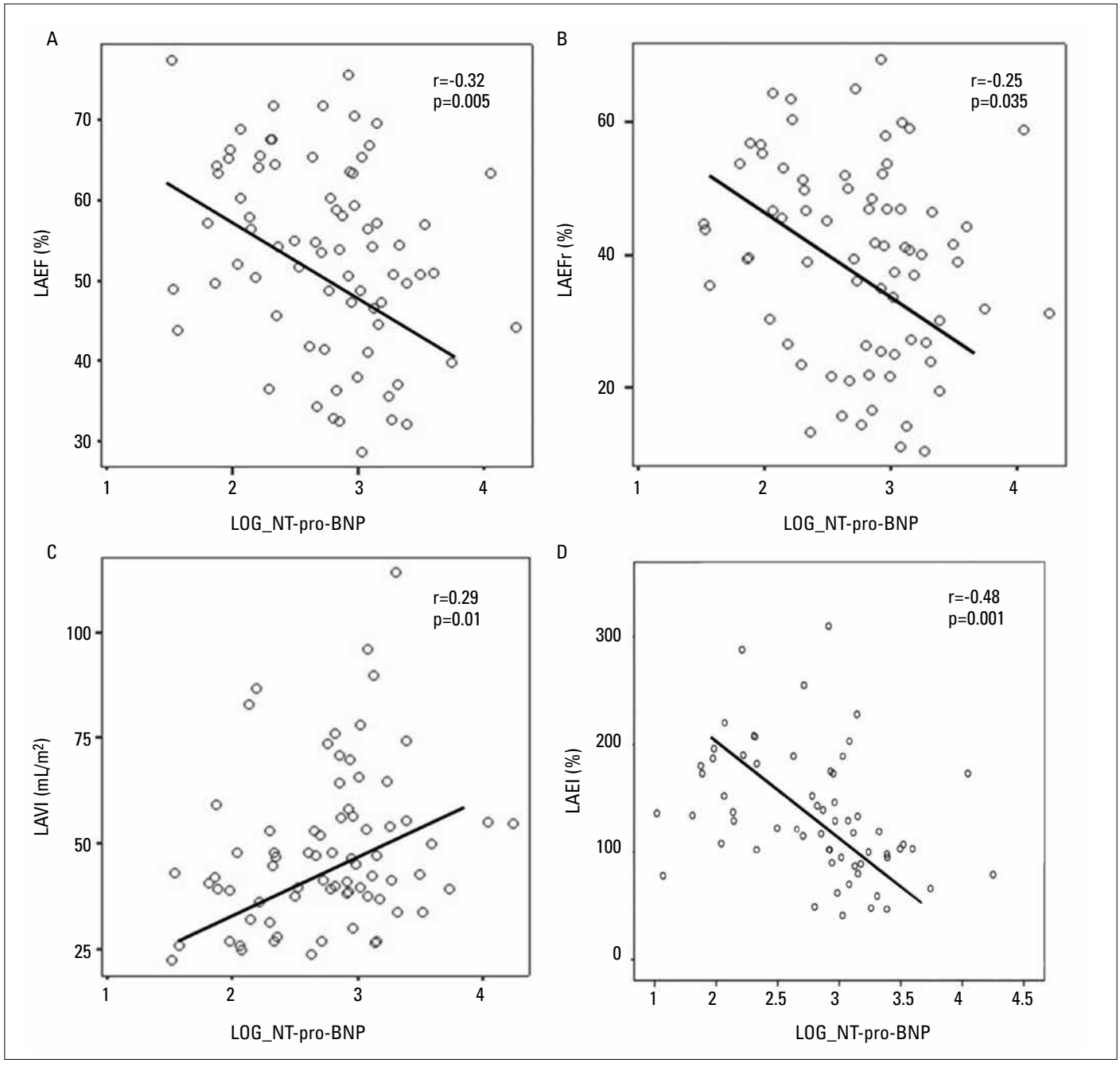


**Figure 3. A-D. Scatter plot showing correlation between Log NT-proBNP and (A) left atrial ejection fraction (LAEF), (B) left atrial active emptying fraction (LAAEFr), (C) left atrial volume index (LAVI), (D) left atrial expansion index (LAEI)**

tively correlated with normal to moderately enlarged LA end-diastolic volume but then reached to a plateau. In accordance with previous studies (3, 18), LA volumetric changes and related functions proceeded according to the Frank-Starling mechanism in our HCM population. An inverse relation of the E/E′ ratio with LA phasic functions and the presence of the Frank-Starling mechanism in the LA suggest the existence of a secondary atrial myopathy rather than primary involvement of the atrial tissue in patients with HCM. These two findings might be explained by the distinct embryonic development of the LAA and LA (19), and also by the similarity of the ultrastructure of the myocardium of the LAA with the ventricular myocardium (20). Histological examination of the atrial myocardium of HCM patients showing no evidence of myocyte disarray, which is suggested as a primary response to sarcomeric mutation, but the presence of fibrosis in the atrial tissue might also support our findings (21).

### The role of left atrial function in development of heart failure symptoms in hypertrophic cardiomyopathy

Diastolic dysfunction is a common feature of HCM (1). In patients with impaired diastolic but preserved systolic functions, it is not clear why some patients remain asymptomatic while

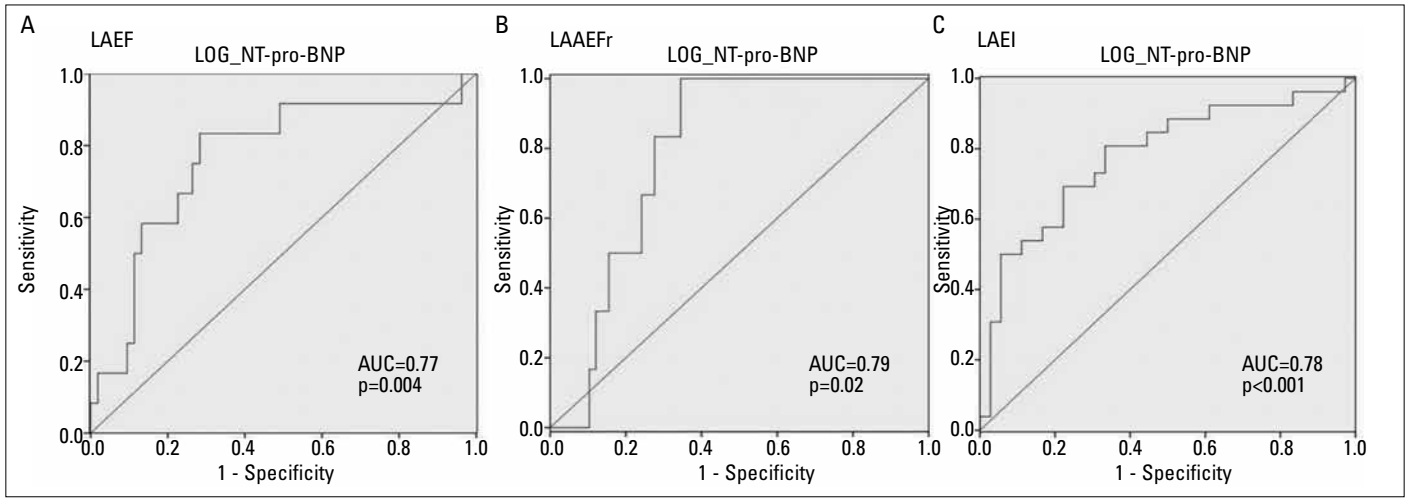


**Figure 4. A-C. Receiver operating characteristic curve referring to the diagnostic performance of log NT-proBNP in identifying patients with impaired (A) Left atrial ejection fraction (LAEF) and (B) left atrial active emptying fraction (LAAEFr) (C) Left atrial expansion index (LAEI)**

others present with severe heart failure (HF) symptoms. The development of HF symptoms in HCM is common. In several studies, determinants of poor functional capacity, including LVOT obstruction (22), high diastolic filling pressure leading to the inability to augment stroke volume during exercise (23), increased LV chamber stiffness myocardial ischemia and mitral regurgitation (18), were postulated as mechanisms of exercise intolerance in these patients. In addition, studies focusing on LA demonstrated high LAVI (7) and impaired LA contractile function detected by speckle-tracking echocardiography (STE) (18) to be predictors of development of symptoms.

In the current study, symptomatic patients had higher LAVI values and impaired reservoir and pump functions compared to the patients without symptoms. When phasic LA functions were compared, the LAAEFr was the only variable which was similiar in controls and asymptomatic patients, but significantly impaired in symptomatic patients. This data indicates that LA booster pump dysfunction represents the main correlate of deterioration of the functional capacity. Our finding is in line with a previous study that evaluated LA phasic functions by STE and reported LA booster pump function as the main correlate of functional disability (18). Demonstration of atrial functional failure has a diagnostic utility for distinguishing patients with diastolic HF from those with hypertensive LV hypertrophy (24). Therefore, relation of LA phasic functions with the appearance of symptoms in patients with HCM seems similiar to those in patients with diastolic HF. The other correlates of functional disability were not investigated because they were beyond the aims of this study.

### NT-proBNP levels and relation with left atrial functional failure

Concentrations of NT-proBNP were shown to be elevated in patients with HCM and correlated with indirect measurements of LV end-diastolic pressure (25). Although NT-proBNP levels (7, 26) and LA functions (18) were shown to be associated with functional capacity in these patients, the relation between NT-proBNP levels and LA phasic functions has not been extensively documented.

In our study, plasma NT-proBNP levels were markedly elevated in patients with HCM compared to controls, and were associated with the E/E′ ratio. Patients with poor functional ability had higher plasma NT-proBNP concentrations. We found negative correlations between NT-proBNP levels and LA reservoir and pump functions in patients with HCM.

In a recent study plasma NT-proBNP levels of ≥1500 pg/mL were shown to be predictive of future clinical deterioration in patients with HCM (26). In our study, NT-proBNP levels of ≥ 1320 pg/mL in patients with HCM were associated with failure of LA contractility. In this regard, deterioration of the functional state of patients with HCM might be parallel to the deterioration of LA phasic functions. Our results show that NT-proBNP is a reliable marker of LA dysfunction in our HCM cohort, and correlates with HF symptoms.

### Clinical perspective

The Frank-Starling mechanism predicts the deterioration of LA phasic functions due to chronic exposure to high LV filling pressure. Increased LA afterload might contribute to fibrosis detected in atrial myocardium in patients with HCM. Left atrial dysfunction might be a cause of atrial fibrillation (AF), the most common sustained arrhythmia observed in this population (27). Impairment of LA phasic function with increasing LV filling pressures beyond a threshold may explain the relatively high incidence of AF and thromboembolic events in this patient population. Therefore, patients with HCM having LAVI ≥40 mL/m$^2$ warrant careful follow-up to avoid complications.

The integrated use of echocardiography and plasma NT-proBNP levels in patients with HCM may provide accurate and early detection of patients with impaired LA phasic function. NT-proBNP may guide more effective use of echocardiography in screening at-risk patients for clinical deterioration. Thus, NT-proBNP levels and LA phasic functions might be used to guide therapeutic strategies before symptoms occur. Our results

should prompt further studies concerning utility of implementing more aggressive treatment strategies before LA dysfunction occurs and NT-proBNP levels rise above the cut-off values presented in our study.

## Study limitations

Our study had several limitations. The diagnosis of HCM was made without analysis of sarcomere mutations. Left atrial function was assessed only by echocardiography in our study. Obtaining pressure volume loops of the LA by the transeptal approach would have been a more accurate strategy. However, only a small number of patients would agree to such an invasive procedure that is not part of routine clinical practice. The E/E′ ratio was used for the estimation of LV end-diastolic filling pressure instead of an invasive measurement. However, several studies and the recent guidelines regarding evaluation of LV diastolic function by echocardiography recommended the use of the E/E′ ratio for the prediction of LV filling pressures (14, 28, 29). The lack of evaluation of diastolic function with new techniques of echocardiography (strain and strain rate) may also be accepted as a limitation. It is also worth noting that our HCM cohort included few patients with NYHA class III and none with NYHA class IV. Therefore, our results need to be validated by studies including larger numbers of patients with NYHA classes III and IV.

## Conclusion

In patients with HCM, LA phasic functions alter according to the Frank-Starling mechanism indicating occurrence of a secondary atrial myopathy. Deterioration of LA booster pump function correlates with worsening of functional capacity. NT-proBNP levels predict the impairment of LA phasic functions in HCM population.

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