STUDY OF THE EFFECT OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION ON PULMONARY HYPERTENSION IN CHRONIC SYSTOLIC HEART FAILURE AND ITS EFFECT ON PROGNOSIS

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ABSTRACT

BACKGROUND

Pulmonary hypertension (PH) complicating left ventricular systolic dysfunction carries worse prognosis than LVSD alone. Though nonlinear relation between the severity of the LVSD and the presence of PH exists, diastolic dysfunction (DD) may play some major driving role in determining the degree of PH and henceforth may predict incremental prognostic information. This is a comparative analysis of the parameters of different DD groups in determining the prognostication with special context to PH.

MATERIALS AND METHODS

Prospective analysis was conducted in patients with LVSD (EF-45%) in the Department of Cardiology, R G Kar Medical College, Kolkata, for a period of two years. Clinical characteristics, biochemical parameters and quantitative Doppler measurement of pulmonary systolic pressure (PSP), indices of diastolic function were recorded and followed up for at least one year.

RESULTS

Out of a total 256, only 94 patients met the pre-specified criteria and different parameters were analysed. The patients are classified as mild, moderate and severe DD groups. There was significant difference in mean ± SD of Heart rate, BMI and BNP level. Among the Doppler parameters only E/e is significantly (p value 0.01) different in these groups along with LVEF and PASP. 26 out of a total of 94 patients died in follow up period with Kaplan Meier survival curve for all cause death showing significant log rank test (χ² 15.94), with p value <0.001 between these 3 groups. In multivariate regression analysis, age, PASP and TAPSE (Tricuspid Annular Peak Systolic Excursion) remain significant predictors of mortality whereas the ROC (Receiver Operating Curve) shows the E/e ratio as additional risk factor (AUC is 0.768).

CONCLUSIONS

Assessment of diastolic function provides added prognostic information in HFrEF. Though presence of PH increased the risk for clinical endpoints, the magnitude of diastolic dysfunction contributes to development of PH and has an impact on prognosis and overall mortality.

found to be important independent determinants of filling pressures in the perspective of LVSD. The value of Doppler-derived indirect parameters of LV diastolic function in evaluation of LV filling pressures has been put into question. Hence, in routine clinical practice, the importance of Doppler derived parameters of diastolic function in patients with LVSD, especially the E/e ratio, remains to be elucidated.

Aim of The Study
The purpose of the study is comparative analysis of the parameters of different DD groups in determining the prognostication with special context to PH.

MATERIALS AND METHODS
Study Design, Setting and Patient Selection

Patients attended in RGKMC with dyspnoea or known cases of heart failure under treatment were evaluated for LV systolic dysfunction. The selected cases, echo-Doppler derived diastolic parameters [(mitral valve(MV) transmitral flow velocity (E)/mitral annular diastolic velocity(e) ratio (E/e)], MV deceleration time (DT), Isovolumetric Relaxation time (IVRT)]. Left ventricular ejection fraction (LVEF) etc as well as estimation of Pulmonary systolic pressure (PSP) were done and the patients were kept under follow up for prognostication (By clinical worsening, hospitalisation, death due to cardiac cause etc.).

Study Type and Design
Prospective observational study.

Study Place
R. G. Kar. Medical College.

Time Period

Sample Size
94 patients.
Sample size has been taken based on convenience of the study

Inclusion Criteria
1. Age above 18 years.
2. left ventricular ejection fraction(LVEF) <45%;
3. PASP can be measurable by doppler echo using velocity of tricuspid regurgitation jet.
4. other doppler indices including tissue doppler derived parameters like mitral valve (MV) E/e ratio, MV deceleration time(MVDT), IVRT etc can be measurable by doppler echo.

Exclusion Criteria
1. Organic mitral, tricuspid, or aortic valvular disease or
2. History of any valve replacement or repair;
3. Infiltrative, constrictive, or hypertrophic cardiomyopathy.
4. Myocardial infarction within 6 months period.
5. Chronic obstructive lung disease or sleep apnoea;
6. Congenital heart disease;
7. Presence of tachyarrhythmias including atrial fibrillation.
8. Primary pulmonary arterial hypertension.
9. Prior chest radiation therapy;
10. Cardiac or lung transplantation.
11. Any concurrent chronic systemic disease/ infection like collagen vascular diseases, chronic HIV infection etc.
12. Patients unwilling to participate in the study.

Patients were followed up for 12 months for prognostic evaluation.

Doppler Echocardiography
A clinical, comprehensive two dimensional and doppler echo evaluation were done in all patients' LV size and function was measured as per the standard recommendations of American Society, of Echocardiography. Continuous wave Doppler was used to assess maximal tricuspid regurgitation flow velocity to estimate the systolic pressure gradient between the right ventricle and right atrium. Right ventricular systolic pressure will then be calculated by adding an estimated right atrial pressure to the pressure gradient between RA&RV. In the absence of any organic abnormality of the pulmonary or tricuspid valves this derived pressure will be considered to be identical to PASP. Early transmitral flow velocity (E) and early diastolic mitral annular velocity (e) will be measured with D-E in the apical 4-chamber view with pulsed wave doppler and pulsed wave tissue doppler respectively to provide an estimate of LV diastolic function. The ratio of peak (E) to peak (e) will be calculated (mitral E/e ratio) from the average of at least 3 cardiac cycles. The deceleration time of the E-wave and IVRT were also be measured. Left atrial volume index was calculated using the biplane area length method at end systole. Severity of diastolic dysfunction if present is to be evaluated after considering different constellation parameters of diastolic function along with LA volume status.

Statistical Analysis
For continuous data, analysis was done as mean, SD or median with 25th and 75th percentiles and for categorical data analysis was done as number and percentage. To compare continuous variables two-sample t tests was utilized and signed-rank analysis was done to compare medians of values with nonparametric distributions, with statistical difference accepted for p < 0.05. Multiple linear regression analysis was utilized to evaluate associations among continuous clinical and two dimensional and Doppler echo derived variables with PSP. Analyses were done with the help of SPSS software 24 version.

RESULTS
Clinical and Echo Characteristics
Although larger number (256) of patients had initial requirement of LVEF of <45%, only 94 patients could be finally selected after fulfilling the study inclusion/exclusion criteria and having completed the stipulated echo evaluation and follow up. The patients of different grade of diastolic dysfunction (DD) have been compared using ANOVA and chi square test according to their clinico-demographical and echocardiographic parameter as shown in Table. 1. There is no statistical significance among these three groups in terms of age, sex and systemic BP, however it has been seen that elderly patients are mostly present in the severe DD group. They differ significantly in variation of heart rate and in BMI.
(p value 0.04 and 0.03 respectively) with incremental prognostic value with the grade of DD class. Difference of prevalence of diabetes and coronary artery disease (CAD) not significantly identified though the revascularisation is mostly present in moderate and severe DD group. Patients were receiving standard oral HF medication which were fortnightly/monthly supervised showed no difference of distribution of dose of medicine except the angiotensin receptor and neprilysin inhibitor (ARNI) which was mostly prescribed for moderate and severe groups(26% Vs. 58% Vs 60.3% p=0.02) and the Digoxin (31% Vs 38% Vs 46%, p=0.04). There was not remarkable difference in status of creatinine clearance i.e. GFR value (p=0.17)but significant difference (p=0.01) in terms of BNP level(measured before the initiation of any novel medication e.g. ARNI). Several Doppler derived hemodynamic parameters were also compared and most notable were mean EF (p 0.014), PASP (p value 0.04) and MV E/e (p 0.01).

### Table 1. Comparative Analysis of Clinical, Demographic and Echocardiographic Profile of Patients with Mild, Moderate and Severe LV Diastolic Dysfunction in Patients with EF<45%

<table>
<thead>
<tr>
<th></th>
<th>Mild N=28</th>
<th>Moderate N=35</th>
<th>Severe N=31</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Yrs.</td>
<td>52.6 ± 4.6</td>
<td>58.3 ± 6.2</td>
<td>59.6 ± 7.8</td>
<td>0.263</td>
</tr>
<tr>
<td>Sex, Male</td>
<td>61</td>
<td>70.3</td>
<td>55.1</td>
<td>0.175</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>24.5</td>
<td>21.7</td>
<td>20.8</td>
<td>0.034</td>
</tr>
<tr>
<td>Systemic BP, mmHg</td>
<td>Systolic-124 ± 21</td>
<td>Diastolic-71 ± 12</td>
<td>119 ± 17</td>
<td>74 ± 6</td>
</tr>
<tr>
<td>HR, Beats per Min</td>
<td>78 ± 12</td>
<td>83 ± 14</td>
<td>87 ± 11</td>
<td>0.045</td>
</tr>
<tr>
<td>H/O CAD/Revascularisation</td>
<td>68.6%</td>
<td>73.1%</td>
<td>72.4%</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>17 (60.7%)</td>
<td>20 (70%)</td>
<td>21 (67.7%)</td>
<td>0.08</td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>75.8 ± 45</td>
<td>81.5 ± 37</td>
<td>79.5 ± 61</td>
<td>0.17</td>
</tr>
<tr>
<td>BNP, pg/ml</td>
<td>302 ± 201</td>
<td>462 ± 183</td>
<td>704 ± 374</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>35.3 ± 17</td>
<td>30.6 ± 12.4</td>
<td>28.3 ± 11.2</td>
<td>0.014</td>
</tr>
<tr>
<td>LAVI</td>
<td>40.5 ± 16.6</td>
<td>42.4 ± 21.3</td>
<td>43.7 ± 27.2</td>
<td>0.08</td>
</tr>
<tr>
<td>MV E/e</td>
<td>10.6 ± 8.2</td>
<td>18.2 ± 11.4</td>
<td>21.7 ± 6.9</td>
<td>0.01</td>
</tr>
<tr>
<td>PASP, mmHg</td>
<td>42.6 ± 31.2</td>
<td>49.4 ± 26.8</td>
<td>56.32.9</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Midterm Outcome
Out of 94 patients 48 patients remained stable after clinical and hemodynamic parameter (Evaluated by Doppler) study whereas 32 got worsened and 14 patients actually showed improvement in follow up period of at least 1 year. Out of these 32 patients 26 succumbed. The cumulative survival curve in different DD classes as shown in the Fig.1 demonstrate that the mortality is significantly varying among these three groups with Breslow log rank (Generalised Wilcoxon) test χ² 15.94(p value <0.001).

![Figure 1. Kaplan Meier Survival Curve Analysis for The Three Groups Categorised According to DD, as Mild DD by Grade I, Moderate DD to be Grade II and Severe by Grade III](image1)

![Figure 2. Boxplot Distribution of Median Value of PASP in Different DD Groups in Relation to Survival Outcome](image2)

![Figure 3. Receiver Operating Curve for Sensitivity Analysis for All Causes Mortality in Terms of Different Variables](image3)
Prediction of Outcome

<table>
<thead>
<tr>
<th>Step 1</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>-0.521</td>
<td>0.371</td>
<td>1.970</td>
<td>1</td>
<td>0.160</td>
</tr>
<tr>
<td>PASP</td>
<td>-0.509</td>
<td>0.204</td>
<td>6.201</td>
<td>1</td>
<td>0.013</td>
</tr>
<tr>
<td>Age</td>
<td>-0.422</td>
<td>0.149</td>
<td>7.998</td>
<td>1</td>
<td>0.005</td>
</tr>
<tr>
<td>Gender(1)</td>
<td>1.918</td>
<td>1.668</td>
<td>1.322</td>
<td>1</td>
<td>0.250</td>
</tr>
<tr>
<td>TAPSE</td>
<td>0.362</td>
<td>0.171</td>
<td>4.482</td>
<td>1</td>
<td>0.034</td>
</tr>
<tr>
<td>Constant</td>
<td>67.281</td>
<td>28.486</td>
<td>5.579</td>
<td>1</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Table 2. Multivariate Regression Model Analysis for Risk Prediction for Mortality

Gender (1) for Male
In multivariable regression model age, PASP and TAPSE have been identified as significant (p value 0.005, 0.013 and 0.034) predictor of mortality as demonstrated in table 2. The distribution of median value of PASP is shown in Fig 2 in different DD groups in relation to survival outcome.

Sensitivity Analysis of Predictors
The sensitivity analysis of the covariates in ROC system Fig. 3 shows that PASP of cut off level of 51.5 mmHg has sensitivity of 80% and specificity of near 70% and cut off for TAPSE of 16.5 has sensitivity of >70% and specificity of 62% using c statistics. ROC analysis demonstrates the E/e and LAVI as additional risk factor with AUCs is 0.768 and 0.648 (p value of< 0.001 and 0.027).

DISCUSSION
Our study shows that the patients with SD had an incremental impact of diastolic dysfunction on clinical outcome. Whereas majority studies showed that the severity of left ventricular systolic dysfunction was the key prognostic marker, but diastolic dysfunction had an important role in modifying the clinical outcome, hereby opened an important dimension rendering in research works consequent necessary therapeutic intervention. Luers et al. in their study showed that DD had incremental effect on prognosis in patients with less severe SD compared to patients with more severe SD.14 Kuijk et al. in their study showed that in the patients with peripheral arterial disease, the increased cardiovascular mortality and morbidity was associated independently with presence of isolated diastolic, systolic, or combined LV dysfunction irrespective of the presence of other risk factor (e.g. diabetes mellitus etc.). Patients with combined systolic and diastolic dysfunction had the worst cardiovascular prognosis.15 Lee et al. showed that a decrease of an initially high e/a ratio predicted a more favorable long term clinical outcome with therapy in otherwise clinically stable patients with chronic HF and severe LVSD.16 Meluzin et al. studied a systolic and a diastolic parameter of RV function, the peak systolic tricuspid annular velocity, and peak early diastolic tricuspid annular velocity respectively for delineating prognostic value of patients with heart failure. The authors categorized patients into 4 groups with different combination of the parameters of diastolic function and with different risk of cardiac events and death. It is already known that the impaired relaxation of ventricle due to increased stiffness which is the prime mechanism of DD often leads to the compromised state of cardiac performance status particularly the cardiac output during exercise or on exertion.

This failing response of contractile function may be one of the precursor of systolic dysfunction which can be shown by the deterioration of the systolic longitudinal strain.17,18 This might explain the issue of incremental relative risk of additional DD irrespective of the degree of SD.19 On the other hand, in severe LVSD, pathophysiological processes postulated, may well coincide with those responsible for diastolic dysfunction. Whether a severely compromised LVEF always represents the final common pathway of exaggerated systolic and diastolic dysfunction, is yet to be established.20,21 An increasing number of studies have assessed the risk of readmission and mortality in patients with HFrEF-related PH over the last decade, and mostly in North America and Europe. In a systematic review of literature on predictors of mortality and hospitalization of patients of PH with left heart disease in 24 studies out of 26, PH has been shown to be an independent risk factor, however uniformity is lacking in association between magnitude of reduction of EF and the presence of PH and the mortality.22 In addition to effect of PH; age, NYHA class, decreased GFR and RV function were also integrated in the multivariable analysis for outcome risk in this review.23

Study Limitation
In presence of systolic dysfunction, the present study did not investigate the validity of the echocardiographic diastolic measurements. On the other hand, there is no head to head comparison with the reference standard was available (i.e., invasive hemodynamic assessment). The study population is very small as well as the duration of follow up period for reflecting statistical significance to draw any conclusion.

CONCLUSION
The present study shows that the degree of diastolic dysfunction in patients with HFrEF modifies the status of PH by change of LV filling pressure and provides further prognostic information particularly in presence of RV dysfunction irrespective of degree of LVEF.

REFERENCES


