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# The alterations of left atrial functional parameters in high left atrial volume index and diastolic dysfunction

## *Yüksek sol atriyal hacim indeksi ve diyastolik disfonksiyonunda sol atriyum fonksiyonel parametrelerindeki değişiklikler*

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**Abstract**

**Purpose:** Previous studies have shown the relationship between left ventricular diastolic dysfunction (DD) and left atrial volume index (LAVi). However, limited studies have been reported on the relationship of functional parameters of left atrium (LA) with LAVi and DD. Therefore, we aimed to examine the changes of functional parameters of LA in high LAVi and DD in this study.

**Materials and methods:** Transthoracic echocardiography was performed in 81 healty subjects (LAVi<30 ml/m2) and 81 patients with DD (LAVi>30 ml/m²). Maximum, minimum and preatrial volumes were measured using area-length method. The functional parameters of LA and other parameters including miyocardial performance index (MPI), left ventricular mass index, relative wall thickness, max LAVi/A', LA sphericity index, the total atrial conduction time (PA-TDI) were calculated and DD was determined by using transmitral and pulmoner ven inflow, pulsed wave Doppler and tissue Doppler.

**Results:** Initially; max LAVi, min LAVi, preA LAVi, max LAVi/A', LA sphericity index, LA total emptying volume (EV) index, LA active EV index, LA passive EV index, PA-TDI, left ventricular relative wall thickness, left ventricular mass index and MPI were significantly higher in patients with DD and high LAVi ($p$<0.05). The groups had similar total LA emptying fraction (LAEF) when age difference was removed with Ancova test analysis. LA expansion index decreased with age in patients with DD and high LAVi in correlation analysis (r=-0.408, $p$<0.001).

**Conclusion:** Max LAVi, min LAVi, preA LAVi, max LAVi/A', LA sphericity index, LA total EV index, LA active EV index, LA passive EV index, PA-TDI, relative wall thickness, left ventricular mass index and MPI were higher in DD and high LAVi regardless of age. Although LA expansion index and total LAEF did not show significant alterations until 57 years in healthy subjects in this study, both of them may decrease in patients with DD and high LAVi, especially in advanced ages, due to prolonged exposure to high filling pressure of left ventricle.

**Key words:** Diastolic dysfunction, echocardiography, functional parameters, left atrial volume index.

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**Öz**

**Amaç:** Önceki çalışmalar, sol ventrikül diyastolik disfonksiyon (DD) ile sol atriyal hacim indeksi (LAVi) arasındaki ilişkiyi göstermiştir. Bununla birlikte, sol atriyumun (LA) fonksiyonel parametrelerinin LAVi ve DD ile ilişkisi hakkında sınırlı sayıda çalışma bildirilmiştir. Bu nedenle, biz bu çalışmada yüksek LAVi ve DD'deki LA'nin fonksiyonel parametrelerindeki değişiklikleri incelemeyi amaçladık.

**Gereç ve yöntem:** 81 sağlıklı kişiye (LAVi <30 ml/m2) ve diyastolik disfonksiyonu olan 81 hastaya (LAVi>30 ml/m²) transtorasik ekokardiyografi yapıldı. Maksimum, minimum ve preatriyal hacimler alan-uzunluk yöntemi kullanılarak ölçüldü. LA'nin fonksiyonel parametreleri ve miyokardiyal performans indeksi (MPI), sol ventrikül kitle indeksi, rölatif duvar kalınlığı, maks LAVi / A', LA sferisite indeksi, toplam atriyal iletim süresi (PA-TDI) gibi diğer parametreler hesaplandı ve DD transmitral giriş, pulmoner ven girişi, pulse dalga (PW) Doppler ve doku Doppler (TDI) kullanılarak belirlendi.

**Bulgular:** Başlangıçta; maks LAVi, min LAVi, preA LAVi, maks LAVi/A ', LA sferisite indeksi, LA total boşalma hacmi (EV) indeksi, LA aktif EV indeksi, LA pasif EV indeksi, PA-TDI, sol ventriküler rölatif duvar kalınlığı, sol ventriküler kitle indeksi ve MPI, DD ve yüksek LAVi'li hastalarda anlamlı olarak daha yüksekti ($p$<0,05). Yaş farkı Ancova test analizi ile kaldırıldığında gruplar benzer toplam LAEF değerine sahipti. Korelasyon analizinde DD ve yüksek LAVi'si olan hastalarda LA genişleme indeksi yaşla birlikte azaldı (r=-0,408, $p$<0,001).

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**Sonuç:** Maks LAVi, min LAVi, preA LAVi, maks LAVi/A ', LA sferisite indeksi, LA toplam EV indeksi, LA aktif EV indeksi, LA pasif EV indeksi, PA-TDI, rölatif duvar kalınlığı, sol ventriküler kitle indeksi ve MPI yaşa bakılmaksızın DD ve yüksek LAVi'si olan hastalarda daha yüksekti. Bu çalışmada sağlıklı kişilerde LA genişleme indeksi ve toplam LAEF, 57 yaşına kadar anlamlı değişiklikler göstermemekle birlikte her ikisi de DD'li ve yüksek LAVi'li hastalarda, özellikle ileri yaşlarda uzamış sol ventrikül yüksek dolum basıncına uzun süre maruz kalması nedeniyle azalabilir.

**Anahtar kelimeler:** Diyastolik disfonksiyon, ekokardiyografi, fonksiyonel parametreler, sol atriyal hacim indeksi.

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## Introduction

The cardiac contractility performance is generally measured using ejection fraction (EF) which is an indicator of systolic function. However diastolic dysfunction (DD) also plays an important role in mortality and morbidity similar to systolic dysfunction [1]. Diastolic function is affected by ventricular filling pressures, relaxation and stretching capacity of the myocardium, passive filling of the ventricle and heart rate [2]. Left ventricular pressure increases due to various reasons and causes left ventricular DD over time. DD can be demonstrated by the deterioration of the mitral internal flow rate or pulmonary vein flow pattern in two dimensional transthoracic echocardiography (2D-TTE) [3].

Contribution of atrial contraction, which is the last phase of diastole, to left ventricular filling is 15-25% in healthy people [4]. In DD, left atrium (LA) may be exposed to high filling pressure of the left ventricule and LA dilatation may occur with atrial remodeling [5]. The studies have showed that LA volume measurements may predict left atrial size more reliable than M-mode measurements. Therefore left atrial volume index (LAVi) and LA functional parameters which were derived from LAVi have been recently used to evaluate the ventricular filling pressure [6]. However limited studies have reported the relationship between LA functional parameters with LAVi. We aimed to investigate the changes of max LAVi, min LAVİ, preA LAVİ, max LAVi/A', LA sphericity index, LA total emptying volume (EV) index, LA active EV index, LA passive EV index, total LA emptying fraction (LAEF), LA expansion index, total atrial conduction time (PA-TDI), left ventricular relative wall thickness, left ventricular mass index and miyocardial performance index (MPI) in patients with increased LAVi and DD in this study.

## Materials and methods

### Study population

This cross-sectional observational study was carried out with 162 subjects (81 healty volunteers, 81 patients with DD) with left ventricular ejection fraction (LVEF)>50% who admitted our hospital cardiology outpatient clinic between September 2018 and January 2019. We tried to increase the sample size in the trial to reveal a statistically more significant difference between groups whereas at least 100 cases (50 controls and 50 patients) were suffient in the statistical analysis before study. The subjects without clinical evidence of any cardiac diseases and no DD findings with LAVi<30 ml/m$^2$ was defined as control group and the subjects with DD and LAVi>30 ml/m$^2$ was defined as patient group. Previous myocardial infarction (MI), acute coronary syndromes (ACS), supraventricular and ventricular arrhythmias including atrial fibrillation (AF), moderate to severe heart valve diseases, congenital heart diseases, pacemaker implantation, poor image quality were defined as exclusion criteria.

This study was approved by the local ethics committee under protocol number 2018-05/11 in Pamukkale University Medical Faculty Hospital and informed consent form was obtained from all registered patients.

### Echocardiography

#### Standard conventional and tissue doppler imaging

2D-TTE was performed with Vivid 7 GE (General Electric Vingmed Ultrasound, Horten, Norway) by using left lateral decubitus position. Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters, interventricular septum, posterior wall thickness were measured by M-mode (mm) and LVEF calculated by biplanar Simpson method (mL and %). Pulse wave (PW) Doppler and tissue Doppler (TDI) techniques were used to determine diastolic functions. Mitral inflow was assessed from the apical 4-chamber by placing a 1–2 mm sample volume between the tips of the mitral leaflets during diastole. From this profile, the E wave and A wave velocity, E deceleration time (DT), A wave duration and E/A were measured. The pulmoner venous velocities were obtained from the same window with the sample volume placed 1 cm into the right upper pulmonary vein and the ratio of systolic to diastolic flow (S/D ratio) and duration of atrial reversal flow was measured. In TDI, sample volume was placed in the septal and lateral mitral annulus and E' velocity, A' velocity, isovolumetric relaxation and contraction time, E/E' ratio and left ventricular ejection time (ms) were measured [7].

**Assessment of LA functional parameters and other markers**

The endocardial area of LA was traced using apical 4-chamber (A1) and apical 2-chambers (A2) views at ventricular end systole. The length of LA (L) was measured from back wall to line across hinge points of mitral valve and LA volume was calculated using the formula (0.85) x(A1xA2/L). Then LA volume was divided by the body surface area (BSA) to get LAVi [8]. LA maximum volume (max LAV) at the end-systolic phase, LA minimum volume (min LAV) at the end-diastolic phase and LA volume before atrial systole (preA LAV) were mesured and indexed to body surface area to obtain max LAVi, min LAVi and preA LAVi [4]. The max LAVi/A' ratio was calculated by dividing LAVi by the late diastolic tissue Doppler velocity A' at the septal mitral annulus [9]. The LA expansion index was calculated as ([Vmax−Vmin]/Vmin)×100% and by dividing the LA transverse length with the LA longitudinal length (t/L) at the max LAV, the sphericity index was obtained [10, 11]. We also calculated the total EV index (max LAVi-min LAVi), the active EV index (preA LAVi-min LAVi) and the passive EV index (max LAVi- preA LAVi). We computed the total LAEF by using the formula (max LAV-min LAV/max LAV)x100 [12]. PA-TDI was assessed by measuring the time interval between the beginning of the P wave on the surface ECG and point of the peak A wave on TDI from LA lateral wall just over the mitral annulus [13]. The relative wall thickness and the left ventricular mass index were calculated by using the formulas respectively 2xPWth/Dd and 0.8x1.04x[(Dd+VSth+PWth)3-Dd3]+0.6 [3]. Finally MPI was obtained as the summation of the isovolumic contraction and the relaxation times divided by ejection time [14].

**Statistical analysis**

The data were analyzed with SPSS 25.0 (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.) package program. Shapiro Wilk test was used for determination of normal distribution. Continuous variables were defined as mean ± standard deviation and categorical variables were expressed as numbers and percentages. For independent groups comparisons, Independent samples t test was used when parametric test assumptions were provided and Mann-Whitney U test was used when parametric test assumptions were not provided. Comparison of categorical variables was performed using the Chi-square test. Ancova test was used to eliminate the age difference between the groups and the mean age of whole participants were determined as 47.43 years. Spearman correlation analysis was used to analyze the relationships between age and LA expansion index and $p<0.05$ was considered statistically significant.

**Results**

The demographic-clinical features and echocardiographic parameters are shown in Table 1. The mean age of the patients with DD were significantly higher (31.78±10.68 years vs 63.10±10.72 years; $p<0.001$) and the incidence of hypertension, diabetes and coronary artery disease were 93%, 44% and 36% respectively in this group. In 2D-TTE, there were significant differences in max LAVi (19.67±4.02 ml/m$^2$, 44.49±10.01 ml/m$^2$; $p<0.001$), in min LAVi (8.51±2.29 ml/m$^2$ vs 21.59±8.11 ml/m$^2$; $p<0.001$), in preA LAVi (12.90±3.34 ml/m$^2$ vs 32.76±9.24 ml/m$^2$; $p<0.001$), in max LAVi/A' (2.21±0.55 vs 6.50±3.52; $p<0.001$), in PA-TDI (92.9±10.10 msn vs 135.21±17.47 msn; $p<0.001$), in total EV index (11.60±2.55 vs 22.93±6.36; $p<0.001$), in active EV index (4.46±1.96 vs 11.20±4.22; $p<0.001$), in passive EV index (6.70±2.28 vs 11.70±4.27; $p<0.001$), in LA sphericity index (0.72±0.06 vs 0.90±0.06; $p<0.001$), in left ventricular relative wall thickness (0.33±0.03 cm vs 0.45±0.06 cm, $p<0.001$), in left ventricular mass index (68.49±8.98 g/m$^2$ vs 134.89±30.30 g/m$^2$; $p$<0.001), and in MPI (0.44±0.06 vs 0.72±0.12; $p$<0.001) and these parameters were increased in patient group. However LA expansion index (139.81±39.36 vs 120.16±51.53; $p$=0.007), and total LAEF (56.83±7.04 vs 51.72±11.60; $p$=0.009) were significantly lower in patient group. Then, the mean age of groups was fixed to 47.43 years by using Ancova test to remove the age effect on diastolic functions and the parameters were recompared (Table 2). After Ancova test analysis, total LAEF was similar in two groups and the patients had significantly increased LA expansion index unlike the initial analysis ($p$=0.151, $p$=0.037 respectively). Therefore the groups were reclassified into age ranges among themselves. LAEF and LA expansion index were re-evaluated to better determine the effect of age on these two parameters. LA expasion index and total LAEF showed no significant differences with age in healty subjects but it was found significant differences in two parameters between 37y-59y and 71y-88y age ranges in patients ($p$=0.001, $p$=0.03 respectively) (Table 3).

In correlation analysis, we did not investigate the relationship between DD and the parameters including max LAVi, min LAVİ, preA LAVİ, max LAVi/A’, LA sphericity index, LA total EV index, LA active EV index, LA passive EV index, PA-TDI, left ventricular relative wall thickness, left ventricular mass index and MPI due to not losing of the statistical significances after the ancova test analysis. However in correlation analysis, there was no relationship between age and LA expansion index in controls (r=-0.186; $p$=0.097) and LA expansion index showed a negative correlation with age in patients (r=-0.408; $p$<0.001).

**Table 1.** Baseline characteristics and echocardiographic parameters of study subjects

| Variable | Controls (n=81) | Patients (n=81) | *p* value |
|---|---|---|---|
| Age (years) | 31.78±10.68 | 63.10±10.72 | <0.001 |
| Height (cm) | 165.01±8.34 | 159.63±9.07 | <0.001 |
| Weight (kg) | 68.72±15.18 | 79.14±14.79 | <0.001 |
| Hipertension, n (%) | - | 75 (93) | <0.001 |
| Diabetes Mellitus, n (%) | - | 36 (44) | <0.001 |
| Coronary artery diseases, n (%) | - | 29 (36) | <0.001 |
| max LAVi (ml/m$^2$) | 19.67±4.02 | 44.49±10.01 | <0.001 |
| min LAVi (ml/m$^2$) | 8.51±2.29 | 21.59±8.11 | <0.001 |
| preA LAVi (ml/m$^2$) | 12.90±3.34 | 32.76±9.24 | <0.001 |
| max LAVi/A’ | 2.21±0.55 | 6.50±3.52 | <0.001 |
| LA sphericity index | 0.72±0.06 | 0.90±0.06 | <0.001 |
| LA expansion index | 139.81±39.36 | 120.16±51.53 | 0.007 |
| Total EV index | 11,60±2.55 | 22.93±6.36 | <0.001 |
| Active EV index | 4.46±1.96 | 11.20±4.22 | <0.001 |
| Passive EV index | 6.70±2.28 | 11.70±4.27 | <0.001 |
| Total LAEF | 56.83±7.04 | 51.72±11.60 | 0.009 |
| PA-TDI (msn) | 92.9±10.10 | 135.21±17.47 | <0.001 |
| Relative wall thickness (cm) | 0.33±0.03 | 0.45±0.06 | <0.001 |
| Left ventricular mass index (g/m$^2$) | 68.49±8.98 | 134.89±30.30 | <0.001 |
| MPI | 0.44±0.06 | 0.72±0.12 | <0.001 |

A’: doppler tissue A’ velocity; DD: diastolic dysfunction; EV: emptying volume;
LA: left atrium; LAEF: left atrial emptying fraction; max LAVi: left atrial maximum volume index; min LAVi: left atrial minimum volume index; MPI: miyocardial performance index; PA-TDI: total atrial conduction time; preA LAVi: preatrial contraction volume index

**Table 2.** The comparison of echocardiographic parameters by using Ancova test

| Variable | Controls (n=81) | Patients (n=81) | *p* value |
|---|---|---|---|
| max LAVi (ml/m$^2$) | 21.283±1.215 | 42.877±1.215 | <0.001 |
| min LAVi (ml/m$^2$) | 10.916±0.921 | 19.183±0.921 | <0.001 |
| preA LAVi (ml/m$^2$) | 15.842±1.073 | 29.886±1.073 | <0.001 |
| max LAVi/A’ | 2.568±0.404 | 6.14±0.404 | <0.001 |
| LA sphericity index | 0.696±0.010 | 0.922±0.010 | <0.001 |
| LA expansion index | 117.241±6.948 | 142.735±6.948 | 0.037 |
| Total EV index | 10.373±0.775 | 23.714±0.775 | <0.001 |
| Active EV index | 4. 932±0.527 | 10.723±0.527 | <0.001 |
| Passive EV index | 5.436±0.533 | 12.971±0.533 | <0.001 |
| Total LAEF (%) | 52.429±1.466 | 56.114±1.466 | 0.151 |
| PA-TDI (msn) | 99.808±2.170 | 128.390±2.170 | <0.001 |
| Relative wall thickness (cm) | 0.328±0.007 | 0.449±0.007 | <0.001 |
| Left ventricular mass index (g/m$^2$) | 66.44±3.593 | 136.942±3.593 | <0.001 |
| MPI | 0.434±0.015 | 0.733±0.015 | <0.001 |

A’: doppler tissue A’ velocity; DD: diastolic dysfunction; EV: emptying volume; LA: left atrium; LAEF: left atrial emptying fraction; max LAVi: left atrial maximum volume index; min LAVi: left atrial minimum volume index; MPI: miyocardial performance index; PA-TDI: total atrial conduction time; preA LAVi: preatrial contraction volume index

**Table 3.** The comparison of LA expansion index and total LAEF according to age ranges

| Variable (patients) | 37y-59y (n=32) | | 71y-88y (n=23) | *p* value |
|---|---|---|---|---|
| LA expansion index | 142.75±57.05 | | 91.47±35.55 | 0.001 |
| Total LAEF (%) | 56.09±10.99 | | 45.65±11.03 | 0.003 |
| **Variable (controls)** | **18y-24y (n=33)** | **25y-39y (n=23)** | **40y-57y (n=25)** | ***p* value** |
| LA expansion index | 147.84±43.69 | 139.26±38.38 | 129.72±32.75 | 0.223 |
| Total LAEF (%) | 58.15±6.74 | 56.78±6.70 | 55.12±7.59 | 0.536 |

LA: left atrium; LAEF: left atrial emptying fraction

## Discussion

In initial analysis, we found that max LAVi, min LAVİ, preA LAVİ, max LAVi/A’, LA sphericity index, LA total EV index, LA active EV index, LA passive EV index, PA-TDI, left ventricular relative wall thickness, left ventricular mass index and MPI were increased in patients with DD and high LAVi regardless of age. When the age difference was removed, LA expansion index was higher in the patients and total LAEF was similar in the groups. These two parameters did not change with aging in healthy controls. But there were significant differences in these parameters between the youngest and oldest patient group.

LA is a dynamic structure and has three functional phases including reservoir during ventricular systole, conduit (for blood from the pulmonary veins to enter the LV) during early diastole and active pump function during late diastole. Volumetric evaluation of LA phasic function is provided by the measurements of maximum, minimum and preA LA volumes and their increased levels were associated with DD in the studies [15, 16]. Miyoshi and Ieda showed that max LAVi, min LAVi and preA LAVi were positively correlated with LAVi similar to our study in patients with DD [12, 17]. The characteristics of the subjects in these studies were similar to our study and LAVi cut off determined by Miyoshi et al. [12] was close to our cut off. However we did not design our study as age matched unlike these studies. Indeed, we removed the age factor using the Ancova test and showed that max LAVi, min LAVi and preA LAVi were still higher in patients compared to healthy controls, regardless of age. We can explain this situation as the presence of comorbidities such as hypertension, diabetes, and coronary artery disease, that may cause the impairment of LA volumetric functional parameters by increasing left ventricular stiffness depending on fibrosis, increased collagen and calcium deposition in the early period or by disrupting its contraction or its relaxation regardless of age [18].

The LAVi/ A' is a parameter that provides to determine patients with DD whose E/e' value is between 8-15 called the gray zone. Park et al. [9] showed that LAVi / septal A' was correlated with increased LAVi and DD severity in patients with HFpEF. LAVi / septal A 'level was also higher in patients with DD and high LAVi in our study. However, we did not evaluate the relationship between LAVi / septal A' and DD severity. Long time high filling pressure exposure may cause the LA dilatation and LA spherical shape. This is a risk factor for AF and a study showed that increased sphericity index was associated with AF recurrence after catheter ablation [11]. It may be considered that there is a correlation between high LAVi and sphericity index. But the studies investigating the sphericity index were generally designed to predict AF recurrence. We found increased sphericitiy index in patient group but we did not follow-up the patients for the development of AF. PA-TDI is one of the parameters showing the electrical and structural remodeling of the atria and PA-TDI gets longer in LA dilatation. In a study a linear relationship was found between left atrium size and PA-TDI [19]. In our study, PA-TDI was longer in subjects with LAVi>30 ml/m$^2$ than in subjects with LAVi <30 ml/m$^2$, and our result was confirmed with this study.

The LA expansion index is a parameter that reflects the reservoir function of LA and decreases due to impaired left atrial compliance depending on increased left ventricular filling pressures. The studies investigating the association between LAVi and LA expansion index are inconsistent. In a prospective study, the patients who had a lower LA expansion index developed HFpEF in years [20]. In another study LA expansion index did not differ in the groups classified as HT+LAVi max>29 ml/m$^2$, HT+LAVi max<29 ml/m$^2$ and control group [12]. In our study, LA expansion index was lower in the patients at the first analysis, but this result changed inversely after age adjustment by Ancova analysis. However in correlation analysis, there was no relationship between age and LA expansion index in the healty controls, but LA expansion index showed a negative correlation with age in the patients. This situation can be explained that prolonged exposure of chronic filling pressure is seen in older the patients and elderly patients usually have advanced stage of DD or multiple comorbidities associated with DD leading to a decrease in reservior functions. Although Ancova test was used, the study had to be performed without a significant age difference between the groups to obtain more accurate results.

Other parameters derived by using max LAVi, min LAVi and preLAVi are LA total EV, active EV and passive EV. These parameters show the reservoir, active pump and conduit functions of the LA respectively [21]. A study showed that increased max LAVi was associated with total EV index, active EV index and passive EV index similar to our study [12]. However the passive EV decreased in patients with DD compared to healty subjects in another study. They explained this as compensatory active pump function may increase in the early stages of DD, according to Frank Starling's mechanism and prolonged high filling pressure exposure may cause LA wall tension and stretching of the LA myocardium resulting in lower active EV and lower total EV over time [22]. Differences in results, including our study, may linked to heterogeneity of DD exposure time or DD severity in the study populations.

Initial analysis showed that total LAEF was higher in healthy controls than in the patients. Indeed, Kurt et al. [23] supported our result by showing its increased levels in healty subjects compared to patients with DD. However total LAEF was similar between the groups after age adjustment (47.43 years) and LAEF did not alter in the healty subjects until 57 years in our study. A study supported our result by showing in reduction of LAEF since age of 50 years [24]. In our study, there was a significant difference in the total LAEF between the youngest and the oldest age ranges in only patient group. We agree that total LAEF did not change depending on decreasing comorbidity incidences and absence of DD like LA expansion index, due to the slow progress of this process in healty subjects. However prolonged exposure of chronic filling pressure in advanced age and cardiovascular risk factors may accelerate this process.

The relative wall thickness, left ventricular mass index and MPI were also examined and we found that these parameters were higher in the patients regardless of age. Similar to our study, Melenovsky et al. [25] showed that left ventricular mass index and relative wall thickness increased in DD and high LAVİ group. In another study, Cacciapuoti et al. [26] investigated the relationship between max LAVi and MPI, and they showed that max LAVi and DD were associated with increased MPI similarly to our study.

There were some limitations in our study. The study had relatively small sample size and there was a significant age difference between the groups. Although we removed the age effect using Ancova test, age matched design may change the study results. Also, the drug treatments may affect the outcomes of the study In addition we did not categorize DD according to its severity. Because we designed the study to investigate the differences of the echocardiographic parameters evaluated above between high LAVİ group with DD (LAVİ>30 ml/m$^2$) and low LAVİ control group without DD (LAVİ<30 ml/m$^2$) rather than the detailed relationship of DD degrees and LA functional parameters. Finally, 3D-TTE was not used to obtain more accurate results or 2D speckle tracking echocardiography was not performed to evaluate left atrial strain.

In conclusion, max LAVi, min LAVİ, preA LAVİ, max LAVi/A', LA sphericity index, LA total EV index, LA active EV index, LA passive EV index, PA-TDI, relative wall thickness, left ventricular mass index and MPI are correlated with the DD and high LAVi regardless of age. However total LAEF and LA expansion index may change with aging depanding on high incidence of comorbidites and prolonged exposure to increased filling pressure in patients with DD. In addition, these two parameters may not change until 57 ages in absence of comorbidities and DD according to this study findings.

**Conflict of interest**: No conflict of interest was declared by the authors.

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**Contributions of authors**

H.A.K.T and M.F.O. conceived the study design. M.F.O. was involved in data collection. H.S. performed the statistical analysis. S.C.S. and M.F.O. interpreted data and prepared the manuscript draft. H.A.K.T, S.C.S. and M.F.O. critically reviewed the final version of the manuscript. All authors approved the final version of the manuscript.