The Right Ventricular Free Wall Strain and Functional Capacity Assessed by 6 Minutes Walk Test in Heart Faiure Patients with Reduced Ejection Fraction

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Abstract

Introduction The correlation of the right ventricular (RV) systolic function and functional capacity (FC) assessed by cardiopulmonary exercise testing (CPET) in HFrEF patients were demonstrated in previous studies In this study, we aimed to determine the correlation of RV free wall strain (RVfwlS) , left ventricular (LV) strain parameters and other standart echocardiographic parameters with the FC assessed by the 6 minutes walk test 6MWT in HfrEF patients. Also, according to the calculated RVfwlS, the differences among HFrEF patients were examined. Method Dilated cardiomyopathy patients with an EF lower than 40 % included in our study. After echocardiographic examinations, and venous blood sampling for NT-pro-BNP, the 6MWT performed for each participant by a physician blinded to echocardiographic examination. Results 50 patients with a mean EF of 28,78 $\pm$ 6,0 % were included. The distance walked in 6MWT (6MWT-dis) was significantly correlated with the NT-pro-BNP levels, E/Em-mean, left atrial volume index, RvfwlS, Sc (circumferential strain) and the Sl (longitudinal strain) . The Sc and the RVfwlS were found to be the independent predictors of the 6MWT-dis in multivariate analysis. According to mean RvfwlS which was -18,50 $\pm$ 4,83, we grouped patients; Group 1 (n= 26) RvfwlS > -18.5% and Group 2 (n=24) RVfwlS < -18.5%. The Group 2 patients have higher NT-pro-BNP levels (p<0.01) , lower 6MWT-dis (p<0.01), higher E/Em-mean (p<0.01) and lower Sl (p<0.01). Conclusion The low RVfwlS in HFrEF patients could indicate cumulative exposure of RV to chronic increased LV filling pressures due to LV remodelling and dilatation.

Method

Dilated cardiomyopathy patients with an EF lower than 40 % included in our study. After echocardiographic examinations, and venous blood sampling for NT-pro-BNP, the 6MWT performed for each participant by a physician blinded to echocardiographic examination.

Results

50 patients with a mean EF of 28,78 $\pm$ 6,0 % were included. The distance walked in 6MWT (6MWT-dis) was significantly correlated with the NT-pro-BNP levels, E/Em-mean, left atrial volume index, RvfwlS, S_c (circumferential strain) and the S_l(longitudinal strain) . The Sc and the RVfwlS were found to be the independent predictors of the 6MWT-dis in multivariate analysis. According to mean RvfwlS which was -18,50 $\pm$ 4,83, we grouped patients; Group 1 (n= 26) RvfwlS > -18.5% and Group 2 (n=24) RVfwlS < -18.5%. The Group 2 patients have higher NT-pro-BNP levels (p<0.01) , lower 6MWT-dis (p<0.01), higher E/Em-mean (p<0.01) and lower S_l (p<0.01).

Conclusion

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The low RVfwlS in HFrEF patients could indicate cumulative exposure of RV to chronic increased LV filling pressures due to LV remodelling and dilatation.

Introduction

Right ventricular (RV) systolic dysfunction is common in heart failure (HF) and associated with poor prognosis. Chronic RV exposure to increased afterload due to impaired left ventricular (LV) filling and also chronic RV exposure to increased preload due to functional tricuspit insufficiency are the main factors of RV systolic dysfunction in HF patients with reduced ejection fraction (HFrEF) (1,2). Prevalence of RV systolic function in HFrEF vary among studies (3,4) In some studies, rather than the increased pulmonary pressures, the degree of LV systolic dysfunction was found to be correlated with the RV systolic function in these patients (5,6).

The exact mechanisms of exercise intolerance in HF patients are not still completely understood. Pulmonary vascular congestion due to increased LV filling pressures and lower perfusion of skeletal muscles due to diminished cardiac output are the main pathophyisologic explanation for impaired functional capacity (FC) in HFrEF patients. Also abnormalities in peripheral vasodilatation response, metabolic changes in skeletal muscles, and changes in pulmonary alveolar-capillary bed are other explanatory mechanisms for reduced FC in HFrEF patients (7).

Previous studies could not determine any correlation of ejection fraction (EF) and FC in HFrEF patients (8). Also many studies adress the increased LV filling pressures for the major cause of FC limitation in these patients (9,10) Although the RV systolic function could not be considered independently from LV systolic and diastolic abnormalities, the correlation of the RV systolic function and FC assessed by cardiopulmonary exercise testing (CPET) in HFrEF patients were demonstrated in previous studies (11,12,13) . 6 minutes walk test (6MWT) is a reliable method of evaluation of FC in HFrEF patients and correlates with the prognosis (14). Correlation of the distance walked in 6MWT with the peak oxygen consumption in CPET was shown in previous studies (15).

2d speckle tracking echocardiography (2DSTE) technique enables the assessment of myocardial strain and strain rate and it is an usefull tool to determine subtle myocardial changes. 2DSTE to calculate RV systolic function became a common tool in recent studies. RV strain is an objective marker of RV systolic function and the RV strain well correlates with calculated RV ejection fraction with cardiac magnetic resonance imaging (CMR) (16).

In this study, we aimed to determine the correlation of RV free wall strain (RVfwlS) and other standart echocardiographic parameters with FC assessed by the 6MWT in HfrEF patients. Also, according to the calculated RVfwlS, we aimed to determine the differences among HFrEF patients in terms of other echocardiographic parameters including 2DSTE assessment of LV systolic function , NT-pro-BNP levels and FC assessed by 6MWT.

Method

Dilated cardiomyopathy patients whether ischemic or non-ischemic etiology with an EF lower than 40% included in our study. Exclusion criteria were; acute decompensated HF and New York Heart Association (NYHA) class III and IV patients, inability to perform the 6MWT due to ocular, mental and orthopaedic problems, atrial fibrillation, mechanical or biologic valve replacement surgery, moderate and severe mitral and aortic stenosis and severe mitral, tricuspid and aortic insufficiency, end stage renal failure requiring dialysis, documented symptomatic obstructive chronic pulmonary disease and interstitial pulmonary disease, malignancy, cirrohosis, inadequate acoustic window. Study was approved by Akdeniz University Ethical Comission. Informed consents were taken from each patient. Each patients demographical, clinical data were gathered and echocardiographic examinations were performed and recorded to database.

Body mass indices and body surface areas by Mosteller formula calculated. Venous blood of each participant were sampled for NT-pro-BNP analysis and other laboratory data just before the 6MWT. The Cockroft –

Gault formula was used to estimate creatinine clearance rates. Elecsys NT-proBNP test (Roche Diagnostics,) was used to measure NT-pro-BNP levels.

GE – Vingmed Vivid 7 system (GE-Vingmed Ultrasound AS, Horten, Norway) echocardiography device was used for echocardiographic examinations. According to American Society of Echocardioraphy (ASE) 2D, M-mode, Doppler examinations were performed (17,18,19). In addition, we used ratio of tricuspid regurgitant velocity (TRV) to RV outflow time-velocity integral (TVI-RVOT) for estimation of pulmonary vascular resistance, (20) 2D speckle tracking echocardiography analysis were performed with Echopac PC version 8 GE, off-line from previous recordings according to recommendations of ASE and European Association of Cardiovascular Imaging (EACVI) (21). RV free wall strain (RVfwlS) were calculated from RV free wall views in apical four chamber according to the recommendations of ASE and EACVI (22).

The following echocardiographic parameters were examined : LAd: left atrium diameter, EF: ejection fraction calculated with bi-plane Simpson method, EDV: End diastolic volume calculated by bi-plane Simpson method, LAVI: left atrial volume index, RV-FAC %: RV fractional area change, TAPSE: Tricuspid annular plane systolic excursion, Est-sPAP: estimated systolic pulmonary artery pressure, E/Em-mean : ratio of early diastolic mitral inflow velocity (E) to arithmetical mean of early diastolic lateral and septal tissue velocities (Em), TRV/TVI RVOT: ratio of tricuspid regurgitation velocity to the time velocity integral of the RV outflow tract systolic flow, Sr : radial strain, Sc : circumferential strain, Sl : longitudinal strain, RVfwlS: RV free wall longitudinal strain

After echocardiographic examination, 6MWT performed for each participant by a physician blinded to echocardiographic examination according to the guidelines and the distance (in meters) walked by each patient were recorded (23).

IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). was used for statistical analysis. In order to test for normality of distribution the Kolmogorov Smirnow test used. The Pearson test and Spearman tests were used for correlation analysis. In order to determine the effect of echocardiographic parameters to distance walked in 6MWT, the multivariable logistic regression analysis was used. According to the mean value of RVfwlS, patients divided into two groups (high RVfwlS group "Group 1" (RvfwlS > -18.5%) and low RVfwlS group "Group 2" (RVfwlS < -18.5%) . In order to determine difference among two groups ; for categorical variables, the chi square test, and for continous variables, the independent samples T-test and the Mann Whitney U tests were used.

Results

A total of 50 patients with a mean EF of 28,78 $\pm$ 6,0 % were included in our study . Demographic, clinical , laboratory and echocardiographic parameters were given in Table 1 and 2.

The distance walked in 6MWT (6MWT-dis) was significantly correlated with the NT-pro-BNP levels and RVfwlS. Also, strong correlation of 6MWT-dis with the LAVI , E/Em-mean, Est-sPAP , TRV/TVI RVOT, TAPSE, S_c and the S_l was observed. The S_r (%), RV-FAC (%) and BMI was also weakly correlated with the 6MWT-dis (Table 3).

Multivariate regression analysis among echocardiographic parameters, the S_c and the RVfwlS were found to be the independent predictors of the 6MWT-dis (Table 4).

Because of the mean RVfwlS was -18,50 $\pm$ 4,83 % in our study, we sought appropriate to examine patients in two groups : Group 1 (n= 26) the RvfwlS > -18.5% and Group 2 (n=24) the RVfwlS < -18.5% . When we compare two groups ; the Group 2 patients have higher NT-pro-BNP levels (p<0.01) , lower 6MWT-dis (p<0.01), higher TRV/TVI RVOT (p<0.01), higher E/Em-mean (p<0.01), lower Sl (p<0.01) and also lower TAPSE (p<0.01).

The Group 2 patients have lower EF ,higher EDV, higher LAVI and lower Sr , but there was a only a trend towards for statistical significance (Table 5).

Table 1. Demographical and clinical parameters, and the 6MWT results of all study participitants

Age (years):	56.6 ± 11.45
Female sex:	9 (18%)
Ischemic etiology:	37 (74%)
Diabetes Mellitus:	15 (30%)
BMI (kg/ m^2):	26.2 ± 4.74
Treatments used	
Beta Blocker :	42 (84%)
ACE-I or ARB:	37 (74%)
Spironolacton:	20 (40%)
Ivabradin :	2 (4%)
Statin :	15 (30%)
CRT:	4 (8%)
Laboratory data	
Hemoglobin (g/dl):	13.5 ± 1.5
NT-Pro-BNP (pg/ml):	2876.3 ± 3535.4 , (median : 1312.5)
GFR (ml/dk/1,73 m^2)*:	74.7 ± 21.2
6MWT result	
6 MWT-Dis (meter)	411.3 ± 159.3

Abbreviations: BMI: Body mass index, ACE-I: Angiotensin converting enzyme ihnibitor , ARB: angiotensin receptor blocker, CRT: Cardiac resynchronization treatment, GFR: Glomerular filitration rate, 6MWT: 6 minutes walk test. 6MWT-dis: The distance walked in 6 minutes walk test

* Calculated according to Cockroft formula.

Table 2. Echocardiographic parameters of all participants

Parameter	Mean ± Std. Dev.
LAd (mm)	45.26 ± 4.19
EF (%)	28.78 ± 6.0
EDV (ml)	173,40 ± 55,64
LAVI (ml/m^2)	45.59 ± 18.43
RV-FAC (%)	41.89 ± 11.61
TAPSE (mm)	18.88 ± 3.69
Est- sPAP (mmHg)	47.6 ± 19.3
E/Em-mean	19.58 ± 8.22
TRV/TVI RVOT	0.18 ± 0.09
S$_r$ (%)	11.73 ± 6.77
S$_c$ (%)	-5.11 ± 2.50
S$_l$ (%)	-7.35 ± 2.90
RVfwlS (%)	-18.50 ± 4.83

Abbreviations: Std.Dev.: standart deviation, LAd: left atrium diameter,. EF: ejection fraction (bi-plane Simpson method), EDV: End diastolic volume (bi-plane Simpson method), LAVI: left atrial volume index, RV-FAC: right ventricular fractional area change, TAPSE: Tricuspid annular plane systolic excursion, Est-sPAP: estimated systolic pulmonary artery pressure, E/Em-mean : ratio of early diastolic mitral inflow velocity (E) to arithmetical mean of early diastolic lateral and septal tissue velocities (Em-mean), TRV/TVI RVOT: ratio of tricuspid regurgitation velocity to the time velocity integral of the right ventricular outflow

tract systolic flow, S_r : radial strain, S_c : circumferential strain, S_l : longitudinal strain, RVfwlS: right ventricular free wall longitudinal strain.

Table 3. The correlation between 6 MWT-Dis (meter) and clinical and echocardiographic parameters

Parameter	6 MWT-Dis (meter)
Age	-.120 +
BMI (kg/ m²)	.306 + *
Hemoglobin (g/dl)	.249 +
GFR (ml/dk/1.73 m²)	.214 +
NT-Pro-BNP (pg/ml)	-,699 ¥ **
LAd (mm)	-.204 ¥
EF (%)	.192 +
EDV (ml)	-.306 + *
LAVI (ml/m2)	-.519 + **
RV-FAC (%)	.343 + *
TAPSE (mm)	.475 ¥ **
Est- sPAP (mmHg)	-.413 ¥ **
TRV/TVI RVOT	-.631 ¥ **
E/Em-mean	-.555 + **
S_r (%)	.309 + *
S_c (%)	-.444 + **
S_l (%)	-.443 + **
RVfwlS (%)	-.574 + **

Abbreviations: 6MWT-dis: The distance walked in 6 minutes walk test, BMI: Body mass index, GFR: Glomerular filitration rate, LAd: left atrium diameter,. EF: ejection fraction (bi-plane Simpson method), EDV: End diastolic volume (bi-plane Simpson method), LAVI: left atrial volume index, RV-FAC: right ventricular fractional area change, TAPSE: Tricuspid annular plane systolic excursion, Est-sPAP: estimated systolic pulmonary artery pressure, E/Em-mean : ratio of early diastolic mitral inflow velocity (E) to arithmetical mean of early diastolic lateral and septal tissue velocities (Em-mean), TRV/TVI RVOT: ratio of tricuspid regurgitation velocity to the time velocity integral of the right ventricular outflow tract systolic flow, S_r : radial strain, S_c : circumferential strain, S_l: longitudinal strain, RVfwlS: right ventricular free wall longitudinal strain.

+ Pearson correlation coefficient. * Significant correlation (p<0,05)

¥ Spearman rho correlation coefficient. ** Significant correlation (p<0,01)

Table 4. Multivariate regression analysis results of the correlated echocardiographic parameters in determination of 6MWT-dis.

Parametre	β	P value
E/Em-mean	-.250	0.082
TRV/TVI RVOT	-.314	0.061
S_l (%)	.121	0.380
S_c (%)	-.263	0.028*
RVfwlS (%)	-.271	0.035*

Adjusted R^2: 0,516

P<0,001

*statistical significance

Abbreviations: E/Em-mean : ratio of early diastolic mitral inflow velocity (E) to arithmetical mean of early diastolic lateral and septal tissue velocities (Em-mean), TRV/TVI RVOT: ratio of tricuspid regurgitation velocity to the time velocity integral of the right ventricular outflow tract systolic flow, S_l : longitudinal strain, S_c : circumferential strain, RVfwlS: right ventricular free wall longitudinal strain.

Table 5. Comparision of participants clinical and echocardiographic parameters according to RVfwlS; Group 1 (> -18.5%) and Group 2 (< -18.5%)

Parameter	Group 1, (n=26) RVfwlS >-%18.5	Group 2, (n=24) RVfwlS <-%18.5	P value
Age	54,8 ± 9,3	58,3 ± 9,7	0,196
Sex (Female)	6 (%23,0)	3 (%12,5)	0,467
BMI (kg/ m²)	26,3 (25,25*)	25,8 (25,77*)	0,900
Ischemic etiology	19 (%73,1)	18 (%75)	1,0
Hemoglobin (g/dl)	13,6 ± 1,5	13,5 ± 1,5	0,705
GFR (ml/dk/1.73 m²)	74,6 ± 19,5	74,7 ± 23,3	0,984
NT-pro-BNP	967,5 (20,15*)	2724,0 (31,29*)	<0,01
6 MWT-Dis (meter)	488,2 ± 130,9	327,9 ± 146,2	<0,01
EF (%)	30,4 ± 5,7	27,0 ± 6,0	0,046
EDV (ml)	158,3 ± 52,4	189,7 ± 55,3	0,044
LAVI (ml/m2)	41,3 (21,92)*	52,1 (29,38)*	0,071
RV-FAC (%)	46,9 ± 8,3	36,4 ± 12,3	0,01
TAPSE (mm)	20,6 ± 2,8	17,0 ± 3,6	<0,01
Est- sPAP (mmHg)	39,6 (20,87)*	44,5 (30,52)*	0,019
TRV/TVI RVOT	0,147 (18,58)*	0,255(33,0)*	<0,01
E/Em-mean	16,64 ± 7,91	22,76 ± 7,46	<0,01
S_r (%)	10,8 (29,62)*	7,69 (21,04)*	0,038
S_c (%)	-5,15 (23,08)*	-4,53 (28,12)*	0,221
S_l (%)	-8,45 ± 2,59	-6,16 ± 2,78	<0,01

* Mann Whitney U test mean rank

Abbreviations: BMI: Body mass index, GFR: Glomerular filitration rate, 6MWT-dis: The distance walked in 6 minutes walk test, LAd: left atrium diameter,. EF: ejection fraction (bi-plane Simpson method), EDV: End diastolic volume (bi-plane Simpson method), LAVI: left atrial volume index, RV-FAC: right ventricular fractional area change, TAPSE: Tricuspid annular plane systolic excursion, Est-sPAP: estimated systolic pulmonary artery pressure, E/Em-mean : ratio of early diastolic mitral inflow velocity (E) to arithmetical mean of early diastolic lateral and septal tissue velocities (Em-mean), TRV/TVI RVOT: ratio of tricuspid regurgitation velocity to the time velocity integral of the right ventricular outflow tract systolic flow, S_r : radial strain, S_c : circumferential strain, S_l : longitudinal strain, RVfwlS: right ventricular free wall longitudinal strain

Discussion

The S_c and RwflS were found to be independent predictors of FC in HFrEF patients in our study. According to our study results, the patients with lower RVfwlS have greater echocardiographic increased LV filling pressure markers and NT-pro-BNP.

Previous studies seeking the question whether the echocardiography parameters are associated with the

FC in HfrEF patients sign the elevated estimated LV filling pressures denoted by the increased E/Em ratios especially during exercise (24). Also in our study, the echocardiographic markers of elevated LV filling pressures and the NT-pro-BNP were also found to be correlated with the 6MWT results. As a similar finding in previous studies, both the LAVI and the Est- sPAP (mmHg) which are the markers of chronic exposure to increased LV filling pressures were found to be well correlated with the 6MWT results in our study(25). As a marker of pulmonary vascular resistance estimate the TRV/TVI RVOT ratio was also found to be well correlated with the 6MWT result. Reduced functional capacity and its association with the echocardiographic estimate of pulmonary vascular resistance and RV contractile reserve was well demonstrated in a previous study (26).

In our study the mean RVfwlS values in our study was concordant with the previous studies performed in HFrEF patients and the RVfwlS is well correlated with FC assessed by the 6MWT in HFrEF patients (27). Also in previous studies the RVfwlS was also found to be correlated with the FC assessed by the CPET (13,28).

All of the three LV systolic strain parameters were found to be correlated with the FC assessed by the 6MWT. Previous studies demonstrated the correlation of the global longitudinal strain with the FC assessed by the CPET in HFrEF patients , however the association of the both S_c and S_r with the FC in these group of patients was not evaluated in these studies (28,29).

The Sc and RVfwlS were found to be independent predictors in a best fit model to predict the FC assessed by 6MWT. Further dilatation of the LV results with transverse orientation of basal and apical myocardium which are normally arranged in an oblique geometry(30). The lower S_c in these group of patients may indicate the further systolic dysfunction due to further decrement of the systolic function of these transverse myocardial fibers. Also, in a study of Sveric et al. the torsion dysfunction and its association with the Sc was demonstrated in HFrEF patients (31).

The increased LV filling pressures resulting from further loss of LV twist / torsion was previously demonstrated (32). In our study we did not calculate the LV torsion, however the S_c which is a systolic marker of the transversely oriented myocardial fibers which comprise for the LV twist / torsion mechanics was found to be an strong independent variable in our model to predict the FC assessed by 6MWT. In patients with reduced S_c, especially during exercise, the further LV filling pressure increase may limit the FC. The presence of greater LV filling pressure estimates in patients with the low RVfwlS group in our study results support this pathophysiologic explanation.

Despite the RVfwlS seems to be an independent predictor of FC assessed by the 6MWT in our study, the FC strongly correlated both with the hormonal (NT-pro-BNP) and echocardiographic (E/Em -mean and LAVI) markers of increased left LV filling pressures. Also, the patients with the lower RVfwlS have higher LV filling pressure markers.

We consider that the decrement of the RVfwlS eventuate as a result of cumulative exposure of RV to increased LV filling pressures. However the reason of why the RVfwlS rather than the E/Em mean ratio is an independent variable in our multivariate model may have two explanations . First , we do not have an echocardiographic information during exercise. The increased LV filling pressure is well documented in a previous study (26). The amount of LV filling pressure increase during exercise may have an greater impact. Second, the RVfwlS can be a long term monitoring marker of exposure to increased RV afterload.

Despite the S_c determined as the strongest predictor of the FC assessed by 6MWT, the absence of statistical difference for the Sc among high and low RVfwlS patients can be explained by the our low study population.

According to our study results, HFrEF patients with lower RVfwlS exhibit patients who chronically exposed to increased resting RV afterload. As evidenced by the echocardiographic parameters in a previous study, the further increase of both the RV preload and afterload during exercise may also have an additional cumulative negative effect on the RV systolic functions (31).

Our results indicate that the RV systolic functions correlates with the LV remodelling process. As the LV

becomes dilated , the oblique myocardial fibers become oriented in a more transverse fashion which in turn result with further increase of LV filling pressures due to decreased function of these fibers. The cumulative exposure of RV to increased LV filling pressures result with RV systolic dysfunction concurrent with the further FC impairment.

Conclusion

The RVfwlS and the S_c in HfrEF patients were found to be strong independent predictors of the FC assessed by the 6MWT in our study. The low RVfwlS in HFrEF patients indicate cumulative exposure of RV to chronic increased LV filling pressures due to LV remodelling and dilatation. The conventional echocardiographic tools to evaluate RV functions may have limitations in HFrEF patients. The RV systolic functions of HFrEF patients can be better evaluated with 2DSTE method.

Limitations of our study

As well as our study lacks the information regarding the mitral insufficiency exacerbation during exercise, the absence of other exercise echocardiographic data also might have an influence on the analysis of the RV afterload impact on RV systolic function. Although the patients with poor acoustic window excluded from our study, speckle tracking echocardiography measurements may be affected by the thinned myocardium due to LV dilatation. Besides these limitations, the low study population may have an influence on our study results.

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