Echocardiography and N-terminal-pro-brain natriuretic peptide in assessment of left ventricular diastolic dysfunction in stable COPD in relation to disease severity

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Abstract
Introduction: Left ventricular diastolic dysfunction (LVDD) is found to be frequent in COPD patients. Relationship between airflow obstruction and cardiovascular risk can be explained by inflammation which is considered one of systemic manifestations of COPD.
Objective: To assess the LVDD in COPD patients in relation to disease severity using echocardiography, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high sensitive C-reactive protein (hs-CRP).
Patients and methods: This prospective study was carried out on 60 stable COPD patients who were recruited from outpatient chest clinics, Tanta University Hospitals. Diagnosis of COPD was made according to criteria of the Global Initiative for Chronic Obstructive Lung Disease. Patients were subjected to medical history and physical examination, chest X ray, pulmonary functions, ECG and echocardiography. Blood samples were withdrawn for assessment of NT-proBNP and hs-CRP.
Results: Diastolic function of the heart was evaluated by echocardiography using: isovolumetric relaxation time (IVRT), deceleration time of early transmitral flow, ratio of the peak velocity of the early E wave/A wave which suggested that LVDD was recorded more in severe/very severe compared to mild/moderate COPD. Significant positive correlations were found between Nt-pro BNP and hs-CRP, IVRT, deceleration time of early transmitral flow and E/A wave ratio. Sensitivity, specificity and accuracy were 83.1, 90 and 0.94% for Nt-pro BNP.
Conclusions: Evaluation of NT-proBNP was important for detection of LVDD in COPD patients, which was correlated with disease severity. Echocardiographic assessment of COPD patients, especially in combination with NT-proBNP can be considered as good diagnostic tools of LVDD in COPD.

Introduction
Chronic Obstructive Pulmonary Disease (COPD), a common, preventable and treatable disease is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients [1].

High prevalence of a 10 year cardiovascular risk by more than 20% was found in COPD patients aged 55–74 than the general population [2].

One study supports the relationship of COPD with smoking and age as the most important cardiovascular risk factors which associated with COPD patients [3].

Left ventricular diastolic dysfunction (LVDD) is found to be frequent finding in COPD patients. The relationship between airflow obstruction and cardiovascular risk can be explained by inflammation, which is considered one of the systemic manifestations of COPD [4].

An independent predictor of cardiovascular outcome is arterial stiffness which was exaggerated in COPD patients [5] even if these
patients were free of cardiovascular disease indicating acceleration of the age dependent stiffening [6].

Echocardiographic assessment of left and right ventricular function in COPD patients is difficult, due to lung hyperinflation, but tissue Doppler echocardiography (TDE) may improve the study of regional systolic and diastolic function, myocardial deformation indices, myocardial and annular velocities and such as strain and strain rate [7].

Patients with COPD have numerous cardiovascular complications including cor pulmonale, [8] which, increase cardiovascular risk by 2–3-fold [9] in addition to more than fourfold excess risk of chronic heart failure [10].

Brain natriuretic peptide (BNP) and N-terminal-pro-BNP (NT-proBNP) are derived from Pro-B-type natriuretic peptide (proBNP) that is synthesized in response to stretching by ventricular myocytes [8].

Chronic obstructive pulmonary disease is characterized by an abnormal inflammatory response causing a systemic inflammatory reaction which could be assessed by numerous inflammatory markers. Among these markers, hs-CRP is as an important and widely accepted biomarker related to the airflow obstruction [11].

Gan and colleagues found that CRP is elevated in smokers, patients with reduced lung functions and stable COPD patients. They also reported that CRP levels can predict cardiovascular mortality, and decreased following treatment with inhaled corticosteroids [12].

Elevated CRP level was associated cardiovascular mortality in COPD patients especially those with mild-to-moderate airway obstruction [13]. However, the potential role of hs-CRP as a marker is to reflect all aspects of pulmonary and extra-pulmonary complications in COPD and its prognostic value in COPD needs further investigation.

Objective

The objective of this study was to assess the left ventricular diastolic dysfunction in COPD patients in relation to disease severity using echocardiography, NT-proBNP and Hs-CRP.

Patients and methods

This prospective study was carried out on 60 stable COPD patients who were recruited from outpatient clinics, Chest Department, Tanta University Hospitals.

The diagnosis of COPD was made according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [14]. In the COPD group, 11 patients were mild (GOLD stages I), 20 patients were moderate (GOLD stages II), 16 patients were severe (GOLD stages III) and 13 patients were very severe (GOLD stage IV). Twenty apparently healthy individuals were enrolled in this study as controls. This study was performed according to the ethical rules in our region; a written consent was obtained from each individual.

Exclusion criteria:

1. COPD patients during acute exacerbation period.
2. Patients with bronchial asthma or pneumonia or idiopathic pulmonary fibrosis.
3. Longstanding uncontrolled hypertension.
4. Evidence of ischemic Heart Disease or valvular pathology.
5. Left ventricular ejection fraction <55%.
6. Atrial fibrillation.
7. Diabetes Mellitus.
8. Obesity with body mass index ≥30 kg/m².

All patients were subjected to full medical history and physical examination, Chest X ray, pulmonary Function tests, ECG and Echocardiography. Venous blood sample was taken and analyzed for complete blood picture, renal and liver function tests, fasting blood glucose level and total lipid profile. Blood samples were withdrawn for assessment of NT-proBNP and hs-CRP.

Pulmonary function tests

Spirometry pre and post-bronchodilator was performed 15 min following administration of 400 μg of inhaled salbutamol. Forced expiratory volume in 1 s (FEV1)/forced vital capacity ratio (FVC), FEV1 (% of predicted) were done using spirometer (Model: CHEST GRAPH Hi-101 Tokyo Japan). COPD was diagnosed in patients with FEV1/FVC ratio <70%.

Echocardiography

Echocardiography was performed in Cardiology Department, Tanta University Hospitals, transthoracic echocardiography (Vivid 3; GE Healthcare, USA) was performed by the same cardiologist. Images were recorded from the parasternal views (long axis view and short axis view), the apical four-chamber view. All measurements were made in accordance with the American Society of Echocardiography/European Association of Echocardiography recommendations. Then an average of three measurements was taken for each of the variables used [15].

The left ventricular systolic function was evaluated by measuring the ejection fraction (EF) according to the Teichholz method [16].

We evaluated the diastolic function of the heart using: isovolumetric relaxation time, deceleration time of the early transmural flow, and ratio of the peak velocity of the early E-wave to A-wave. Diastole is divided into relaxation, represented by isovolumetric relaxation time, and diastolic filling, represented by deceleration time of the early trans-mitralflow and ratio of the peak velocity of the E-wave to A-wave.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high sensitive C-reactive protein (Hs-CRP)

Peripheral blood samples were withdrawn, centrifugated as soon as possible for 20 min at 2000×g divided into two aliquots and stored them at −20 °C. They were examined for high sensitivity C-reactive protein (Hs-CRP) by enzyme immunoassay provided by Sigma-Aldrich Catalog Number SE120041. NT-proBNP levels were measured using enzyme immunoassay (Biomedica Gruppe CAT. NO. SK-1204). CV (%) of Hs CRP intra- & inter-assay precision were 5.28% and 8.34%, while in NT-proBNP intra- & inter-assay precision were 4% and 3%.

Statistical analysis

The data was entered on Statistical Package for Social Sciences (SPSS) version 21. Proportions were calculated for all the variables of interest and chi-square test were used, t-test, ANOVA one way, Pearson correlation, ROC curve and Logistic regression. P value of <0.05 was considered statistically significant throughout the study.

Results

The patients in COPD group were aged 57.733 ± 5.93 years and the subjects in control group were aged 57.42 ± 6.44 years with no significant difference, they were 42 (70%) males and 12 (60%) males in COPD and control group respectively (Table 1).
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