

Differences in left ventricular structure, functions and elastance in the patients with normotensive blood pressure

Normotansif kan basıncı olan hastalarda sol ventrikül yapı, fonksiyon ve elastisite farklılıkları

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ABSTRACT

Objective: We aimed in this study to investigate the differences in left ventricular (LV) structure, function and elastance parameters in the patients with normotensive blood pressure (BP) levels.

Methods: A total of 294 normotensive patients (<140/90 mmHg) (135 males, mean age: 45±11 years; 159 females, mean age 38±10 years) were enrolled into the present cross-sectional study. Patients were categorized into three groups according to their BP levels as optimal BP (<120/80 mmHg), normal BP (120-129 / 80-84 mmHg) and high normal BP (129-139 / 84-89 mmHg) groups. We evaluated LV structure and functions by using Doppler echocardiography in all participants. Afterwards we compared the measurements for revealing the echocardiographic differences among the BP groups. In this study, one-way ANOVA Kruskal-Wallis, one-way ANCOVA and partial correlation analysis tests were used for the statistically evaluation of the data. In addition, relative risk ratios (RR) were also calculated for determination of the effects of BP levels to echocardiographic parameters.

Results: There were significant statistical differences in left atrial diameter (LA) (p=0.002), transmitral A wave velocity (A) (p=0.002), meridional wall stress (MWS) (p<0.001), pulmonary capillary wedge pressure (PCW) (p=0.029) among BP groups. After the correction of the data for anthropometric measurements, multiple comparisons have shown that only end-systolic (Es) and end-diastolic elastance (Ed) were different between the normal and high-normal BP groups (for Es, p=0.013; for Ed, p=0.007). But it was found that optimal BP group had significant differences in LV structure and function parameters when compared to high normal BP group (for LA, p=0.028; for A, p=0.035; for MWS, p=0.002; for Es, p<0.001; for Ed, p<0.001). Besides, increased RR were detected for increased left atrial diameter index and pulmonary capillary wedge pressure values in high-normal BP group (RR: 1.537, 95% CI (1.197-1.974), p=0.005 and RR: 1.272, 95% CI (1.089-1.485), p=0.032, respectively).

Conclusion: Pathologic changes in LV due to increasing BP begin at below-hypertensive BP levels. It could be possible that normal BP stage is the beginning level of these changes. (*Anadolu Kardiyol Derg 2008; 8: 413-21*)

Key words: Blood pressure, hypertension, echocardiography, heart ventricle, ventricular function, predictive test

ÖZET

Amaç: Bu çalışmada normotansif kan basıncı düzeylerine sahip hastalar arasında sol ventrikül yapı, fonksiyon ve elastisite farklılıklarını araştırmayı amaçladık. **Yöntemler:** Enine-kesitli bu çalışmaya toplam 294 hasta alındı (<140/90 mmHg) (135 erkek, ortalama yaş: 45±11 yıl; 159 kadın, ortalama yaş: 38±10 yıl). Hastalar kan basıncı (KB) düzeylerine göre optimal KB (<120/80 mmHg), normal KB (120-129 / 80-84 mmHg) ve yüksek normal KB (129-139 / 84-89 mmHg) olmak üzere 3 gruba ayrıldı. Bütün katılımcılarda sol ventrikül yapı ve fonksiyonları Doppler ekokardiyografi kullanılarak değerlendirildi. Daha sonra KB grupları arasındaki farkların ortaya konulabilmesi için ekokardiyografik ölçümler karşılaştırıldı. Bu çalışmada tek-yönlü ANOVA, Kruskal-Wallis, tek-yönlü ANCOVA ve parsiyel korelasyon analizi testleri uygulandı. Ayrıca KB düzeylerinin ekokardiyografik parametreler üzerine etkilerinin değerlendirilebilmesi için göreceli risk (RR) oranları hesaplandı.

Bulgular: Kan basıncı grupları arasında, sol atriyal çap (SAÇ) (p=0.002), transmitral A dalga hızı (A) (p=0.002), meridyonel duvar stresi (MDS) (p<0.001), pulmoner kapiller kama basıncı (PCW) (p=0.029) için önemli farklılıklar vardı. Çoklu karşılaştırmalarda verilerin antropometrik ölçüm değerlerine göre düzeltilmesinden sonra normal ve yüksek normal KB grupları arasında sadece sistol (SSE) ve diastol sonu elastisite (DSE) değerleri için farklılık saptandı (SSE için, p=0.013; DSE için, p=0.007). Fakat Optimal KB grubu ile yüksek normal KB grubu arasında sol ventrikül yapı ve fonksiyonları açısından önemli farklılıklar saptandı (SAÇ için, p= 0.028; A için, p=0.035; MDS için, p=0.002; SSE için, p<0.001 ve DSE için, p<0.001). Ayrıca yüksek normal KB grubunda sol atriyal çap indeksi ve pulmoner kapiller kama basıncı için artmış rölatif risk oranları tespit edildi (sırasıyla, RR: 1.537, %95 GA (1.197 – 1.974), p=0.005 ve RR: 1.272, %95GA (1.089 – 1.485), p=0.032).

Sonuç: Artan kan basıncına bağlı olarak sol ventrikülden oluşan patolojik değişiklikler hipertansif kan basıncı düzeylerinin altında başlamaktadır. Normal KB düzeyleri bu değişikliklerin başlangıç seviyesi olabilir. (*Anadolu Kardiyol Derg 2008; 8: 413-21*)

Anahtar kelimeler: Kan basıncı, hipertansiyon, ekokardiyografi, kalp ventrikülü, ventriküler fonksiyon, prediktif testler

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Introduction

The effects of hypertension (HT) on the left ventricular (LV) structure and functions are well known. Left ventricular hypertrophy and dilatation and LV systolic or diastolic dysfunction commonly appear as complications of HT (1). Similarly, white coat HT, nocturnal HT and masked HT have been shown as a reason for changes in cardiac structure and performance (2, 3). Changes in myocyte expression of both contractile and noncontractile proteins and increased interstitial fibrosis are typical changes occurring during hypertensive heart disease (4-6). Concentric hypertrophy is regarded as an adaptation process to normalize wall stress with HT (6-8) and it is associated with a reduction in beta-adrenergic receptor responsiveness and subsequent altered myocardial contractile function (8, 9). In the literature, there are relatively few studies on the effects of blood pressure (BP) in normotensive levels (<140/90 mmHg) on the LV. Many studies have shown that the risk of death displays an approximately linear relationship with BP levels below this cut-off value (10). Additionally, there is no threshold of BP >115/70 mmHg that identifies cardiovascular risk (i.e., risk is linear and doubles for each 20/10-mmHg BP increase) (11). Therefore, more attention is now being paid to the portion of the population characterized by BP levels remaining within normal limits but approaching the 140/90 mmHg level. The last European Society of Hypertension (ESH)-European Society of Cardiology (ESC) guidelines define BP between 130/85 and 139/89 mmHg as "high-normal", while the Joint National Committee (JNC)-7 guidelines introduced a new category of "Prehypertension" (PHT) (BP between 120/80 and 139/89 mmHg) (10, 12, 13). Both these conditions affect a significant portion of a general population (14). Although some studies have shown that LV structure, systolic and diastolic functions and aortic-elastic properties were impaired in subjects with normotensive BP level; these studies were generally performed to reveal the differences between normal and PHT BP levels (JNC-7) (13, 15, 16). Moreover, there are only few studies in the literature about the differences in pulmonary capillary wedge pressure, LV elastance, LV wall stress, dP/dT, noninvasive Tau, and LV systolic and diastolic elastance according to normotensive BP levels.

In this study, we aimed to investigate the differences in LV structure and diastolic or systolic dysfunction according to the BP levels. We also investigated the differences in the above-mentioned LV elasticity, pressure and performance criteria according to the BP levels. We focused on the differences among optimal, normal and high-normal BP levels, which were introduced by the ESC (12).

Methods

This cross-sectional study was approved by the Local Ethical Committee. Detailed information was given to enrolled patients, and Informed Consent Forms were signed by all participants.

Patient selection

All patients were selected from among those admitted to the Cardiology Department for general health examination and they were evaluated with detailed history and physical examination.

Patients with acute or chronic renal dysfunction, diabetes mellitus, metabolic syndrome, impaired glucose tolerance, heart failure (EF<50%), valvular heart disease, cardiomyopathies, history of coronary artery disease or proven coronary artery disease at coronary angiography or noninvasive tests, familial hyperlipidemia, morbid obesity (body mass index >40 kg/m²), asthma or chronic obstructive lung disease, pregnancy or taking oral contraceptives, concurrent therapy with medications that might affect BP, history of smoking, aortic disease (Marfan's syndrome, coarctation of aorta, aortic aneurysm or aortic surgery, etc.), and connective tissue disorders were excluded from the study.

Finally, a total of 294 patients (135 males aged between 16 and 75, mean age 45.00±11.94 and 159 females aged between 17 and 71, mean age 38.57±10.74) were included into the present cross-sectional study.

Patients were categorized into three BP groups, which were defined as Optimal (under 120 mmHg systolic and 80 mmHg diastolic), Normal (120-129 mmHg systolic and 80-84 mmHg diastolic) and High-Normal (129-139 mmHg systolic and 84-89 mmHg diastolic) according to the ESC guidelines (12). When a patient's systolic or diastolic BP level moved into a different BP category, it was categorized as to the higher BP category (12).

Cardiologic evaluation: Patients were kept in a silent and quiet test room at 20°C, and were rested for 15 minutes in supine position at the beginning of the test in the Cardiology Department. A detailed medical history was taken and physical examination was performed.

Blood pressure measurements

Blood pressure was measured three times for each patient with a standard mercury sphygmomanometer on the right arm in sitting position following a 10-minute rest. Phase I and V Korotkoff sounds were used to determine systolic and diastolic BP measurements. In each patient, measurements were performed in the same room and at the same time of the day by a paramedic. The average of three measurements was used for the analysis. We also followed up and evaluated the BP recordings measured by the patients themselves at home. Patients were asked to measure their BP levels over seven consecutive days. We then compared the BP measurements recorded by the paramedics in our clinics with the average of the BP levels over seven consecutive days as recorded by the patients at home. When contradictory results between the BP measurements were detected, we repeated the measurements three times at the clinic. We used this method to confirm the averages of our clinical BP measurements. Patients with suspected or diagnosed HT (>140/90 mmHg, at home and office), white coat HT (elevated office BP + normal BP out of the office), or masked HT (normal office BP + elevated BP out of the office) were excluded from the study.

Diagnostic tests

Biochemical blood analysis, 12-lead electrocardiography (ECG), color Doppler echocardiography (Ge-Vivid 7 Pro, General Electric, FL, USA) were performed for all subjects. Postero-anterior chest radiography and treadmill test (Quinton 4500 treadmill, Seattle, WA, USA) were also performed for differential diagnosis when necessary.

Biochemical blood analysis

A fasting blood sample was drawn between 09:00 and 10:00 A.M. Laboratory work-up involved detailed biochemical analysis.

Serum lipid profile, fasting blood glucose, renal and liver function tests, and complete blood count were performed.

Venous blood samples were withdrawn into tubes containing K₃ EDTA and into tubes containing no anticoagulant agent. After all tubes were spun at 5000 rpm for 15 minutes, plasma and serum samples were stored at -80°C until analysis was performed. Total plasma cholesterol, triglyceride and high-density lipoprotein (HDL) cholesterol were measured by an enzymatic calorimetric method with the Olympus AU 610 autoanalyzer using reagent from Olympus Diagnostics GmbH (Hamburg, Germany). Low-density lipoprotein (LDL) cholesterol levels were calculated by Friedewald formula. Serum glucose was measured by the glucose oxidase method. Renal and liver function tests were also measured using the autoanalyzer.

Electrocardiography (ECG)

After the skin was rubbed, electrodes were applied. Twelve-channel ECG was then performed (Cardioline Delta1 plus, Remco, Italy).

Echocardiographic examination

Transthoracic color Doppler echocardiography was performed by using Ge-Vivid 7 Pro 2.5 MHz probe (General Electric, FL, USA) in the left lateral decubitus position according to standard protocol. Echocardiographic measurements were made on the screen by two cardiologists unaware of the patients' clinical data. M mode tracing of the LV were obtained in the parasternal long-axis views at a speed of 50 mm/s. five consecutive cardiac cycles were averaged for every echocardiographic measurement.

All echocardiographic measurements were performed by using standard methods (17). M-mode measurements were obtained from the parasternal long-axis view. Two-dimensional echocardiographic and Doppler echocardiographic measurements were obtained from the apical four-chamber view (17).

The peak early transmitral filling during early diastole [E], peak transmitral atrial filling velocity during late diastole [A], deceleration time [DT] (time elapsed between peak E velocity and the point where the extrapolated deceleration slope of the E velocity crosses the zero baseline), ejection time [EJT], isovolumetric relaxation time [IVRT] (time period between the end of aortic ejection flow Doppler tracing and the starting point of mitral diastolic flow Doppler tracing), isovolumetric contraction time [IVCT] (time period between the end of mitral diastolic flow Doppler tracing and the starting point of aortic flow Doppler tracing), TEI Index (myocardial performance index), tissue Doppler E wave [Et], tissue Doppler A wave [At], [E/Et] ratio were used to assess LV diastolic functions (17).

The transmitral diastolic flow Doppler tracing was obtained from the apical four-chamber view by using pulsed Doppler echocardiography with the sample volume size of 1 to 2 mm between the tips of the mitral valve during diastole. To measure IVRT and IVCT, a 3- to 4-mm size sample volume was placed in the area of the mitral leaflet tips. Next, the transducer beam was angulated toward the LV outflow tract until aortic valve closure appeared above and below the baseline (17).

Tissue Doppler echocardiographic measurements: these measurements were obtained from apical four-chamber view. The sample volume was placed on mitral-interventricular septum junction for obtaining tissue Doppler echocardiographic measurements (17).

All measurements used in this study for evaluation of LV structure and systolic and diastolic functions are shown in Table 1.

Additionally, we calculated:

- Aortic diameter index (AOI)(mm/m²): Aortic root diameter / Body Surface Area (BSA) (M-Mode)
- Left atrial diameter index (LAI) (mm/m²): Left atrial diameter / BSA (M-Mode): LAI values were categorized into two groups, which were defined as the groups under 17 mm/m² and 17 mm/m² and upper.
- Left ventricle mass (LVM)(g) by using Devereux formula (18): LVM: [1.04 x (LVIDd + LVPWd + IVSDd)³ - LVIDd³] x 0.8 + 0.6
- Left ventricle mass index (g/m²): LVM / BSA
- TEI Index (17, 18) (myocardial performance index): (IVRT+IVCT) / EJT
- Circumferential fiber shortening (VCF) (17, 42, 43): (LVIDd – LVIDs) / LVIDd x Ejection Time (ET)
- Left ventricular endsystolic meridional wall stress (MWS) (17, 42, 43): 0.334 x Systolic arterial pressure (P) x LVIDd / [LVPWd x (1 + (LVPWd / LVIDd))]
- Left ventricular preejection wall stress (LVPWS) (at opening of aortic cusps) (17, 42, 43): [(Diastolic arterial pressure x (LVIDd / 2)) / LVPWd] x [1-LVIDd / 8 x (LVIDd + LVPWd)]
- Left ventricular filling pressure: Pulmonary capillary wedge pressure (PCW)(mmHg) (17, 18): 1.9 + 1.24 (E / Et) The PCW values were categorized into two groups, which were defined as the groups 12 mmHg and lower and upper than 12 mmHg.
- Left ventricular dP / dT (19): (Aortic diastolic pressure-left ventricular end diastolic pressure) / IVCT
- Left ventricle elastance calculations (LV): We calculated the LV end-systolic (Es) and end-diastolic (Ed) elastance values using the formulas defined by Chen et al. (20).
- TAU: The time constant of ventricular relaxation (tau) is a quantitative measure of diastolic performance. We assessed the Tau noninvasively using the formulas defined by Scalia et al. (21).

Statistical Analysis

All statistical analyses were performed using SPSS version 15 (SPSS Inc., Chicago, IL, USA).

Kolmogorov-Smirnov test was used for determination of the data distribution.

Data with normal distribution were expressed as mean± standard deviation (SD) and one-way ANOVA test was used for this type of data. (If variance of the groups was not equal we also performed Brown-Forsythe test). On the other hand, data with non-normal distribution were expressed as median value (25%-75% percentile) and Kruskal- Wallis test was used for this type of data in the statistical evaluation of the differences between the groups.

Multiple comparisons: Bonferroni post-hoc test was used for the data with equal variance. If the variance of the data not equal, we used Tamhane T2 test for multiple comparisons among the groups.

For the purpose of evaluation of statistical differences among BP levels with corrected data for age, gender and body mass index, we used one-way ANCOVA (Analysis of covariance) test.

Table 1. Acronyms, abbreviations and explanations

BP	Blood Pressure	DECT	Transmitral Flow Deceleration Time
BSA	Body Surface Area	IVRT	Isovolumetric Relaxation Time
AO	Aortic Diameter	IVCT	Isovolumetric Contraction Time
AOI	Aortic Diameter Index	EJT	Left Ventricular Ejection Time
LA	Left Atrial Diameter	TEI	TEI Index Myocardial Performance Index
LAI	Left Atrial Diameter Index	BMI	Body Mass Index
LV	Left Ventricle	At	Tissue Doppler A Wave Velocity
LVM	Left Ventricular Mass	Et	Tissue Doppler E Wave Velocity
LVMI	Left Ventricular Mass Index	E / Et	Transmitral E Wave Velocity / Tissue Doppler E Wave Velocity Ratio
EDV	Left Ventricular End Diastolic Volume	VCF	Circumferential Fiber Shortening
ESV	Left Ventricular End Systolic Volume	MWS	Meridional Wall Stress
SV	Left Ventricular Stroke Volume	LVPWS	Left Ventricular Preejection Wall Stress (at opening of aortic cusps)
FS	Fractional Shortening	PCW	Pulmonary Capillary Wedge Pressure
EF	Ejection Fraction	dP / dT	Change in LV Pressure Acceleration Over Time
A	Transmitral A Wave Velocity	Es	LV End-Systolic Elastance
E	Transmitral E Wave Velocity	Ed	LV End-Diastolic Elastance
E / A	Transmitral E Wave Velocity / Transmitral A Wave Velocity Ratio	En	Left Ventricular Elastance at the Onset of Ejection Period (Normalized Elastance)

Afterwards, we performed correlation analysis to show the relationships between blood pressure (systolic and diastolic) and echocardiographic parameters. For the purpose of controlling the effects of age, gender and body mass index (BMI) to the statistical results, we used partial correlation analysis.

Additionally, we also calculated the relative risk (RR) ratios about the effects of BP levels to echocardiographic parameters. A p value of <0.05 was accepted as statistically significant.

Results

All participants had normal ECG and biochemical blood test analysis. Additionally, there were no differences in biochemical blood test analysis according to the BP levels. We did not detect any differences in fasting blood glucose, total cholesterol, triglyceride, LDL or HDL cholesterol levels between groups ($p>0.05$). There were no differences in anthropometric values among the groups (Table 2).

On the other hand, there were significant statistical differences throughout the groups in LA ($p=0.002$), LAI ($p=0.024$), fractional shortening (FS) ($p=0.025$), transmitral A wave ($p=0.002$), transmitral E wave / tissue Doppler E wave ratio (E/Et) ($p=0.002$), MWS ($p<0.001$), LVPWS ($p=0.018$), PCW ($p=0.029$), dP/dT ($p=0.031$), Es ($p<0.001$) and Ed ($p<0.001$) (Table 3).

Table 4 shows corrected differences for age, gender and BMI according to echocardiographic parameters, which were found as statistically significantly different among the BP levels. According to results, there were significant statistical differences between groups in LA ($p=0.015$, $F=4.289$), LAI ($p=0.023$, $F=3.835$), transmitral A wave ($p=0.015$, $F=4.310$), MWS ($p<0.001$, $F=7.932$), transmitral E wave / tissue Doppler E wave

ratio (E/Et) ($p=0.017$, $F=4.224$), PCW ($p=0.017$, $F=4.224$), dP/ dT ($p=0.042$, $F=3.280$), Es ($p<0.001$, $F=12.993$) and Ed ($p<0.001$, $F=12.441$) after the correction for age, gender and BMI parameters.

Multiple comparisons

Multiple comparisons were performed among the BP groups to reveal the origin of the differences in measurements between them.

Table 5 shows the multiple comparisons regarding those measurements that were detected as statistically significantly different between the groups using one-way ANOVA and one-way ANCOVA analyses with post-hoc Bonferroni test results. Table 5a shows the results of comparisons among the BP levels groups for echocardiographic parameters before the correction of the data for age, gender and BMI. These comparisons show that only Ed was different between the Normal and High-Normal BP groups ($p=0.032$). On the other hand, echocardiographic measurements in the Optimal BP group differed significantly from Normal and High-Normal BP groups in terms of left atrial size, LV diastolic function, LV wall stress, pressures and elastance (all $p<0.05$). Table 5b shows multiple comparisons between the BP levels according to data, which were found as statistically significantly different among the BP levels and were maintained after the correction of the data for age, gender and BMI. The results of covariance analysis show that differences were still significant after the adjustment between the Optimal and High Normal BP groups in terms of left atrial size, LV diastolic function, LV wall stress, pressures and elastance (all $p<0.05$). On the other hand, the differences between the Optimal and Normal BP levels groups were true only for dP/dT ($p=0.038$), MWS ($p=0.003$) and Es ($p=0.049$) after the correction of the data. As for differences between Normal and High Normal BP groups only LV elastance variables maintained significant differences (both $p<0.05$).

Table 2. Antropometric values and differences according to the BP levels

Parameters	OPTIMAL BP LEVEL (n=113)	NORMAL BP LEVEL (n=104)	HIGH-NORMAL BP LEVEL (n=77)	p*
Age, years	39.6±11.0	41.9±11.5	43.7±12.6	NS
Height, cm	165.2±9.1	167.3±7.0	166.9±7.6	NS
Weight, kg	78.4±14.5	79.5±16.0	81.0±11.7	NS
BMI, kg/m ²	28.9±6.1	28.4±5.6	29.1±4.6	NS
Waist, cm	92.6±15.6	93.8±14.0	97.8±11.5	NS
Hip, cm	92.2±12.9	93.9±11.8	95.6±11.7	NS
Waist/Hip ratio	1.00±0.09	0.99±0.08	1.02±0.10	NS

Data are expressed as mean±SD
* - One-way ANOVA test
SD - standard deviation. NS - non-significant - p>0.05, other abbreviations as in Table 1.

Correlations between the BP values and echocardiographic variables among the BP groups. Are shown in Table 6. These data show moderate but significant (p<0.05) relationship between the systolic BP and echocardiographic parameters after controlling the effects of age, gender and BMI.

Risk estimates

We detected statistically significantly high RR ratio for increased LAI values in individuals with High-Normal BP in (RR=1.272, 95% CI (1.089 – 1.485), p=0.032). On the other hand, there was also statistically significant increased risk for increased PCW values in individuals with High-Normal BP (RR=1.537, 95% CI (1.197 – 1.974), p=0.005).

Discussion

In this study, we investigated the differences in LV structure and systolic and diastolic functions between the three BP levels as introduced by the ESC (13). We found that the Optimal BP group demonstrated many differences in echocardiographic measurements when compared with the other BP groups. Normal and High-Normal BP groups demonstrated few differences with regard to LV structure and functions.

It is well known that vascular changes associated with elevated BP may precede the clinical diagnosis of HT. Even after the diagnosis is made, associated coronary heart disease and renal disease continue to progress, despite adequate BP control. Hence, the studies about the adverse effects of BP levels remaining within normal limits but approaching the hypertensive level come into prominence.

Since the publication of several studies describing the presence of differences in morbidity in normotensive BP levels, many studies have focused on the pathophysiologic changes in these BP levels. According to the results of previous studies, the PHT group had higher insulin resistance (22, 23), higher levels of blood glucose, total cholesterol, LDL cholesterol, and triglycerides, higher BMI, and lower levels of HDL cholesterol than the normotensive group (22). In another study, subjects with high-normal BP were found to have greater risk factors for cardiovascular disease, including microalbuminuria, than those with normal BP (25). It also appears that PHT is strictly correlated with cardiometabolic syndrome (26). Additionally, comorbidities can exacerbate the pathologic changes in PHT. The presence of hypercholesterolemia was shown as a promoting factor for the

development of stable HT through its interaction with the circulating renin-angiotensin system in patients with high-normal BP (27). Recently, additional independent associations of diabetes, arterial structure and function and some genes with higher LV mass have been defined; angiotensin II and insulin have also been suggested to be additive stimuli to LV hypertrophy (28, 29). At this point, it seems that the beginning of the pathologic changes in the LV partially depends on individual factors and comorbidities.

According to our study results, a statistically significant difference was found with respect to LA diameter and LAI between the three BP level groups. There was a statistically significant difference in LA diameter between the Optimal and High-Normal BP levels. While there was only a mild difference in LA diameter between Optimal - Normal BP levels, no difference in LA diameter was found between Normal and High-Normal BP levels. Besides, there was statistically significant difference between Optimal and High-Normal BP levels in LAI values. Interestingly, differences in LAI values were still remain as statistically significant even after the correction of the data for age, gender and body mass index. It was considered that differences in LAI values among BP groups are not effected by mentioned anthropometric parameters.

It is well known that, LA diameter and LAI parameters are important indicators for LV diastolic functions if a primary valvular pathology do not exist (44-47). Both of these parameters are also important for the prediction of morbidity and mortality in many of pathological conditions like arrhythmias, heart failure, thromboembolic events and stroke (44-47). According to our results, we detected increased RR ratio for High Normal BP about increased LAI and PCW values. On the other hand, some studies have shown that abnormalities of left ventricular functions might predict the onset of hypertension independent of blood pressure (48). In our study, we found that the measurements of fractional shortening in High Normal BP group were lesser than those of the other groups. We considered that High Normal BP level may be preparative and predictive to evaluation of arrhythmias, hypertension, heart failure, thromboembolic events and stroke.

A mild statistical tendency to decrease in transmitral E/A ratio was detected in conjunction with increasing BP levels, but this finding was not statistically important. However, our results on transmitral A wave, E/Et and PCW support our findings about the differences in LA diameter. We detected a statistically significant difference in transmitral A wave and E/Et between Optimal and High-Normal BP levels. Increased transmitral A

Table 3. M-mode, Doppler, tissue Doppler echocardiographic measurements according to the blood pressure levels

Variables	Normal ranges**	Optimal BP level (n=113)	Normal BP level (n=104)	High-Normal BP level (n=77)	p*
AO, mm	20.0-36.0	26.0±4.8	26.6±4.8	27.0±4.0	NS
AOI, mm/m ²	12.0-22.0	14.1±2.7	14.3±2.7	14.3±2.2	NS
LA, mm	19.0-40.0	31.6±4.5	33.4±4.9	34.3±4.8	0.002
LAI, mm/m ²	12.0-22.0	17±2.3	18±2.9	18±2.3	0.024
EDV, ml	56.0-155.0	104.2±30.9	107.8±28.7	109.1±25.1	NS
ESV, ml	19.0-58.0	34.6±12.8	38.6±16.3	36.4±12.7	NS
SV index, ml/m ²	32.0-58.0	38.4±10.9	36.9±8.8	38.2±8.9	NS
FS, %	25.0-45.0	37.7(35.1-40.4)	36.0(33.0-39.0)	35.9(34.2-39.6)	0.025
EF, %	55.0-82.0	67.7±5.3	65.7±5.5	67.4±6.5	NS
E, m/s	0.5-0.9	0.83±0.21	0.88±0.18	0.86±0.20	NS
A, m/s	0.3-0.8	0.65(0.55-0.78)	0.71(0.63-0.86)	0.74(0.64-0.84)	0.002
E/A	0.8-2.0	1.22±0.29	1.19±0.34	1.11±0.31	NS
DECT, ms	160-258	215±60	227±82	227±64	NS
IVRT, ms	45.0-85.0	61.2(49.8-70.6)	66.5(55.4-75.4)	60.9(49.8-66.5)	NS
IVCT, ms	35.0-55.0	40.2(31.3-49.2)	40.2(31.3-48.7)	40.2(31.3-49.2)	NS
EJT, ms	220.0-320.0	280±33	287±38	292±41	NS
Et, m/s	0.06-0.14	0.10±0.03	0.11±0.02	0.09±0.02	NS
At, m/s	0.07-0.14	0.11±0.04	0.12±0.05	0.16±0.12	NS
E/Et	4.62-11.25	8.2±1.7	8.4±2.0	9.3±1.9	0.012
LVM, gr	67.0-224.0	156.7±43.9	163.0±47.6	173.6±45.6	NS
LVMi, gr/m ²	44.0-102.0	84.2±22.1	84.8±24.1	90.9±21.6	NS
TEI	0.34-0.44	0.39(0.30-0.44)	0.38(0.32-0.44)	0.34(0.28-0.42)	NS
MWS, x10 ³ dyne/cm ²	45.3-84.3	56.4±19.3	68.0±19.4	69.3±22.6	<0.001
LVPWS, x10 ³ dyne/cm ²	200.0-700.0	440.0±205	496.0±201	532.0±192	0.018
VCF, circ/s	1.02-1.94	1.14±0.2	1.18±0.2	1.18±0.2	NS
PCW, mm Hg	4.00-12.00	12.01±2.10	12.26±2.58	13.45±2.30	0.029
dP/dT, mm Hg/ms	>1200	1459(1280-1604)	1677(1278-2334)	1722(1407-2288)	0.031≠
TAU, ms	25.0-40.0	28.6±8.1	28.0±9.0	26.4±6.4	NS
Systolic LV Elastance (Es), mm Hg/ml	-1.0-4.0	-1.5±0.4	-1.7±0.4	-2.0±0.7	<0.001
Diastolic LV Elastance (Ed), mm Hg/ml	10.0-36.0	16.5±5.0	18.3±4.7	21.0±7.4	<0.001
Normalized Elastance (En), Ed/Es	-10.0 - 0.18	- 10.8±0.8	- 10.6±0.9	- 10.8±1.0	NS

Data are expressed as mean±SD and median (25%-75% percentile) values
 * - One-way ANOVA and Kruskal-Wallis tests
 ≠ - Because of not equal variance, Brown-Forsythe test was used for dP/dT parameter
 ** - Established ranges in our hospital
 SD - standard deviation. NS - non-significant - p>0.05, other abbreviations as in Table 1

wave and E/Et ratio were determined in the High-Normal BP level group even after the correction of the data for age, gender and BMI. While there were statistically significant differences in transmitral A wave between Optimal - Normal BP and between Optimal - High-Normal BP levels, there was no difference between Normal - High-Normal BP levels. There were no

differences in E/Et ratio between Optimal and Normal and Normal and High-Normal BP levels. Finally, although it was not statistically important, there was an increase in LVM and LVM index as the BP approached the High-Normal BP level. Our findings are concordant with previous studies. Erdogan et al. (16) found that aortic elastic properties were significantly impaired in PHT patients compared to

Table 4. Differences among the blood pressure levels according to echocardiographic variables after the correction for age, gender and BMI

	Variables										
		LA	LAI	A*	E/Et	PCW	MWS	LVPWS	dP / dT*	Es	Ed
Differences among BP levels#	F	4.289	3.835	4.310	4.224	4.224	7.932	2.307	3.280	12.993	12.441
	p	0.015	0.023	0.015	0.017	0.017	<0.001	NS	0.042	<0.001	<0.001

- One way ANCOVA test
* These parameters were corrected by logarithmic method to perform variance analysis
NS - non-significant - p>0.05, other abbreviations as in Table 1

Table 5. Multiple comparisons between the blood pressure levels according to echocardiographic variables

A) Before the correction of the data for age, gender and body mass index

BP LEVEL COMPARISON	Variables									
	LA	LAI	A*	E/Et	PCW	MWS	LVPWS	dP/dT≠	Es	Ed
OPTIMAL - NORMAL	0.045	NS	0.041	NS	NS	0.002	NS	0.052	<0.001	NS
OPTIMAL - HIGH NORMAL	0.002	0.050	0.007	0.014	0.014	<0.001	0.018	0.008	<0.001	<0.001
NORMAL - HIGH NORMAL	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.032

One-Way ANOVA test, Bonferroni Post-Hoc analysis
*: The parameter of "A" were corrected by logarithmic method to perform post hoc analysis.
≠: Because of not equal variance Tamhane T2 Post-Hoc Test was used for post hoc multiple comparisons
NS - non-significant - p>0.05, other abbreviations as in Table 1

B) After the correction of the data for age, gender and body mass index

BP LEVEL COMPARISON	Variables									
	LA	LAI	A*	E/Et	PCW	MWS	LVPWS	dP/dT≠	Es	Ed
OPTIMAL - NORMAL	NS	NS	NS	NS	NS	0.003	NS	0.038	0.049	NS
OPTIMAL - HIGH NORMAL	0.028	0.050	0.035	0.020	0.020	0.002	NS	0.026	<0.001	<0.001
NORMAL - HIGH NORMAL	NS	NS	NS	NS	NS	NS	NS	NS	0.013	0.007

One-Way ANCOVA test, Bonferroni Post-Hoc analysis
* -The parameter of "A" were corrected by logarithmic method to perform post hoc analysis
≠ - Because of not equal variance Tamhane T2 Post-Hoc Test was used for post hoc multiple comparisons
NS - non-significant - p>0.05, other abbreviations as in Table 1

the normal BP group in their study. Studies have shown that PHT patients had early pathologic cardiovascular markers including increased pulse pressure, LV hypertrophy, increased arterial stiffness, and endothelial dysfunction (11).

After these basic comparisons, we considered that these findings might be attributed to the possible increase in diastolic elastance of the LV with increasing BP levels (30-32). When we calculated dP/dT, the parameters of LV filling pressure (PCW),

Table 6. Correlations between the BP values (systolic and diastolic) and echocardiographic variables

	Variables										
		LA	LAI	A*	E/Et	PCW	MWS	LVPWS	dP / dT*	Es	Ed
Systolic blood pressure	r	0.205	0.146	0.187	0.282	0.282	0.261	-0.168	0.187	-0.340	0.332
	p	0.003	0.034	0.004	0.003	0.003	<0.001	0.015	NS	<0.001	<0.001
Diastolic blood pressure	r	0.090	0.113	0.057	0.240	0.240	0.069	-0.133	0.200	-0.297	0.297
	p	NS	NS	NS	0.012	0.012	NS	0.050	0.049	<0.001	<0.001

Partial Correlation analysis
 * -These parameters were corrected by logarithmic method to perform partial correlation analysis
 BP - blood pressure, NS - non-significant - p>0.05, other abbreviations as in Table 1

and LV systolic and diastolic elastance, we detected an increase in dP/dT when the BP level approached Normal BP level from Optimal BP level. This condition is considered possibly due to the greater shear stress on the arterial walls in Normal and especially High-Normal BP levels compared to optimal BP level (33). For the same reason, in some pathologic conditions like diabetes mellitus, aortic aneurysm, and aortic dissection, decreasing the BP below 130/80 mmHg is among the targets of the treatment if possible (13, 35-37). It is well known that increase in shear stress can cause hazardous consequences in the atheroma plaques (38). Thus, in most of the conditions, decreasing the BP level to a tolerable and asymptomatic level is considered more useful for the patients with ischemic heart disease (12, 13). We also detected the increase in systolic and diastolic elastance and increase in PCW when the BP level approached the High-Normal BP level. It is well known that increases in LV end-systolic or end-diastolic stiffness (i.e. end-systolic or end-diastolic chamber elastance) accomplish the reduced diastolic compliance (30-34). Inevitably, increase in diastolic elastance can cause an increase in LV filling or pulmonary capillary wedge pressure (34). In previous studies, a strong relationship has been shown to exist between ventricular and arterial stiffness (ventricular-arterial coupling). It seems that each can be the cause or consequence of the other (30-32, 41). On the other hand, it is well known that there is a close relationship between arterial stiffness and HT (38-40). We thus considered that the beginning point of the changes in ventricular stiffness is the point of the beginning of HT. From this point of view, "Normal" BP level as classified by the ESC may not be an innocent level. Further studies are required to reveal the interactions of BP and myocardial and endothelial functions.

Limitations of the study

We diagnosed and categorized the BP levels by using the BP measurements that were repeated at least three times in clinical visits. We could not perform ambulatory BP monitoring because of technical limitations; however, it is not an absolute necessity for diagnosis of BP levels. Additionally, our results are based only on noninvasive techniques and measurements. We did not perform any invasive technique to confirm our results due to ethical considerations.

Conclusion

Pathologic changes in LV due to increasing BP begin at below-hypertensive BP levels. It could be possible that Normal

BP level is the beginning of these changes. It seems that the pathologic changes can make an additional contribution to the cardiovascular disease risk of patients whose BP levels are above 120/80 mmHg.

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