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INTEGRATED USE OF ECHOCARDIOGRAPHY AND SPIROMETRY IN EVALUATING PATIENTS WITH BRONCHIAL ASTHMA IN A TERTIARY CARE HOSPITAL AT NORTH KERALA: A CROSS-SECTIONAL STUDY

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Abstract:
Bronchial asthma and coronary vascular disease often co-exist, as they share many common risk factors in their etiopathogenesis. The persistent hypoxia in bronchial asthma compromises cardiovascular haemodynamic to a greater extent. Our objective was to assess the cardiac changes by echocardiography in patients with bronchial asthma and to correlate with its severity and pulmonary function test parameters. A total of 130 patients were selected and classified based on their severity, as per GINA (Global Initiative for Asthma) guidelines. All patients underwent spirometry and echocardiography evaluation. On echocardiographic evaluation, 59.3 % patients had abnormal findings. Majority of cases (60%) had pulmonary hypertension (PH) and the incidence of PH was more in the uncontrolled asthma group (44.4%). The frequency of cor pulmonale and tricuspid regurgitation (TR) were 3.08% and 5.38% respectively. There was a significant association ($p < 0.05$) with a positive correlation between the severity of asthma and frequency of PH, LVDD (Left Ventricular Diastolic Dysfunction) and cor pulmonale.
There was a significant ($p<0.05$) positive correlation between the echo parameter ejection expressed as percentage (EF%) and spirometry parameters. But there was a negative correlation between spirometry parameters and echo parameters PH and LVDD. To conclude, the prevalence of cardiac dysfunction showed a liner relationship with the severity of asthma and pulmonary function parameters, especially, PH and LVDD with a statistical significance ($p<0.05$). Echocardiography detects cardiovascular abnormality in asthma patients at the subclinical stage and helps in the improvement of health care.

Keywords: Asthma, cardiovascular disease, spirometry, echocardiography

Introduction:

Asthma is a major health problem which affects all age groups across the globe. In 2016, Indian council of medical research estimated the mortality rate as 60% in India due to non-communicable diseases and the majority of its proportion is attributed to cardio vascular diseases and chronic respiratory diseases (1). Persistent asthmatics are at 1.6-fold higher risk of developing cardiovascular diseases compared to non-asthmatics (2). Bronchial asthma is a non-communicable and a chronic inflammatory disease of airway with a complex etiopathogenesis. Asthma and cardiovascular diseases share common key factors in the etiopathogenesis (3). The chronic inflammation is associated with airway hyperresponsiveness, intermittent obstruction and remodelling of airway passages (4). Airway remodelling is a progressive dynamic process which results in irreversible structural changes of airways and lung parenchyma, leading to an irreversible obstruction (5). The pathological features are increased extracellular matrix deposition, bronchial angiogenesis and microvascular leakage (5). On long term, the remodelling processes involves pulmonary vessels also, leading to pulmonary hypertension. Also, the physiological adaptive mechanisms to maintain regional perfusion and distribution due to persistent hypoxia and hypercapnia, along with the presence of inflammatory mediators contribute to the development of pulmonary hypertension (6). Abnormal gas exchange produces a severe impact on neurohumoral, renal, cardiac and respiratory systems. The end-organ effect of this multi system processes is pulmonary heart disease. This alters the structure and function of right heart eventually leading to the development of cor pulmonale and heart failure (7). The mismatch of ventilation perfusion ratio during acute exacerbation of asthma greatly impacts the function of left ventricle (7). The cardiopulmonary interactions are complex, dynamic hyperinflation which occurs during airflow obstruction and extreme variation in intrathoracic pressure affects both preload and afterload (8). Inflammatory mediators are potential link for asthma and coronary vascular disease. Eosinophils support formation of atherosclerotic plaque on coronary artery wall by endothelium-platelet interaction (9).

Echocardiography is a non-invasive technique which utilize the ultrasound wave to image the heart (10). Tissue doppler imaging is a relatively new technique which detects the myocardial velocity instead of blood flow velocity. This imaging technique helps to understand the changes in the structure and function of the heart at a stage when manifestations of clinical symptoms are not overt (10). Clinical asthma phenotypes produce different impact on the myocardial performance. Early detection of asthma induced cardiac changes is a prerequisite step to halt the progress and to prevent poor long-term outcomes (11).

The correlation between pulmonary function and cardiac outcome had been established by many studies. The decrease in pulmonary function adversely impacted left ventricular ejection fraction, as evidenced by echocardiography. Also decrease in FVC (Forced Vital Capacity) increased cardiac hospitalization and mortality (12). The "Blood pressure levels, clinical features and markers of subclinical cardiovascular damage of Asthma patients" (BADA) study reveal the positive correlation between echocardiographic parameters (left ventricular mass, right atrial volume, and right ventricular Tei index) and FEV_1 (Forced Expiratory Volume in one second) value (13). To the best of our knowledge, no study been conducted in Kerala population with bronchial asthma, correlating echocardiography with spirometry parameters and severity of asthma.

Materials & methods:

This is a cross-sectional study conducted at Malabar Medical College Hospital & Research Centre (MMC HRC), Kozhikode, Kerala. The study population included clinically stable bronchial asthma patients who attended cardiology out- patient department for a routine check -up. The diagnosis of bronchial asthma was confirmed by pulmonologist. The sample size was calculated using the frequency of bronchial asthma patients visiting cardiology OP at MMC HRC for a routine follow-up. The study was conducted after obtaining institutional ethical clearance. Totally, 136 patients were recruited after signing the written informed consent. The duration of the study is one year from January' 2024 to January' 2025. The study was conducted according to the ethical principles framed

by the declaration of Helsinki. Patients with any other chronic lung disease, any systemic disease that can cause pulmonary hypertension, any primary cardiac disease, patients with poor echo window, patients who were unfit to undergo spirometry procedure and on-treatment with a beta-blocker were excluded from the study.

Patients were subjected to undergo spirometry procedure, after strictly adhering to the 'withholding time' for beta agonist as framed by ATS/ERS (American thoracic society/ European respiratory society) guidelines. The equipment used was Vitalograph spirometer with Spirotrac software, which was calibrated before each use. The technician explained the procedure with a demonstration and counsel the patient for a satisfactory performance. The pre bronchodilator test was performed, before nebulization, by measuring parameters like FEV_1 (Forced Expiratory Volume in one second) FVC (Forced Vital Capacity), FEV_1/FVC. Thereafter patient was nebulized with levosalbutamol 0.63 mg/ml, and the same test was repeated after 15 minutes, to record post bronchodilator values. These values were recorded as percentage predicted values according to Hakinson's equation (14). Patients were divided into three groups (well controlled, partially controlled and uncontrolled) based on the score of asthma control test -7 (ACT 7) questionnaire (15). This questionnaire probed into symptom control, use of beta2 agonist as a rescue medication and utilized predicted FEV_1 value (15).

Echocardiography was done by doppler method using Phillips EPIQ CVx GE T8 model machine at cardiology department. Both 2D and M mode studies were done using a probe with multimode frequency of 3mHz and 6 mHz. Pulmonary hypertension was diagnosed when mPAP(mean pulmonary artery pressure) was more than 20 mmHg at rest, as per latest guidelines (16). The mean pulmonary artery pressure (mPAP)was calculated using Chemla formula, mPAP = 0.61*sPAP + 2; (sPAP- Pulmonary artery systolic pressure) (16). The pulmonary artery systolic pressure was calculated using modified Bernoulli equation (17). Tricuspid regurgitant jet velocity was used as an estimate for calculating the pressure gradient in this equation. The formula was, $RVSP=4V^2 + RAP$, (RVSP= Right ventricular systolic pressure, V = peak velocity of tricuspid regurgitation; RAP=Right atrial pressure) (17). Here, RAP is equal to central venous pressure and RVSP will be the same as pulmonary artery systolic pressure, in absence of vena cava obstruction or pulmonary stenosis. The degree of inferior vena cava collapse during inspiratory phase was used to derive the RAP. The value for RAP was kept as 15mmHg, 10mmHg or 5mmHg in case of no collapse, partial or complete collapse of inferior cava, respectively (17).

The diagnosis of cor pulmonale was made when right ventricular hypertrophy was present, with the thickening of right ventricular chamber wall more than 2.6 cm (17). The diagnosis of RVSD (right ventricular systolic dysfunction) was made when tricuspid annular plane systolic excursion (TAPSE) was less than 16 mm and right ventricular ejection fraction (RVEF) was less than 44% (17). The regurgitant flow across tricuspid valve and its maximum jet velocity were assessed by colour flow technique and continuous wave doppler method, respectively (17). The diagnosis of left ventricular systolic dysfunction (LVSD) was made when left ventricular ejection fraction (LVEF) was less than 56% (17). LVEF is otherwise called as stroke volume, which measures end- diastolic volume of blood ejected during left ventricular contraction (17).

E/A ratio measures the ratio of early and late mitral flow velocity, which helps to determine the impairment of left ventricular relaxation (18). The left ventricle function is said to be declining when the diastolic filling of left ventricle is affected. As, E/A ratio depends on elastic recoiling of left ventricle, which in turn affected by age factor, the diagnosis of left ventricular dysfunction (LVDD) was made according to age adjusted E/A ratio as follows: E/A is <1.3 (age group 45-49 years), <1.2 (age group 50-59 years), <1.0 (age group 60 -69 years), <0.8 (age group ≥ 70 years) (18).

Statistical analysis

The collected data were coded, processed and analysed using the SPSS (Statistical Package for the Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). The normal

distribution of data was tested by Kolmogorov-Smirnov test. Qualitative data were expressed as frequencies and relative percentages. Quantitative data were represented as mean ± SD (Standard deviation) and range. One-way ANOVA test was the parametric test used to compare between the groups of normally distributed variables. The significance of p value was kept below 0.05. Spearman's correlation coefficient was used to correlate the echocardiographic variables with spirometry values and different grades of asthma.

Results:

This study included 130 clinically stable bronchial asthma patients, after excluding 6 patients who have acute respiratory infection making them unfit to undergo spirometry procedure. The majority been female gender, with a male to female proportion of 1:2. The mean duration of symptom presentation is 15.8 ± 2.4 years. The study includes patient with the age range from 37 to 62 with a mean of 48.51 ± 4.16 (table-1).

Table 1: Demographic characteristics of all patients

Variable		**Frequency (n=130)**
Age (years) Mean ± SD (range)		48.51± 4.16 (37-62)
BMI (kg/m^2) Mean ± SD (range)		32.3± 2.14 (24-38)
Duration of symptoms (years) Mean ± SD (range)		15.8± 2.4 (10-21)
		n (%)
Gender	Male	45 (34.62%)
	Female	85 (65.38%)
BMI	Underweight	12 (19.23%)
	Normal	34 (26.15%)
	Overweight	48 (36.92%)
	Obese	36 (27.69%)
Comorbidities	Absent	51 (39.4%)
	DM	24 (7.2%)
	HT	10 (19.3%)
	DM+HT	16 (12.1%)
	CVD	29(22%)

DM- Diabetes mellitus; HT- Hypertension; DM +HT- Diabetes mellitus + Hypertension; CVD-Coronary vascular disease.

The calculated mean BMI of study participants was 32.3 ±2.14. In this study, 22% of asthma population had associated CVD. Other comorbidities like diabetes, hypertension and the combination of both, had a prevalence of 7.2%, 19.3% and 12.1% in our study population (table-1).

The spirometry parameters were significantly decreased with the increase in the severity of disease (table-2).

Table 2: Spirometry values of patients with different grades of asthma (n=130)

Variable	Well controlled (n=43) Mean ± SD	Partially controlled (n=44) Mean ± SD	Uncontrolled (n=43) Mean ± SD	Test	p value
Post bronchodilator FEV_1	80.21± 1.05	42.3± 3.13	26.86± 1.6	F= 1623	P<0.05
FVC	91.75± 2.43	76.13± 4.21	71.42± 4.42	F= 167	P<0.05
Post bronchodilator FEV_1/FVC	67.18± 1.03	41.32± 2.31	28.16± 1.47	F= 1142	P<0.05
PEFR	161.7 ± 34.3	145.3± 13.3	132.3± 12.4	F= 649	P<0.05
PaO_2 mmHg	86.32± 2.34	76.21± 26	71.27± 47	F= 268	P<0.05

FEV_1- Forced Expiratory Volume in one second; FVC- Forced Vital Capacity; PEFR-Peak Expiratory Flow Rate; PaO_2 mmHg- Partial oxygen saturation in mmHg; F- F test value for one-way ANOVA.

Table 3: Echocardiographic findings according to the grade of asthma

Echo Findings	Well controlled (n=43)	Partially controlled (n=44)	Uncontrolled (n=43)	Total numbers	Percentage
Normal study	33	16	4	53	40.77%
PH	06	09	12	27	20.77%
Cor pulmonale	-	01	03	04	3.08%
TR	-	04	03	07	5.38%
RVSD	-	07	02	09	6.92%
LVSD	02	06	06	14	10.76%
LVDD	02	04	10	16	12.30%

PH- Pulmonary hypertension; TR- Tricuspid regurgitation; RVSD-Right ventricular systolic dysfunction; LVSD- Left ventricular systolic dysfunction; LVDD- Left ventricular diastolic dysfunction

As severity of asthma increased the prevalence of cardiac dysfunction also increased as evidence by echocardiogram (table -3). We found a significant positive correlation between the severity of PH, occurrence of LVDD and cor pulmonale with the increase in severity of asthma (table-4)

Table 4: Correlation between echo findings and grades of asthma

Variables---Grades of asthma & echo finding	Spearman correlation coefficient (rho)	p value
RVSD	-0.062	0.45
TR degree	-0.051	0.57
Cor pulmonale	0.238	0.021
PH degree	0.721	**p<0.05**
LVDD	0.811	**p<0.05**
Cor pulmonale	0.731	**p<0.05**

We found a good correlation between the severity of LVDD and the severity of PH (table-5)

Table 5: Frequency of LVDD with severity of PH

Severity of PH	Frequency of LVDD
Mild (08)	04 (50%)
Moderate (13)	10 (76%)
Severe (06)	04 (100%)

PH- Pulmonary hypertension; LVDD-Left ventricular diastolic dysfunction

There was a significant ($p<0.05$) positive correlation between spirometry parameters and ejection fraction expressed as percentage (EF %). A significant ($p<0.05$) inverse correlation was seen between spirometry parameters (FEV_1, FEV_1/FVC, FVC) and PH, LVDD. There was no correlation between other echocardiographic parameters and spirometry values (table-6).

Table 6: Correlation between echo findings and spirometry parameters in asthma patients.

Echo Parameter	FEV_1		FVC		FEV_1/FVC	
	r	p	r	p	r	p
LVSD	0.124	0.171	0.114	0.243	0.531	0.852
LVDD	-0.132	**<0.05**	-0.358	**<0.05**	-0.864	**<0.05**
RVSD	0.247	0.196	0.742	0.642	0.753	0.941
EF%	0.475	**<0.05**	0.874	**<0.05**	0.863	**<0.05**
PH degree	-0.173	**<0.05**	-0.647	**<0.05**	-0.974	**<0.05**
Cor pulmonale	0.632	0.571	0.863	0.425	0.593	0.214
TR degree	0.769	0.24	0.475	0.63	0.264	0.78

r- correlation coefficient; p-p value

Discussion:

In managing patients with bronchial asthma, echocardiography is an inevitable tool that is exceedingly helpful in a variety of situations such as differential diagnosis of dyspnoea with cardiac dyspnoea, to trace the aetiology during exacerbations, and to detect concurrent pulmonary hypertension or congestive cardiac failure (19). Echocardiography is a reliable tool to assess the right ventricular and left ventricular systolic and diastolic function, valve functions, presence of pulmonary hypertension, tricuspid regurgitation and cor pulmonale (10). The impact of asthma on the myocardium depends on its phenotype, severity and lung function parameters (11). This study helps us to correlate the lung function parameters with the echocardiographic variables across different grades of asthma. This helps us to detect the relation between these variables, which in-turn paves way for early detection and prevention of long-term complications. In this study we recruited 130 stable asthma patients and classified according to the GINA guidelines as well controlled, partially controlled and uncontrolled asthma. The number of patients in well controlled, partially controlled and uncontrolled groups were 43, 44 and 43 respectively. The demographic characteristics (table-1) of our study population including female preponderance, were consistent with Reddel HK et al statement about the disease presentation in the GINA (Global Initiative for Asthma 2022) executive summary (20). The calculated mean BMI of study participants was 32.3 ±2.14. The frequency of normal and obese patients was 26.15 % and 27.69 % respectively. This correlates with the prevalence of obesity and overweight in Indian asthma population (21). The negative correlation between BMI and spirometry parameters like functional residual capacity % predicted and expiratory reserve volume % predicted was well documented in Indian population in a study conducted by Ramasamy et al (21). The impact of associated co morbidities on asthma is poor symptom control and worse outcomes (22). Asthma and coronary vascular diseases (CVD) share common risk factors and have a bidirectional association (22). In this study, 22% of asthma population had associated CVD. This finding was similar to the reported prevalence of CVD in Indian ethnic population with bronchial asthma by Tattersall MC et al (22). Other comorbidities like diabetes, hypertension and the combination of both, had a prevalence of 7.2%, 19.3% and 12.1% in our study population.

In our study, the negative correlation between spirometry parameters and impairment of asthma control had significant association ($p<0.05$) (table-2). This was in accordance with the result of the study conducted by Zorlu et al (23). From echocardiography, we found 60 % of patients had abnormal findings and the most common (20.77%) finding was pulmonary hypertension (PH). The frequency of the incidence of pulmonary hypertension was more in the uncontrolled asthma group (44.4%) (table-3). This finding was in compliance with Ferrara et al (24). The prevalence of LVDD according to the control of asthma was 9.3 % in well controlled group, 9.09 % in partially controlled group, 18.6 % in uncontrolled group (table-3). The grades of PH were distributed as 29.62% mild, 48.14% moderate and 22.2% severe, in our study (table-3). The frequency of cor pulmonale and tricuspid regurgitation were 3.08% and 5.38%, respectively (table-3). In our study, the correlation between incidence of PH, LVDD, cor pulmonale and the severity of asthma was statistically significant with a positive correlation (table-4). The prevalence of LVDD and PH was found to be more in our study, so we correlated both parameters and found a significant ($p<0.05$) association between them. Also, we found 33.3 % patients with LVDD don't have PH in association (table-5). This result agreed with Sundar et al (25) conclusion on the frequency of coexistence of LVDD and PH in patients with asthma. In present study, we found a positive significant ($p<0.05$) correlation between spirometry parameters (FEV_1, FEV_1/FVC, FVC) and ejection fraction expressed in percentage (EF%). But there was a significant ($p<0.05$) inverse correlation between spirometry parameters and PH, LVDD. (table-6). The result of this study was in accordance with the study conducted by Kundavaram et al (11) and Ghandi et al (26). The possible explanation for this correlation between spirometry parameters and severity of asthma with LVDD and PH can be explained by the following reasons. Since asthma patients are exposed to beta2 agonists, on long term, tachycardia (a side effect of beta2 agonist) will result in incomplete filling of left ventricle resulting in LVDD (27). Also, the physiological stress of recurrent asthma exacerbations, may affect the ventricular volume (27). Uncontrolled asthma and pulmonary hypertension lead to small airway disease, independently and also synergistically. The presence of small airway disease will result in the drastic fall in spirometry values (28). These studies (Kundavaram et al and Ghandi et al) were conducted in paediatric population. More studies in adult asthma population are needed to substantiate the correlation between cardio pulmonary parameters, in our population.

Limitations:

Monitoring electrocardiographic changes and other vital signs would have added more support to this correlation study.

Conclusion:

In this study, echocardiographic (ECHO) changes were present in 60% of adult asthma patients. The evidence of ECHO changes (14% PH, 2% LVSD and LVDD each) in well controlled asthma patients reflects the potential need of echocardiographic evaluation at an earlier stage of asthma. There exists a significant positive correlation between the severity of asthma and ECHO changes (PH, LVDD and cor pulmonale). There was a significant negative correlation between ECHO changes (PH, LVDD) and lung function parameters. This warrants the need of integrated approach in the treatment of bronchial asthma.

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