TITLE: SUB-CLINICAL LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN EARLY STAGE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Running Title. COPD: a cardio-pulmonary illness even at early stage.

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ABSTRACT

Background: sub-clinical cardiac dysfunction may be significantly associated with COPD of different degree of severity. In a cross-sectional design we aimed at evaluating the frequency of left ventricular diastolic dysfunction (LVdd) and its correlation with lung function, pulmonary arterial pressure and systemic inflammation in a selected population of COPD at an early stage of their disease.

Methods: fifty-five patients (FEV1 69±12 %pred, age 59±11 yrs) with no clinical signs of cardiovascular dysfunction were recruited and compared to 40 matched healthy controls. All the subjects underwent pulmonary function testing, doppler echocardiography, and IL-6 blood sampling. Presence of LVdd was defined and according to the significant change in both E/A ratio (the ratio between early and late diastolic transmitral flow velocity), IVRT (isovolumetric relaxation time), and DT (deceleration time).

Results: the frequency of LVdd was higher in COPD group compared to controls. In these patients decreased E/A ratio, and prolonged IVRT and DT clearly pointed to left ventricular filling impairment, a condition we found to be especially severe in those patients suffering from lung hyperinflation (IC/TLC ratio<25). Circulating levels of IL-6 as well were higher among COPD patients compared to controls.

Conclusions: doppler echocardiography may help the early identification of LVdd in COPD patients with no signs of cardiovascular dysfunction, which in turn may suggests a shared physiopathological pathway for the two conditions.

Keywords: Chronic obstructive pulmonary disease, left ventricular diastolic dysfunction, Interleukin 6, systemic inflammation, Doppler echocardiography.
ABBREVIATION LIST

A max: late diastolic velocity
AP: systemic arterial blood pressure
BMI: body mass index
COPD: Chronic obstructive pulmonary disease
DLCO: diffusion lung capacity of carbon monoxide
E max: early diastolic velocity
EDT: early deceleration time
FEV1: forced expiratory volume at first second
FRC: functional residual capacity
FVC: forced vital capacity
IC: inspiratory capacity
IL-6: interleukine 6
IVRT: isovolumetric relaxation time
LVdd: left ventricular diastolic dysfunction
PaO2: partial pressure of arterial oxygen
PAPs: systolic pulmonary arterial pressure
RV: residual volume
TLC: total lung capacity
VC: vital capacity
Authors’ contributions

MARIO MALERBA: concept and design, final approval

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BODY OF PAPER

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a condition characterized by airflow obstruction that is only partially reversible in nature [1]. It is one of the leading causes of lung disease-related morbidity and mortality worldwide [2]. Recent literature focusing on the systemic implications of COPD has highlighted the role that cardiovascular disease plays in determining the typical clinical picture observed in COPD-patients [3,4]. It thus seems quite plausible to assume that COPD is somehow linked with heart failure, also taking the common risk-factors into account, most notably in case of exposure to smoke inhalation. Moreover, cardiovascular complications in COPD patients have been linked to a 2-to-3 fold increase of events regardless the presence of confounders such as exposure to smoke [5]. Not surprisingly, these observations have led to further investigate the factors linking COPD to the cardiovascular disease, nonetheless leaving a number of questions unanswered. In addition, we ought to note that a considerable portion of COPD patients also suffer from cardiac abnormalities which often remain undiagnosed, particularly during the early stages of the disease. Left ventricular diastolic dysfunction (LVdd) has been linked to a substantial increase of cardiovascular risk even in the presence of a normal ejection fraction [6], and seems to be involved in the etiology of a pre-clinical myocardiopathy together with a variety of diseases such as arterial hypertension [7] and diabetes [8]. More recently, left ventricular filling impairment has been reported in different cohorts of COPD patients [9-12], being the increased circulating level of interleukine-6 associated to the disease, as for a pathological biomarker of both airway and systemic inflammation [13].

The assumption leading to the present research is that LVdd may be the subclinical link between respiratory and cardiovascular morbidity in COPD patients.

Therefore, in a cross-sectional study, we assessed the frequency of LVdd in a sample of mild-to-moderate COPD showing no signs of cardiovascular involvement and compared with normal health
individuals. In the group of patients, we then correlated parameters of LVdd with lung function, derived pulmonary arterial systolic pressure (PAPs), and systemic inflammation (as assessed by IL-6 blood levels) in order to assess the existence and extent of a pathophysiological pathway linking COPD to cardiovascular disease.

METHODS

Subjects

One hundred consecutive patients with confirmed mild-to-moderate COPD [1] and forty age-and sex-matched controls qualifying as current or ex-smokers were recruited from primary and secondary care units.

Criteria of exclusion were as follows: arterial hypertension (ruled out by 24-hour blood pressure monitoring), diabetes mellitus, heart disease including arrhythmia (ruled out by 24-hour EKG Holter monitoring), and/or a history of coronary artery disease. This was ruled out by treadmill exercise tests, or additional Tc-MIBI myocardial scintigraphy in the 6 months preceding this study. Twenty out of the non-eligible patients had arterial hypertension, 10 had coronary artery disease, 5 had atrial or ventricular arrhythmias. In addition patients (n=4) taking oral corticosteroids and those whose ultrasound results proved inconclusive (n=6) were excluded as well. As a result, 55 mild-to-moderate COPD patients were deemed eligible and participated. All of them were under usual treatment with inhaled bronchodilators and/or corticosteroids, which was discontinued 24-hour before assessment.

A control group of 40 healthy individuals matched for age, sex, and smoking habits was also included in the study.

The protocol was approved by the local ethical committee following the Helsinki recommendations; informed consent was obtained from all the subjects.
Measurements

The following measurement were taken in all the studied individuals in the study day.

1. Lung Function

A spirometry and the maximal full-flow volume curve were obtained by means of a pneumotachograph equipped with a volume integrator (CAD/Net system 1070, Medical Graphics Corporation - St. Paul, MN, USA). Static lung volume was measured by the multi-breath nitrogen-washout method. The pulmonary function tests and the lung diffusion capacity for carbon monoxide (DLCO) test were performed following the standards of the American Thoracic Society [14]. Variables were expressed as percentage of the predicted normal values.

2. Echocardiography

Echocardiography was performed by means of an Acuson Siemens Sequoia ultrasound machine equipped with a 2.5-MHz probe. Standard parasternal, apical, and subcostal views were obtained by using a standard two-dimensional echocardiographic approach in order to measure the left and right systolic and diastolic ventricular dimensions and to calculate the left ventricular fractional shortening. Measurements were conducted according to the rules set by the American Society of Echocardiography. [15] Diastolic function of the left ventricle was assessed based on the following parameters: isovolumetric relaxation time (IVRT), deceleration time of the early transmitral flow (EDT), peak velocity of the E and A waves, and E-to-A wave ratio [16]. The Doppler pattern of impaired relaxation is typically characterized by an E-to-A wave ratio reversal (peak A-wave velocity > peak E-wave velocity, or E/A < 1) and an E-wave deceleration time in excess of 220 ms. The left ventricular ejection fraction was calculated either by the area / length method, or semi-quantitatively by visual inspection. Pulmonary artery systolic pressure (PAPs) was estimated by M-Mode and cross-sectional Doppler echocardiography using a phased-array 2.5-MHz transducer. Tricuspid regurgitant flow was identified at the apex by colour Doppler in continuous-wave mode.
The peak pressure difference between the right ventricle and the right atrium in systole was calculated from the peak velocity of the tricuspid regurgitant signal using a simplified Bernoulli equation. The final PAPs estimate was then obtained by further adding the jugular venous pressure (10mmHg). If no tricuspid regurgitation could be detected, we proceeded to rule out other abnormalities normally pointing to pulmonary hypertension, such as right atrial enlargement, right ventricular enlargement, pericardial effusion, and clinical signs suggestive of right ventricular failure [17].

3. Blood sample

Commercially available enzyme-linked immunosorbent assay was used to measure venous serum concentrations of interleukin-6 (IL-6). The intra-assay variation coefficient was 3.1.

Statistical analysis

Descriptive statistics were applied to the participants’ demographics. Continuous data were summarized arithmetically and by standard deviations (SD). Unpaired tests were used when appropriate, while Chi-square analysis was applied to test the non-parametric variables. Spearman’s Rho test to assess rank correlation among variables in the group of COPD patients was used. A two-tailed p<0.05 was considered significant in each performed analysis.

All data were analyzed using statistical software (version 13 of the SPSS software provided by SPSS Co., Chicago, IL, USA).
RESULTS

The participants’ demographics are shown in Table 1. Patients and controls did not differ by body mass index (BMI), and all of them showed normal levels of both heart rate, systemic arterial blood pressure, and arterial oxygen partial pressure (PaO2).

Lung function- The pulmonary function data in both groups are summarized in Table 2. Among the COPD category, 27 patients (49%) showed hyperinflation (IC/TLC ratio ≤ 25). Although notably different between groups, DLCO values fell within the expected range in all cases (84.2 ± 8.1 vs. 92.2 ± 4.5 % predicted in COPD and controls, respectively).

Echocardiography- Table 3 resumes echocardiography-related results. Compared to controls, COPD patients had a significantly different E/A ratio (0.85 ± 0.38 vs. 1.13 ± 0.32 respectively; p=0.016), EDT (232.3 ± 31.8 ms vs. 208.7 ± 33.5 ms; p=0.029), and IRVT (85.3 ± 13.3 ms vs. 73.4 ± 18.0 ms; p=0.032). The frequency of LVdd was 39/55 (70.9%) in COPD compared to 11/40 (27.5%) in controls. The whole left ventricular systolic function, left and right ventricular diameters, and PAPs levels were normal and similar in both groups.

COPD patients with lung hyperinflation (IC/TLC <0.25) showed a notably lower E/A ratio compared to those who did not (IC/TLC ratio >0.25) (0.73 ± 0.3 vs. 0.96 ± 0.4 respectively; p=0.024).

Blood sample- Compared to controls, IL-6 levels were higher in COPD patients (2.58 ±1.11 pg/ml vs. 1.88± 0.88 pg/ml respectively; p=0.024)

Correlation analysis

Correlation analysis has been carried out in the group of COPD only, showing that FEV1% directly correlated with E/A ratio (Rho=490; p=0.001) (see Figure 1). There was no other significant
correlation in this analysis; in particular, circulating levels of IL-6, and PAPs showed no correlation with any of the parameters associated with LVdd definition.

DISCUSSION

The most important finding of this study is the substantial frequency of LVdd in COPD patients at an early stage of their disease, which is even higher when compared with matched healthy controls. Patients showed a significant correlation between E/A ratio and FEV1% levels. E/A ratio impairment, together with the IVRT and EDT prolongation, was likely to indicate the left ventricular filling impairment, especially in those patients with associated lung hyperinflation. Finally, the increased circulating IL-6 levels in these stable COPD confirms the role of systemic inflammation in the complex pathophysiology of the disease.

Several reports and studies have highlighted the presence of LV diastolic filling impairment in COPD patients. Sabit et al. [11] reported sub-clinical left ventricular and right ventricular systolic and diastolic dysfunction in COPD patients free from overt cardiovascular comorbidities compared to age-matched controls. Notwithstanding, authors from that study [11] could have not systematically excluded other sources of LVdd such as systemic arterial hypertension, nor did they match their patients with controls for smoking history. Funk [10] et al. observed LVdd in COPD patients compared to age-and-sex-matched controls despite a normal left ventricular systolic function and even in patients with normal PAP. Quite interestingly, the COPD group showed a decrease in mean PaO2 values compared to controls, a finding typically associated with abnormal ventricular filling, while no information is available as to the participants’ smoking history. More recently, Watz et al. [12] observed reduced cardiac chamber size and LVdd in a cohort of 170 COPD patients with lung hyperinflation and different degrees of severity; in their population LVdd occurred more often in stages III and IV of the disease, at a point in which impairment in both PAP and DLCO are known to occur most frequently.
The eligibility criteria in our study were defined with the utmost accuracy by excluding any possible form of coexisting cardiovascular comorbidity including systemic arterial hypertension, which not surprisingly caused our population to reduce to a relatively small size. In addition, our controls were all matched for smoking history, whereas COPD group only consisted of individuals suffering from mild-to-moderate forms of the disease (FEV1>50%pred), which enabled us to selectively detect LVdd even at its earliest stages.

According to recent literature, prevalence of LVdd in our control group was similar to that reported in populations of randomly selected healthy individuals [18]. Although the pathogenesis still remains to be fully understood, alveolar hypoxia and increased PAPs (neither of which observed in our subjects) are conditions likely to induce LVdd.

Moreover, LVdd has been observed to be often associated with lung hyperinflation [12]; in our population, however, LVdd was also detected in the absence of a reduced IC/TLC ratio, which contradicts the assumption of an exclusive association between emphysema and a decrease in the E/A ratio. Although likely irrelevant to our study, another factor possibly leading to LVdd may be ventricular interdependence as reported in severe COPD cases showing an elevated PAPs [19]. A recent paper [9] suggested the likely etiological role of the sub-clinical loss of lung parenchyma and pulmonary capillary bed typically observed at the earlier stages of emphysema; these factors may indeed cause significant capillary flow decreases while only inducing small increases in PAPs and may be directly related to smoke exposure, which has been proven to induce apoptosis of the pulmonary endothelium [20]. Notwithstanding, this hypothesis does not explain the low LVdd frequency we observed in our smoking controls, which, in light also of the observed relation between FEV1 and E/A ratio, leads us to believe that the presence of airway obstruction may itself play a role in the pathogenesis of LVdd. As a matter of fact, airway obstruction typically leads to abnormal pressure in the thoracic cavity which in turn may affect ventricular filling, the pulmonary vascular bed and venous return [21]. Although the complex interactions among these components are yet to be fully understood, it is well known that an increase in airway obstruction leads to an
increase in respiratory pressure during exercise [22], while it is not known whether similar mechanisms also affect resting haemodynamics or the lung-heart interactions taking place during acute exacerbations of the disease.

It is now well accepted that COPD is an inflammatory disorder characterized by both airway and systemic inflammation [23], and recent evidence further supports the role of IL-6 as a potential biomarker in COPD either associated with dyspnea [24], PAPs elevation [25] and recurrent exacerbations [26]. Our finding confirms the occurrence of increased circulating IL-6 levels in COPD patients compared to controls, regardless of their smoking status. Interestingly, in a murine model, IL-6 overexpression resulted in emphysema-like airspace enlargement and airway inflammation, which suggests the presence of a relationship between inflammation, hyperinflation and LVdd [27]; our data, however, do not support the existence of any correlation between IL-6 levels and parameters suggesting the presence of LVdd in the COPD population studied.

Study limitations include exposure of our cross sectional study to reverse causality and selection bias, and the fact that direct measures of PAPs and heart volumes were not available as imaging estimates of lung emphysema; although well aware of the challenges connected with assessing the left ventricular function of COPD patients by traditional Doppler evaluation (lung hyperinflation), we nonetheless decided not to resort to more modern, yet much less widely available Tissue Doppler Imaging (TDI) technique.

Similarly to other recent reports, we observed that COPD patients frequently show sub-clinical left ventricular filling impairment at the earlier stage of the disease even in the absence of any other cardiovascular dysfunction. The pathogenesis of COPD-related LVdd seems to be both complex and related to multiple alterations in cardio-pulmonary homeostasis. LVdd may be the pre-clinical link between respiratory and cardiovascular morbidity in COPD patients and may well explain the increased cardiovascular risk of these patients.

From a theoretical point of view, COPD may thus be considered as part of a group of other diseases, such as diabetes or hypertension, which have been linked to distinctive forms of cardiomyopathy.
The key and clinical practical message of the present study is that even at the early-stage COPD patients should routinely undergo echo-doppler evaluation to seek for the presence of LVdd and to address adequate therapies.

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Figure 1: Direct correlation between FEV$_1$ %pred. and E/A ratio in COPD patients

FEV$_1$: forced expiratory volume at first second. E/A: E max (early diastolic velocity) / A max (late diastolic velocity)
COPD: Chronic obstructive pulmonary disease
Additional files provided with this submission:

Additional file 1: TABLES.doc, 67K
http://www.biomedcentral.com/imedia/4552332765009047/supp1.doc