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Original Article

Heart Failure and Aortic Stiffening in Patients with Preserved Ejection Fraction

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ABSTRACT

Background This study aimed to explore a possible relationship between aortic stiffness parameters and diastolic function in patients with asymptomatic or symptomatic diastolic dysfunction, and subsequently, the effect of aortic stiffness parameters on the progression from asymptomatic diastolic dysfunction to clinical diastolic heart failure.

Material and Methods Seventy-five subjects were enrolled in the study of whom 20 had diastolic heart failure with the left ventricle ejection fraction (LVEF) >50%, 20 had asymptomatic diastolic dysfunction, 16 had hypertension with normal diastolic function, and 19 were normotensive healthy subjects. Ascending aorta recordings for measuring aortic strain and distensibility as markers of aortic stiffness were obtained from a spot nearly 3 cm above the aortic valve using 2-D echocardiography under M-mode. Doppler echocardiography and 2-D echocardiographic measurements were used to determine diastolic function.

Results While no statistically significant difference in aortic strain or distensibility values was observed between the asymptomatic group and the diastolic heart failure group; however, E/E' values were higher in the heart failure group [12.1(10.0-17.1) vs. 10.0(6.2-22.5)] ($p=0.014$). Aortic strain and distensibility values significantly decreased as E/E' values increased ($r=-0.416$; $p<0.001$ and $r=-0.576$; $p<0.001$, respectively) for pooled data from all groups.

Conclusions Although aortic stiffness parameters did not have a direct effect on the progression from asymptomatic diastolic dysfunction to diastolic heart failure, echocardiographic monitoring of these parameters may be beneficial in identifying patients who would progress to clinical heart failure from diastolic dysfunction.

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Introduction

The adverse effects of cardiovascular risk factors on the heart and vessels have been the subject of many studies. It is known that vessels harden or "stiffen" as the result of structural changes caused in the great vessels by exposure to these risk factors. Aortic stiffness arises from the elastic resistance of the aorta against distension. Aortic stiffness particularly increases with age and also in many pathological conditions such as hypertension, atherosclerosis, diabetes, chronic renal insufficiency or connective tissue diseases. "Stiffness" studies, especially of the great vessels, have demonstrated that this process directly influences cardiovascular morbidity and mortality.[1-3]

Heart failure (HF) can be defined as a complex clinical syndrome where the heart is unable to pump an adequate amount of blood to meet the metabolic needs of the body. It arises from defects in cardiac input and/or output due to structural or functional cardiac impairment.[4] Making a diagnosis of HF can be quite difficult, and is based on the demonstration of an underlying cardiac reason. Recently, another type of heart failure has been described, in that, while the ejection fraction is within the normal range, left ventricle (LV) wall thickness and left atrium (LA) size are increased. Such patients show positive evidence of diastolic dysfunction which is considered to cause HF.[5] Left ventricular diastolic dysfunction may remain asymptomatic for a long time, even while progressing to manifest heart failure from a subclinical myocardial injury. Although the prevalence of diastolic heart failure is increasing, therapeutic options remain limited. Currently, there are no treatments that have convincingly shown a reduction in morbidity or mortality in patients with diastolic HF Therefore, early diagnosis and prompt treatment of asymptomatic diastolic dysfunction, along with clinical and echocardiographic monitoring of these patients, may delay the development of diastolic HF and thus reduce disease-related morbidity and mortality.[6,7]

The nature of the relationship between aortic stiffness and cardiac diastolic function has not yet been clearly defined.[8] Therefore, in the present study, we aimed to investigate whether there is a relation between aortic stiffness parameters and diastolic function by measuring aortic stiffness and diastolic dysfunction markers in asymptomatic and symptomatic diastolic dysfunction patients. Further, we also wanted to investigate if and how differences in aortic stiffness parameters affected the transition from asymptomatic diastolic dysfunction to clinical diastolic heart failure.

Material and Methods

A total of 75 patients who presented to the cardiology polyclinic between July 2012 and November 2012, requiring echocardiographic testing, and meeting the eligibility criteria were recruited. These patients were divided into four groups as follows.

Heart failure group: Patients were assigned to this group in accordance with the European Guidelines for Cardiovascular Disease Prevention in Clinical Practice (version 2012)[9] and consisted of 20 patients aged 40-60 years with hypertension (HT), left ventricle hypertrophy (LVH) (wall thickness >1.3 cm) on transthoracic echocardiography (TTE), history of hospitalization due to class IV heart failure (according to New York Heart Association, NYHA) or already presenting with symptoms of class II or III HF (according to NYHA), and with left ventricle ejection fraction (LVEF) >50%.

Asymptomatic group: Consisting of 20 asymptomatic patients with HT aged 40-60 years with LVH and diastolic dysfunction on TTE.

Control group: Consisting of 16 patients with HT aged 40-60 years but without LVH or diabetes and with normal diastolic functions on TTE.

Normal group: Consisting of completely healthy 19 individuals aged 40-50 years.

Prior to echocardiography, a 12-lead electrocardiography was performed on all the patients. Data on height, body weight, body mass index (BMI), body surface area (BSA), systolic and diastolic blood pressures, cardiac risk factors and any medication history were recorded for all participants. Functional classification of the patients was done in accordance with the criteria issued by the NYHA.

Patients with the following conditions were excluded: Acute decompensated heart failure

or with conditions that cause tissue hypoxia (pulmonary disease, acute manifestations of COPD (chronic obstructive pulmonary disease), recent asthma attack, shock, anemia), suspected coronary artery disease (CAD) based on clinical history and/or stress testing, peripheral artery disease, and mild, moderate or serious aortic stenosis, moderate or serious cardiac valve disease, malignancy, serious liver or kidney disease, atrial fibrillation, and an ejection fraction <50%.

The study was conducted in accordance with the Helsinki Declaration after approved by the ethics committee of our hospital. Informed voluntary consent was obtained from all the subjects.

M-mode, 2-D image, and color-flow Doppler recordings of all study participants were done using a GE Vingmed Vivid 7 echocardiography device with transducers set to adjustable frequencies (2.5-3.5 MHz). Examination was done during three cycles at the parasternal long axis and at the apical four-chamber view (according to the criteria recommended by the American Echocardiography Association), and the arithmetic mean of three values was recorded.[10]

LVEF was calculated for all the patients. In addition, left ventricle end-systolic diameter, left ventricle end-diastolic diameter, left ventricle posterior wall thickness, inter ventricular septum thickness and left atrium diameter were measured, and left atrium volume index (LAVI) and left ventricle mass (LVM) were calculated. LAVI was calculated according to Nagueh et al (2009).[11] LVM was calculated using the following equation developed by Devereux and Reichek, which is based on routinely acquired echocardiographic measurements.[10]

$$LVM = 0.8 \times 1.04([LVEDD + PWT + IVST]^3 - [LVEDD]^3) + 0.6$$

(LVM: Left ventricle mass, IVST: Interventricular septum thickness, LVEDD: Left ventricle end-diastolic diameter, PWT: Posterior wall thickness)

The patients were placed in a slightly supine position; and ascending aorta recordings were obtained using the M-mode under 2-D guidance at a distance of 3 cm above the aortic valve. Aortic diameters were defined as the distance between the internal margins of the anterior and posterior walls of the aorta during systole or diastole. Systolic diameter of aorta (AoS) was measured when the aorta was in the completely open position, and diastolic diameter of aorta (AoD) was measured simultaneously with the QRS peak on ECG. Measurements were made during consecutive 5 pulses and their arithmetic mean was calculated.[10] The measurements were individually evaluated for each patient and the following parameters were calculated to assess the elastic characteristics of the aorta.

Pulse Pressure (PP): Systolic Blood Pressure (SBP)−Diastolic Blood Pressure (DBP)

Aortic Strain (%): [(AoS−AoD)×100/AoD]

Distensibility: 2(Aortic strain)/PP

A Mitral valve trace was obtained by intermittent placing of the Doppler sample on the tips of mitral valve in line with the flow (<20°) on the apical four-chamber images. The E-wave flow rate, A-wave flow rate and E/A ratio were also obtained. Speed of the mitral annulus was recorded throughout the cardiac cycle using the tissue Doppler technique. Volume samples from the apical four-chamber view were placed onto the annulus near to the point where the mitral valve is attached and recordings were obtained from both the septal (medial) and lateral points. Measurements were done at the end of expiration during three or four consecutive cycles. The arithmetic mean of septal and lateral E' values was calculated and it was divided by the E value to obtain the mean E/E' value. Normal diastolic function was defined as follows: septal E' wave ≥8 cm/s, lateral E' wave ≥10 cm/s and left atrial volume index <34 mL/m² on TTE, and abnormal diastolic function was defined as an E/E' ratio greater than 15.[11]

The Kolmogorov-Smirnov test was used to test normal distribution of continuous variables and homogeneity of the variances was tested by the Levene test. Descriptive statistics were represented as mean±standard deviation or median (minimum–maximum) for continuous variables and as case number and percentage (%) for categorical variables. Means between groups were analyzed by One Way Analysis of Variance (One-Way ANOVA), whereas medians between groups were analyzed by the Mann Whitney U test for independent two groups or by Kruskal

Wallis test for more than two groups, with post-hoc Tukey's HSD or Conover's nonparametric multiple comparison test. Categorical variables were analyzed by Pearson's chi-square test and correlation between continuous variables was investigated using the Spearman's correlation test.

The combined effects of all potential risk factors that affected or were considered to affect LV mass indices, aortic strain and distensibility during univariate analyses were investigated using Multivariate Linear Regression Analysis, and the regression coefficient and 95% confidence intervals calculated for each variable. As the measurements of Aortic strain and distensibility were not normally distributed, they were log transformed for regression analyses. The results were considered statistically significant at P<0.05, and all analyses were performed using SPSS (version 11.5).

Results

The group-wise demographic characteristics of the participants are listed in Table 1. Patients in the HF group were significantly older compared to the control group (p=0.014) and normal group, and mean age of the asymptomatic group was higher than that of the normal group. BMI and BSA were also higher in the asymptomatic group and the HF group compared to the normal group. There was no difference among these four groups with respect to gender distribution and the prevalence of smoking. Importantly, there was no difference in baseline characteristics between the asymptomatic and HF groups which are the target groups of the study.

Lipid profiles of the subjects in the asymptomatic group and the HF group were not different. Interestingly, however, differences in triglyceride levels were statistically significant between the control group and the normal group (p=0.007), between the asymptomatic group and the normal group (p<0.002), and between the HF group and the normal group (p<0.001). Subjects in the asymptomatic group and the HF group were similar in terms of other co-existing conditions and prescribed medication *(Table 1)*.

LAVI was higher in the asymptomatic and HF groups compared to the control and normal groups, and there was no difference between the control group and the normal group. The HF group had the highest E/E'ratio *(Figure 1)*. While the E/E' ratio was significantly higher in the HF group compared to the asymptomatic group (p= 0.014), no such difference in LAVI was observed.

LV MASS index was lower in the control group compared to the asymptomatic and HF groups, but no such difference was determined between the asymptomatic group and the failure group. Distensibility and aortic strain values were lower in the asymptomatic, HF and control group compared to the normal group; and no significant difference was found between the control and asymptomatic groups, the control and HF groups, and the asymptomatic and HF groups. Table 2 compares diastolic dysfunction parameters, LV mass index, aortic strain, distensibility and PP values of the groups and Figure 2 compares LV mass index, aortic strain and distensibility measurements among the groups.

As there were differences among the groups in demographic indices such as age and BMI, correlation coefficients between LV mass index, aortic strain and distensibility and other demographic and clinical measurements were calculated and their level of significance was analyzed. While an increase in age, BMI and BSA was positively correlated with an increase in LV mass index (r=0.52, p<0.001; r=0.33, p=0.004 and r=0.25, p=0.030 respectively); it was negatively correlated with aortic strain and distensibility (r=-0.42, p<0.001 and r=–0.579, p<0.001). Moreover, an increase in LV mass index coincided with a decrease in aortic strain and distensibility values. Gender and smoking did not seem to affect LV mass index, aortic strain or distensibility (p>0.05).

Evaluation of effects of overall potential risk factors those are likely to influence the changes in LV Mass index, aortic strain and distensibility of the normal group versus the other groups

Using multivariate linear regression analysis we evaluated the effects of overall potential risk factors (age, female factor, BMI, BSA, triglyceride and pulse pressure) that are likely to influence the changes in LV mass index, aortic strain and

Table 1. Distribution of demographic characteristics, comorbidities and lipid profiles of the cases and the drugs being received among the groups

Variables	Asymptomatic n=20	Failure n=20	Control n=16	Normal n=19	p-value
Age, years	55.3±8.9[b]	57.4±9.7[a,c]	49.2±6.2[a]	44.6±5.0[b,c]	<0.001
Male n(%)	13 (65.0)	8 (40.0)	8 (50.0)	10(52.6)	P>0.05
Female	7 (35.0)	12 (60.0)	8 (50.0)	9(47.4)	
BMI(kg/m^2)	31.0±4.9[b]	32.0±4.6[c]	28.4±4.1	26.1±4.0[b,c]	**<0.001**
BSA(m²)	1.99±0.22[b]	1.96±0.16[c]	1.86±0.15	1.78±0.17[b,c]	**0.002**
History of smoking n(%)	7(35.0)	7(35.0)	8 (50.0)	9(47.4)	P>0.05
HT n(%)	2(100%)	20(100%)	16 (100%)	-	P>0.05
DM n(%)	8(40.0%)	5(25.0%)	-	-	P>0.05
Cholesterol(mg/dL)	188.1±42.9	205.1±39.3	211.3±40.8	195.0±19.9	P>0.05
LDL(mg/dL)	111.6±41.3	124.4±37.3	127.1±27.7	126.8±11.9	P>0.05
HDL(mg/dL)	41.5(22-69)	43.5(29-69)	48.5(19-95)	40(35-90)	P>0.05
Triglyceride(mg/dL)	167.5(48-340)[b]	179.5(74-274)[c]	140.5(61-421)[d]	100(60-180)[b,c,d]	**0.011**
Beta Blocker n(%)	5(25.0)	5(25.0)	2(12.5)	-	P>0.05
CCB n(%)	8(40.0)	9(45.0)	5(31.3)	-	P>0.05
ACEI n(%)	10(50.0)	7(35.0)	5(31.3)	-	P>0.05
ARB n(%)	5(25.0)	9(45.0)	8(50.0)	-	P>0.05
Diuretic n(%)	9(45.0)	14(70.0)	8(50.0)	-	P>0.05
Alfa Blocker n(%)	-	2(10.0%)	-	-	P>0.05
Anti-Lipemic n(%)	3(15.0)	7(35.0)	2(12.5)	-	P>0.05

ACEI, angiotensin–converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BSA, body surface area; CCB, calcium channel blocker; DM, diabetes mellitus; HDL, high density lipoprotein; HT, hypertension; LDL, low density lipoprotein.
aDifference between the Control group and Failure group was statistically significant (p=0.014),
bDifference between the Asymptomatic group and normal group was statistically significant (p<0.01),
cDifference between the Failure Group and Normal group was statistically significant (p<0.05)
dDifference between the Control group and Normal group was statistically significant (p=0.007)

Table 2. Diastolic function parameters, LV mass index, aortic strain, distensibility and Pulse Pressure values

	Asymptomatic	Failure	Control	Normal	p-value
LV MASS Index	113.1±17.7[a,c]	127.7±26.1[b,d]	77.4±10.5[a,b]	72.2±13.8[c,d]	<0.001
Aortic strain	3.9 (2.4-9.3)[c]	4.1 (2.2-9.0)[d]	3.5 (2.5-10.0)[e]	10.3 (6.4-22.2)[c,d,e]	<0.001
Distensibility	0.14 (0.05-0.46)[c]	0.10 (0.06-0.58)[d]	0.16 (0.07-1.00)[e]	0.66 (0.26-12.33)[c,d,e]	<0.001
PP	55 (30-100)[c]	70 (30-105)[b,d]	52.5 (20-80)[b,e]	40 (20-50)[c,d,e]	<0.001
LAVI	28.7 (18.0-62.2)[a,c]	35.0 (18.8-63.3)[b,d]	21.0 (13.4-35.1)[a,b]	20.0 (16.0-25.0)[c,d]	<0.001
Septal E'	6 (2-8)[a,c]	5 (3-7)[b,d]	9 (7-11)[a,b]	9 (8-12)[c,d]	<0.001
Lateral E'	8 (2-13)[a,c]	6 (4-10)[b,d]	11 (9-16)[a,b]	13 (11-15)[c,d]	<0.001
E/E'	10.0 (6.2-22.5)[a,c,f]	12.1 (10.0-17.1)[b,d,f]	7.2 (4.1-8.0)[a,b]	6.3 (4.0-7.7)[c,d]	<0.001

LAVI, left atrium volume index; LV Mass index, left ventricular mass index; PP, pulse pressure
[a]Difference between the Control group and asymptomatic group is statistically significant (p<0.001),
[b]Difference between the Control group and Failure group is statistically significant (p<0.01),
[c]Difference between the asymptomatic group and normal group is statistically significant (p<0.001),
[d]Difference between the failure group and normal group is statistically significant (p<0.001),
[e]Difference between the Control group and normal group is statistically significant (p<0.05)
[f]Difference between the Asymptomatic group and Failure group is statistically significant (p=0.014).

distensibility values. Distensibility and aortic strain values in the control, asymptomatic and HF groups were lower compared to the normal group and statistically independent of all risk factors only distensibility was influenced by age and gender with lower values seen in females than males regression ([Regression coefficient ; p value] [–0.037 {–0.060 - –0.015}; p<0.001 for age and [–0.582 {-1.041 - –0.123}; p=0.014] for females). Also when adjusted to other risk factors, the increase in LV mass index in the asymptomatic and HF groups, compared to the normal group, was not influenced by these risk factors, implying that LV mass index is independent of these risk factors.

Aortic strain and distensibility significantly decreased as the E/E' value increased [(r =–0.416 and p<0.001) and (r =–0.576 and p<0.001), respectively], but only in pooled data from all the subjects.

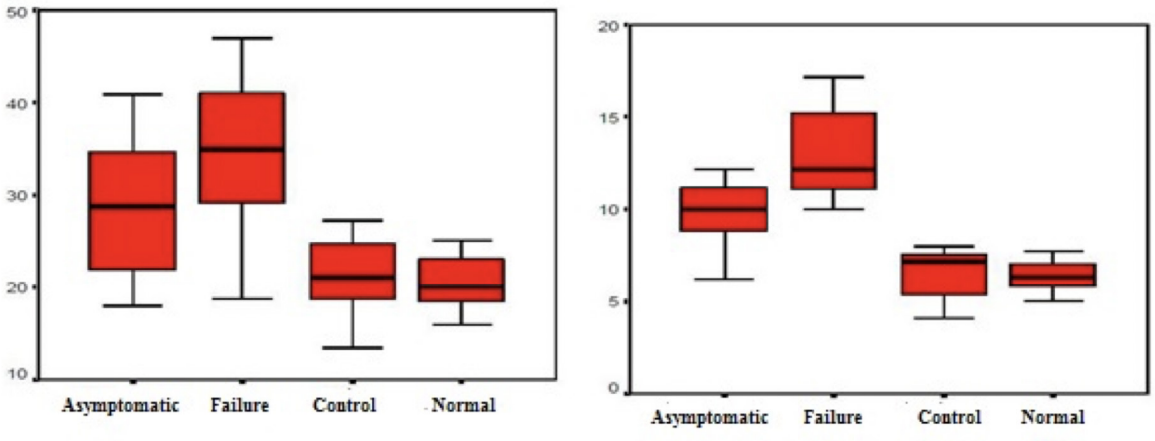

Figure 1. Distribution of E/E' and LAVI measurements among groups.

Box plot of E/E' and LAVI measurements, data represents percentiles. The horizontal line in the middle of each box indicates median value (50th percentile), the bottom and the top margins of the boxes represent the 25th and 75th percentiles, respectively. The vertical lines extending from the upper and lower margins of the box indicate minimum and maximum values, respectively.

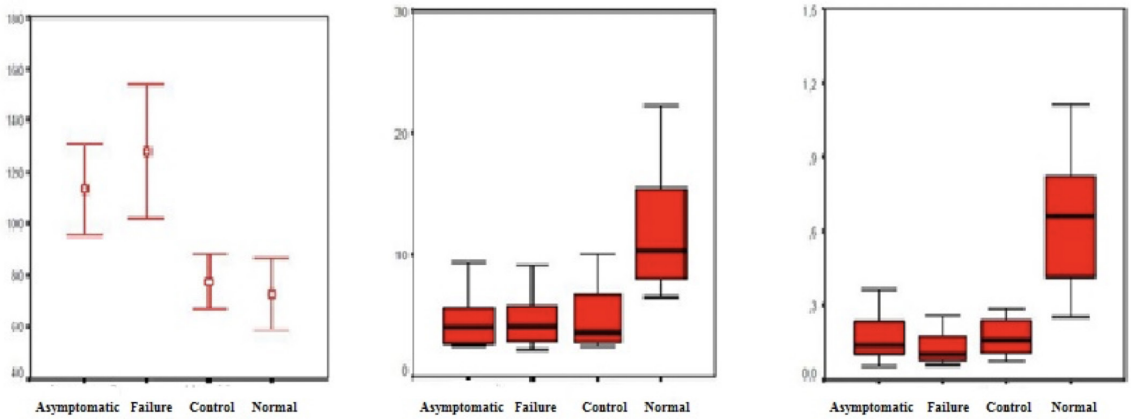

Figure 2. Distribution of LV mass index, aortic strain and distensibility measurements among groups.

Discussion

In the present study, we compared aortic stiffness parameters and diastolic function in asymptomatic and symptomatic diastolic dysfunction patients. While we found no difference between these two groups in terms of aortic stiffness parameters, however, the E/E' ratio, an important and sensitive marker of diastolic dysfunction, was significantly higher in the HF group compared to the asymptomatic group. Furthermore, even though we found that aortic strain and distensibility values significantly decreased as the E/E' ratio increased, we were unable to demonstrate a direct effect of aortic stiffness on the transition from asymptomatic diastolic dysfunction to diastolic heart failure.

It is known that the ventricles and the great vessels become hard or "stiffen", due to structural and functional changes caused by cardiovascular risk factors such as hypertension, diabetes and endothelial dysfunction.[12] Both these processes also directly influence cardiovascular morbidity and mortality.[3] Signs and symptoms of heart failure are clearly apparent in patients suffering from Heart Failure with Preserved Systolic Function even though the EF is within normal range.[3] The main pathophysiological mechanism responsible for this clinical picture is diastolic dysfunction, which is defined as an impaired pressure-volume relationship resulting from a resistance to ventricular filling.[14] LV relaxation and LV diastolic stiffness are the major indicators of diastolic function.[15,16] HF with preserved systolic function accounts for 50-55% of all cases of heart failure, and such patients are usually over the age of 65, female, and present with hypertension, obesity and diabetes.[17] A significant relationship between the degree of aortic stiffness and the LV function in prediabetic population has been shown recently.[18] In line with the available literature, we also found diastolic dysfunction in predominantly older and obese subjects, and the ratio of diabetics was similar to that found in literature.

A review of studies that have investigated aortic stiffness shows that pulse wave velocity (PWV), measured either by invasive or noninvasive methods, has been predominantly used as an index of aortic stiffness.[19] While estimating PWV, it is not possible to accurately measure the distance covered by the pulse wave even though the wave recording is done by Doppler. A superficial measurement method has been suggested for the estimation of this distance but it does not always give a correct result as it requires adjustment for age and factors such as overweight, large breast size, and spinal and thoracic abnormalities can cause errors in measurement. Thus, the correct measurement of this distance requires invasive or angiographic methods, which makes the practical use of PWV difficult. Therefore, aortic strain and aortic distensibility, which can be calculated using echocardiographic aortic diameter and routine blood pressure values, have been suggested as alternate indices of aortic stiffness, and it has been demonstrated that these noninvasively measured parameters are as efficacious as those measured invasively.[20]

Many studies have investigated the relationship between aortic stiffness and cardiac systolic function. However, few studies on aortic stiffness and cardiac diastolic function have investigated whether there is a cause and effect relationship, and have not grouped patients with diastolic dysfunction according to the presence or absence of symptoms of heart failure.[8,21] Moreover, to the best of our knowledge, no study has yet investigated the effect of aortic stiffness on the transition from asymptomatic diastolic dysfunction to symptomatic diastolic heart failure. Besides, a majority of such stiffness studies included patients with coronary artery disease and some studies were particularly conducted on patients with coronary artery disease alone.[22,23] In addition, higher coronary calcium scores were observed more commonly in patients with diastolic dysfunction and found to be strongly correlated with aortic elasticity.[24] The fact that aortic elasticity measurement was performed over the ascending aorta in such patients and that this region is likely to be influenced by the nature of coronary blood flow poses restrictions under certain conditions such as coronary ischemia.[25] Contrarily, CAD was excluded in the participants of the present study by stress testing, which was performed based on either patient history or the suspicion of CAD. Therefore, the margin of error in measuring aortic elasticity due to altered coronary blood flow was minimized. Moreover, as we also

excluded patients with other diseases which are likely to influence aortic stiffness and diastolic dysfunction such as hypoxic pulmonary diseases, aortic stenosis and chronic renal insufficiency and included only patients with documented hypertension and/or diabetes, we aimed to more clearly define the relationship between aortic stiffness and cardiac diastolic function. However, as the participants in the present study were either hypertensive or both hypertensive and diabetic, a control group was formed with the hypertensive subjects alone, apart from a second control group of healthy individuals without any cardiovascular risk factors.

A study conducted in healthy individuals without any cardiac risk factors observed a positive correlation between brachial pulse wave velocity (baPWV) and the E/E' ratio, and demonstrated that the carotid artery stiffness value was beneficial in the early detection of patients with untreated hypertension who would subsequently develop diastolic dysfunction.[22] Further, Xu et al.[26] have demonstrated a significant correlation between baPWV and E/A values in healthy individuals with normal LVEF, and another study ascertained that an increase in arterial stiffness in hypertensive patients is a strong predictor of diastolic dysfunction that is independent of other risk factors.[23] Fujiu et al.[27] demonstrated that, in hemodialysis patients, aortic arch calcification and increased arterial stiffness play an important role in the later development of left ventricular diastolic dysfunction, and an age-related increase in vascular stiffness values and E/E' ratio was discerned in patients even in the absence of cardiovascular disease.[28] Thus, an increase in LV mass index and E/E' ratio along with a decrease in aortic strain and distensibility reported in the present study are consistent with the available data.

Estimation of diastolic function by Doppler echocardiographic methods is not easy because many of the measurements are volume-dependent (preload), show variation with age, and are affected by the time of measurement and by various medications being used by the patient. Therefore, alternative echocardiographic methods or indicators are needed to evaluate diastolic function. Left atrium volume index (LAVI), a parameter independent of volume load, is one such reliable indicator because an increase in left atrium size is the earliest marker of diastolic dysfunction.[11] We used both tissue Doppler and left atrial volume measurement to evaluate diastolic function but found no difference in LAVI values between the control group and the normal group, which is probably due to the absence of diastolic dysfunction in the control group, even though it consisted of subjects with hypertension alone. The fact that among patients with diastolic dysfunction LAVI values were higher in those with heart failure, compared to those without, suggests that there may be factors other than diastolic dysfunction that lead to diastolic heart failure. Furthermore, Kalaycıoglu et al.[29] supported this suggestion by observing an association between impaired left atrial function and ambulatory arterial stiffness index independent of left ventricular diastolic dysfunction in hypertensive diabetic patients.

Our knowledge of the pathogenesis of diastolic HF is still limited but diabetes and hypertension appear to be the most common causes. Characteristic features of HF with preserved systolic function include myocyte hypertrophy, intramyocardial microangiopathy, fibrosis, vascular and ventricular systolic and diastolic stiffness, and impaired relaxation.[30] LVH is present in 90% of patients with hypertension and diastolic dysfunction despite the fact that diastolic dysfunction can occur even in the absence of LVH. An experimental study on rats demonstrated impaired left ventricle compliance/distensibility during the transition from LVH to heart failure with preserved ejection fraction.[31] Further, patients having HF with preserved systolic function show prolonged isovolumic relaxation time, reduced LV filling and increased diastolic stiffness.[15] Another study reported lower resting systolic myocardial velocity (Mean Sm) and mean early diastolic velocity (Mean Em) in patients with hypertensive LVH or hypertensive diastolic HF compared to healthy control subjects.[32] Further, when these two groups were compared with each other, Mean Sm and Mean Em were lower in the hypertensive HF group.[32] Similarly, we also show that, among diastolic dysfunction patients, the E/E' value is higher in patients with the HF phenotype.

LV diastolic dysfunction can remain asymptomatic for a long time and until its transition from subclinical myocardial injury to

manifest clinical HF. Studies have demonstrated that moderate to severe asymptomatic diastolic dysfunction is also associated with increased cardiovascular mortality.[33] Nevertheless, the prognosis is considered to be better for patients with asymptomatic diastolic dysfunction compared to those with diastolic HF, and echocardiographic assessment and monitoring of patients in the subclinical stage is important.[34] Likewise, we also report high E/E' ratio in patients with clinically manifest diastolic HF. Moreover, although aortic stiffness and distensibility values were not different between asymptomatic group and the HF group, pooled data from all the groups showed that both these parameters significantly decreased as the E/E' increased. This result implies that such a decrease in aortic strain and distensibility values together with increase in E/E' ratio can serve as useful criteria for identifying those patients who will subsequently develop clinically manifest HF.

An important limitation of our study is relatively low number of subjects. Another limitation, similar to other studies, is the fact that diastolic dysfunction diagnosed by echocardiography was not verified by cardiac catheterization. While selecting patients for the diastolic heart failure group diagnosis was made based on patient history and echocardiographic criteria and neither serum BNP nor NT-ProBNP levels were estimated.

Conclusions

Although the prevalence of diastolic HF is gradually increasing, treatment options remain limited. Till date no treatment regimen has been shown to convincingly reduce morbidity and mortality in diastolic HF patients. Although we found no difference in aortic stiffness parameters between asymptomatic and symptomatic diastolic dysfunction patients; however, as aortic strain and distensibility values are decreased with an increase in the E/E' ratio; we suggest that echocardiographic monitoring of asymptomatic patients, which is both easy and readily available, will be beneficial in identifying the patients who would show a transition from diastolic dysfunction to clinically manifest HF. Therefore, studies that investigate the effect of an efficient treatment regimen on the development of diastolic heart failure during the asymptomatic period are needed.

Conflict of interest

All authors declare that they have no conflict of interest.

Authors' Contribution

Study Conception: OK, BS; Study Design: AT, OK; Supervision: BS, OK, AT; Funding: AT; Materials: OK, BS; Data Collection and/or Processing: OK, BS; Statistical Analysis and/or Data interpretation: BS, AT; Literature Review: OK, BS, AT; Manuscript Preparation: OK; and Critical Review: BS, AT.

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