THE LEFT ATRIAL FUNCTIONS AND THE ESTIMATED PULMONARY VASCULAR RESISTANCE IN REDUCED EJECTION FRACTION HEART FAILURE PATIENTS : ASSESSMENT ACCORDING TO DIASTOLIC DYSFUNCTION GRADES

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Abstract

Aim : In this study , according to the diagnosed left ventricular diastolic dysfunction (LVDD) grades, we aimed to determine the correlation of the 2D speckle tracking echocardiography (2DSTE) derived left atrial functional parameters and echocardiographic right ventricular (RV) systolic functions and pulmonary vascular resistance (PVR) estimates in reduced ejection fraction heart failure patients (HFrEF). Methods : Dilated cardiomyopathy patients with an EF lower than 40% included. Echocardiographic examinations including PVR calculations and the 2DSTE performed ; LASr: left atrial reservoir strain , LAScd: left atrial conduit strain, LASct: left atrial contraction strain were calculated. LVDD grading was performed according to guidelines. Results: The mean EF was 28.8 ± 6.0 %. The estimated PVR was strongly correlated with LASr, LAScd and LASct ($p<0,0001$ for each parameter) . All of the LA strain parameters were in decreasing trend along with the increased LVDD grades. The LASct were lower in Grade III when compared with the Grade II LVDD ($p<0.01$) . Conclusion: The decrease of LA contraction function in Grade 3 diastolic dysfunction is evident and it may be associated with the extent of LA remodelling in these patients. PVR estimates well correlates with the LA strain parameters. Future studies may evaluate the value of estimated PVR for grading of LVDD.

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Methods : Dilated cardiomyopathy patients with an EF lower than 40% included. Echocardiographic examinations including PVR calculations and the 2DSTE performed ; LASr: left atrial reservoir strain , LAScd: left atrial conduit strain, LASct: left atrial contraction strain were calculated. LVDD grading was performed according to guidelines.

Results: The mean EF was 28.8 ± 6.0 %. The estimated PVR was strongly correlated with LASr, LAScd and LASct (p<0,0001 for each parameter) . All of the LA strain parameters were in decreasing trend along with the increased LVDD grades. The LASct were lower in Grade III when compared with the Grade II LVDD (p<0.01) .

Conclusion: The decrease of LA contraction function in Grade 3 diastolic dysfunction is evident and it may be associated with the extent of LA remodelling in these patients. PVR estimates well correlates with the LA strain parameters. Future studies may evaluate the value of estimated PVR for grading of LVDD.

Introduction

The left atrium (LA) serves as a dynamic station between the arterial and pulmonary circulation. In addition to its mechanical functions, it has reflex-mediated regulatory functions and endocrine functions via atrial baroreceptors and atrial natriuretic peptides. Left ventricular (LV) filling optimization is provided by modification of LA mechanical functions via these mechanisms. The mechanical functions of LA have the following three phases: the reservoir phase, which is during stage of LV systole when blood flows from the pulmonary veins into the LA; the conduit phase, which occurs because LV relaxation, and blood flows from the LA to the LV in early diastole phase; and the contraction phase in which blood passage is promoted from the LA to the LV by the pressure gradient created by the LA contraction (1).

Heart failure patients with reduced ejection fraction (HFrEF) have chronic exposure to increased LV filling pressures, and postcapillary pulmonary hypertension is followed by the progression of the precapillary pulmonary hypertension resulting from chronic changes in the pulmonary vascular system. The chronic increase in the right ventricular (RV) afterload would result as the RV systolic dysfunction, which has adverse prognostic implications in HFrEF patients (2,3).

Grading of the LV diastolic dysfunction (LVDD) helps clinicians to determine which patients will have increased left ventricular filling pressure and guides for the treatment both in preserved ejection fraction heart failure (HFpEF) and HFrEF patients. Exposure of the pulmonary vascular bed to increased LV filling pressure results in pulmonary arterial hypertension because of vascular remodeling (4,5).

The LA functional failure in HFpEF patients along with the increased LVDD were documented in many previous reports. In summary, the atrial reservoir and conduit functions progressively decrease with the increased LVDD grades, but the contractile function is initially augmented in the early stages, which is followed by a reduction in patients with grade II LVDD (6,7).

The correlation between the LA functions and the RV functions were previously reported, along with the increased LVDD grades of the RV systolic function that is reduced in HFpEF patients (8).

In HFrEF, the contractile atrial functions were found to be lower compared with HFpEF patients (9). Additionally, in HFrEF patients, along with the reduced LA reservoir function, there was a reduction in RV systolic function and an increase in pulmonary pressure (10).

However, the exact correlation between the LA functions and the RV systolic functions were not completely assessed, and the role of estimated pulmonary vascular resistance (PVR) in grading LVDD was not evaluated in previous studies.

In this study, we aimed to determine the correlation of the two-dimensional (2D) speckle tracking echocardiography (2DSTE)-derived LA functional parameters, echocardiographic RV systolic functions, and PVR estimates in HFrEF. We also examined patients according to their LVDD grade.

Methods

Ischemic or non-ischemic dilated cardiomyopathy patients with an EF lower than 40% were included in our study. The exclusion criteria were as follows: acute decompensation and New York Heart Association (NYHA) class IV patients, atrial fibrillation, valve replacement surgery, moderate and severe mitral and aortic stenosis, severe valvular insufficiency, renal failure requiring dialysis, malignancy, cirrhosis, and inadequate acoustic window. The study was approved by the Akdeniz University Ethical Commission. Informed consent was obtained from each patient. Each patient's demographic and clinical data were gathered. Body mass index and body surface area (using the Mosteller formula) were calculated. Venous blood samples from each participant were taken and echocardiographic examinations were performed.

Echocardiography

The GE–Vingmed Vivid 7 system (GE-Vingmed Ultrasound AS, Horten, Norway) echocardiography device was used for echocardiographic examinations. Additionally, 2D, M-mode, and Doppler examinations were performed based on the American Society of Echocardiography (ASE) recommendations, and the LVDD was graded (11,12,13).

2DSTE was performed using Echopac PC version 8 GE, and this was used off-line from previous recordings according to the ASE and European Association of Cardiovascular Imaging (EACVI) recommendations. The LA strain parameters were calculated both from apical two and four-chamber views, and the average values were calculated based on the following parameters: left atrial reservoir strain (LASr), left atrial conduit strain (LAScd), left atrial conduit strain (LAScd), and left atrial contraction strain (LASct) (14).

The following echocardiographic parameters were examined: left atrium diameter (LAd); EF and end diastolic volume (EDV) that were calculated using the bi-plane Simpson method; left atrial volume index (LAVI); RV fractional area change (RV-FAC %); tricuspid annular plane systolic excursion (TAPSE); estimated systolic pulmonary artery pressure (sPAP); ratio of early diastolic mitral inflow velocity (E) to arithmetical mean of early diastolic lateral (E/Em average) and septal tissue velocities (Em); left atrial total emptying fraction (LATEF); left atrial passive emptying fraction (LAPEF); left atrial active emptying fraction (LAAEF); and the PVR ,which is derived from the formula that used the ratio of tricuspid regurgitation velocity to the time velocity integral of the RV outflow tract systolic flow (15).

Statistics

IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous variable data were presented as the mean ± standard deviation (SD) or as the median. Categorical variables are presented as the percentage. To test for normality of distribution, the Kolmogorov–Smirnov test was used. The Pearson test and Spearman tests were used for correlation analysis to assess the correlation of the RV parameters and PVR with the LA strain parameters. N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels were analyzed as the logarithmic function to provide a normal distribution.

Patients were grouped according to their LVDD grades. For categorical variables, the trend test was performed, and for continuous variables, the one-way ANOVA test or Kruskal–Wallis tests were used to determine the difference among the diastolic dysfunction grades.

Results

Overall, there were 50 patients with a mean EF of 28.8 ± 6.0% who were included in the study. There were 37 (74%) patients with ischemic etiology and 41 (82%) patients were male. The mean LASr was 14.47 ± 6.19% and 70% of patients had grade 2 or 3 LVDD. The mean E/Em average ratio was 19.58 ± 8.22 and the median NT-pro-BNP level was 1312.5 pg/mL (Tables 1 and 2).

The LA strain parameters were correlated with the parameters assessing the RV systolic function and sPAP. The strong correlation of PVR with LA strain parameters was remarkable (Table 3).

As expected, the markers of increased LV filling pressure, the maximal LAVI, E/Em average, sPAP, and the NT-pro-BNP levels were higher in LVDD grades 2 and 3 compared to grade 1. Along with the increasing LVDD grades, the PVR showed an increasing trend and the echocardiograph RV systolic function parameters showed a decreasing trend.

The all patients with Grade 3 LVDD were male and NYHA class III patients were predominant in Grades 2 and 3 LVDD. The NT-pro-BNP levels were greater in Grade 2 and 3 LVDD patients compared to patients with grade 1 LVDD. All of the Grade 3 patients were using loop diuretics at various doses, and the other medications among groups were not different (Table 1).

All of the LA strain parameters and the conventional LA function parameters showed a decreasing trend along with the increased LVDD grades. The LAPEF and the LAScd in Grade 2 diastolic dysfunction were not different compared to the Grade 3 diastolic dysfunction. However, the LASct were lower in Grade 3 compared with the Grade 2 diastolic dysfunction (Table 2).

Discussion

In our study, along with the increasing LVDD grades, the PVR were increasing and all of the LA functions and the RV systolic functions showed a decreasing trend. There was a strong correlation between the LA strain parameters and the PVR.

The RV systolic dysfunction was apparent in grade 3 LVDD in which the LA contraction function was found to be depressed compared to grade 2 diastolic dysfunction.

In the early stages of LVDD in HFpEF patients, the LA can adapt to increasing LV filling pressures. When the LA compliance is adequate, increased LV pressures has no effect on pulmonary circulation. However, as the LA compliance decreases because of remodeling and fibrosis, the LA reservoir and the conduit function declines. After this stage, the pulmonary venous system is exposed to increased LV filling pressure. These may summarize the progression of grade 1 to grade 2 LVDD in HFpEF patients (7).

As the pulmonary vascular bed is exposed to increased LV filling pressure, remodeling in the pulmonary vascular system also takes place, which in turn results in increased pulmonary vascular resistance and pulmonary arterial hypertension (16).

Grade 3 LVDD patients have a lower atrial contraction function compared to both Grade 1 and Grade 2 LVDD patients. PVR estimates showed an increasing trend with higher LVDD grades. Especially in the Grade 3 LVDD patient group, the RV-FAC % was found to be lower than the other groups.

Atrial contraction failure and increased pulmonary vascular resistance are characteristics of Grade 3 diastolic dysfunction. In further LVDD grades, LA pump failure and the increase in PVR are concurrent. The following vicious cycle could cause an increase in the LVDD grade: LA pump failure results in a further increase of pulmonary venous pressure, and the further increase of pulmonary venous pressure leads to LA pump failure.

Simultaneous LA remodeling and pulmonary vascular remodeling could be a more appropriate explanation for these results. The fibrosis and hyalinosis especially in the intima of pulmonary veins and simultaneous fibrosis in LA myocardium may share a common pathophysiology. Inflammation from mechanical stress on the pulmonary veins and the LA may result in activation of various neurohumoral-mediated events that cause fibrosis of both the pulmonary veins and the LA. The severity and the duration of heart failure syndrome may determine the extent of both pulmonary venous and LA remodeling (17,18).

The correlation of the peak LA strain with the estimated pulmonary artery pressures especially in heart failure patients compared with mid-range EF patients was shown in a previous study. In that study, the LA strain parameters were worse in patients with mid-range EF, although the groups have similar LA volumes and LVDD. Possible further LA remodeling and fibrosis resulting from LV dysfunction could explain these results in that study (9).

A similar study in HFrEF patients assessed the prognostic significance of LA reservoir function that was determined using 2DSTE, but the data were not analyzed according to the LVDD grade. However, in that study the characteristic features of Grade 3 LVDD, the restrictive mitral inflow pattern, and the increased pulmonary pressures were predominant in the lowest peak atrial longitudinal strain tertile. Patients with acute decompensation were not included in that study and all of the patients were under optimal medical treatment at least for 3 months. Chronic exposure of the LA to pressure/volume overload could explain the results of that study (10).

Another study in HFrEF patients demonstrated the recovery of both of the reservoir and pump function after appropriate treatment of pulmonary congestion. These study results could explain the heart failure syndrome severity impact on LA functions, especially in the acute volume/pressure overload setting (19).

The parameters to determine RV systolic function were shown to be correlated with the LA strain parameters in our study. The trend for the difference in TAPSE and Tr-Sm among groups were also significant, but the difference for the RV-FAC% was more prominent in Grade 3 diastolic dysfunction patients. Unlike RV-FAC, TAPSE and Tr-Sm are dependent on longitudinal RV myocardial function and it may not be informative for the radial RV function and RV ejection function (20).

The estimated PVR correlates well with the LA strain parameters in our study. The estimated PVR value that was used in diastolic dysfunction grading was not evaluated in previous studies for either HFpEF or HFrEF patients. However, it is well known that the severity of the HF syndrome and the duration of exposure to increased LV filling pressure determines both the LA and PV remodeling. In previous studies on the LVDD grading in HFpEF patients who were evaluated using the 2DSTE-derived LA functions, LA function deterioration especially for the conduit and reservoir functions were demonstrated. The calculated LA reservoir strain parameters were greater in HFpEF patients compared with our results. This difference suggests the presence of a greater extent of LA remodeling and fibrosis in HFrEF patients (7). A less severe and shorter the duration of heart failure syndrome in HFpEF patients could explain these results.

A longer duration of exposure to increased LV filling pressure and a more severe heart failure syndrome in HFrEF patients resulted in LA tissue fibrosis, which suggests that irreversible LA remodeling occurred. Reduction of atrial pump function in these patients because of extensive LA remodeling, especially in the Grade 3 LVDD, could explain our findings.

The estimated PVR correlates well with the LA functions in HFrEF patients. The possible increased extent LA remodeling and pulmonary vascular remodeling resulting from a longer duration of exposure to increased LV filling pressure in HfrEF patients may explain this finding.

Study Limitations

Magnetic resonance imaging may demonstrate the extent of LA fibrosis in these patients. Patients with severe mitral regurgitation were excluded, but we did not analyze the effect of moderate mitral regurgitation on LA parameters. Additionally, we did not have exercise echocardiography information. These all may influence our study findings.

Conclusion

Our study demonstrated the deterioration of 2DSTE-derived LA functions along with the advanced grades of diastolic dysfunction. The decrease in LA pump function in Grade 3 diastolic dysfunction is evident and it may be associated with the extent of LA remodeling and fibrosis in these patients. The strong correlation of the echocardiographic pulmonary vascular resistance estimates with the LA strain parameters, and their association with the diastolic dysfunction grades may inspire future studies in HFpEF patients.

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