Evaluation of antiendothelial cell antibodies in COPD patients, with and without corpulmonale

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KEYWORDS
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Abstract  Background: Antiendothelial cell antibodies (AECA) were studied in the pathogenesis of emphysema in chronic obstructive pulmonary disease (COPD) and pulmonary hypertension (PH) in vasculitis, connective tissue disease and idiopathic pulmonary arterial hypertension.

Aim of the study: This study aimed to compare the level of AECA between COPD patients with corpulmonale and those without corpulmonale.

Methods: The study involved 30 male COPD patients without corpulmonale (group 1), 30 male COPD patients with corpulmonale (group 2) and 30 male healthy controls, (group 3). All subjects underwent spirometric pulmonary functions' testing, echocardiography and measurement of AECA in serum.

Results: There was highly significantly elevated AECA level in COPD patients with corpulmonale compared to other groups. This was associated with highly significant correlation of AECA level and right ventricular systolic pressure (RVSP), FEV1 % of predicted and significant correlation with arterial oxygen tension (PaO2) and oxygen saturation (Sao2) in the same group.

Conclusion: The significantly higher level of AECA in COPD patients with corpulmonale together with RVSP suggests a role for these autoantibodies in the pathogenesis of PH and corpulmonale complicating COPD.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a global disease caused by chronic exposure to tobacco smoke and other airway irritants, like biofuel smoke [1].

The functional hallmark of COPD is airflow obstruction that is not fully reversible and is usually progressive. The disease usually presents with respiratory symptoms
especially dyspnea and the diagnosis is confirmed by spirometry [2].

The prevalence of pulmonary hypertension (PH) in stable COPD varies from 20–91% depending on the definition of pH (mPAP > 20 versus > 25 mmHg), severity of COPD and the method of measuring the pulmonary artery pressure (echocardiography versus right heart catheterization) [3,4].

Corpulmonale refers to the altered structure (hypertrophy or dilatation) and/or impaired function of the right ventricle that results from pulmonary hypertension that is associated with diseases of the lung, vasculature, upper air way, or chest wall.

Right-sided heart disease due to left-sided heart disease or congenital heart disease is not considered corpulmonale [5–7].

Pulmonary hypertension is the common link between lung dysfunction and the heart in corpulmonale; echocardiography can be a useful tool to estimate pulmonary artery systolic pressure [8]. In addition it can be used to identify other causes of PH such as congenital, valvular and myocardial disease. Specifically, the WHO has defined pH as a systolic pressure greater than 30 mmHg; this corresponds to a tricuspid regurgitant velocity of 3 m/s on echocardiography [9].

Pulmonary vascular endothelial dysfunction is a major factor in the pathogenesis of pulmonary hypertension, inflammatory and autoimmune processes may play a role in this regard, through induction of endothelial dysfunction [10,11].

Antiendothelial cell antibodies (AECA) are a heterogeneous family of antibodies reacting with endothelial cell antigens. These antibodies are found in various diseases and recognize several antigen determinants. Different pathophysiological effects have been observed in in vitro experiments, which include direct or indirect cytotoxicity and endothelial cell apoptosis. Furthermore, some AECA activate endothelial cells, resulting in increased leucocyte adhesiveness, activation of coagulation and vascular thrombosis. In animal models, it has been shown that AECA could promote vascular damage [12]. Recently, autoimmune mechanisms have been recognized as being partly involved in the pathogenesis of COPD [13,14]. Circulating autoantibodies have been detected in patients with COPD [15,16]. AECA are involved in COPD because of their possible pathogenic function [17]. Neither the endothelial cell antigens nor their precise role, in the pathogenicity of different diseases in which AECA are found, is well characterized. Nowadays, it is not known whether AECA are an epiphenomenon accompanying vascular injury or whether they are pathogenic [18].

Rationale

Antiendothelial cell antibodies were studied in the pathogenesis of pulmonary arterial hypertension in idiopathic pulmonary arterial hypertension (iPAH), several vasculitides and connective tissue diseases, likewise, it may have a pathogenetic role in PH and corpulmonale in some patients with COPD [19–21].

Aim of the study

The present study aimed to estimate the level of AECA in patients with moderate-to-severe or very severe COPD and to compare its level between COPD patients who developed corpulmonale and those who did not.

Subjects and methods

This case-control, cross-sectional study was conducted to assess the level of AECA in 2 patient groups, 30 patients each, COPD without corpulmonale (group I) or with corpulmonale (group II) and a third group including 30 healthy control subjects. All subjects were males, older than 40 years of age. Patients were recruited from the attendants of chest outpatient clinic in Suez Canal University hospitals, Ismailia and in Ain Shams University hospitals, Cairo, Egypt. All COPD patients met the global initiative for chronic obstructive pulmonary disease (GOLD) criteria for diagnosis of COPD with moderate to severe and very severe disease.

All the study population gave informed written consent to participate in the study. The following subjects were excluded: those who experienced chest infection or acute exacerbation of COPD in the preceding one month, subjects who could not undergo echocardiography because of technical difficulty. Patients who were under systemic steroid therapy as well as patients with chest diseases other than COPD or with associated left-sided heart failure, vasculitis and collagen disease.

All subjects were subjected to the following: Frontal chest radiograph, electrocardiogram (ECG), oxygen saturation (Sao2) by pulse oximetry, arterial blood gas analysis (ABG-patients only), spirometric pulmonary function, echocardiography and quantitative estimation of AECA in serum samples.

Echocardiography

Echo machine Vivid-5 GE was used to study all subjects. Subjects underwent a detailed “M-mode, two dimensional, color Doppler, and CW Doppler imaging analysis performed on resting patient” according to the recommendation of the American Society of Echocardiography (2005) [22].

The following echocardiographic variables were measured:

1. Tricuspid annular plane systolic excursion: recorded by M-mode from apical four chamber view by placing the cursor on the RV free wall and tricuspid annular motion during systole was measured (1.5–2 cm).

2. Right ventricular (RV) dimensions were taken at end diastole from RV focused apical 4 chamber view dimensions at basal level, mid level (at the tip of tricuspid valve leaflets) and longitudinal dimensions were measured from RV apex to the base, maximum accepted values for normal RV dimensions for these parameters were 28, 33 and 79 mm respectively.

3. Free RV wall thickness, hypertrophy of right ventricular free wall “more than 5 mm” was measured by 2D in subcostal four-chamber view at the tricuspid chordal level at the peak of the R wave on ECG.

4. Peak tricuspid regurgitant jet velocity was measured by using Bernoulli equation to calculate RV systolic pressure (RVSP) after adding right atrial pressure [15]. The pulmonary artery systolic pressure (PASP) is equal to RVSP, provided there is no pulmonary valve outflow tract obstruction or stenosis.

Antiendothelial cell antibody (AECA) level in serum was measured using the enzyme linked immunosorbent assay (ELISA) technique (AECA, MyBioSource, San Diego, USA). Normal value of AECA in adult male was up to 53.8 ng/ml [23].
Statistical analysis

All values will be analyzed using software statistical Package of Social Science (SPSS 20 for Window-Evaluation version An ANOVA test and Chi-square test were used. Correlations between different parameters were evaluated using spearman rank correlation coefficient; p-values < 0.05 were considered significant. All data are expressed as the mean ± SD.

Results

This study comprised 3 groups of male subjects with matched age group I, COPD patients without corpulmonale; group II: COPD patients with corpulmonale and group III healthy control subjects. All individuals were subjected to pulmonary function testing, arterial oxygen saturation measurement (SapO₂), arterial oxygen tension (PaO₂; patients only), echocardiography, measurement of antiendothelial cell antibody (AECA) in serum (Figs. 1–8, Tables 1–7).

Discussion

Chronic obstructive pulmonary disease (COPD) is defined in terms of airflow obstruction that is not fully reversible and
usually progressive. It results from an inflammatory process affecting the airways and lung parenchyma. Studies conducted at early disease revealed significant vascular abnormalities which result in PH and corpulmonale in more advanced disease [24–26]. Previous studies [17,27,28] suggested that an autoimmune process might have a role in the pathogenesis of emphysema and COPD. In the present study, we compared the level of AECA measured quantitatively, between 2 groups of COPD, patients with and without corpulmonale, and versus a group of healthy control subjects. It was found that there was a highly significant difference in patient groups compared to control subjects and this is consistent with the results of karayama et al. who found significantly higher prevalence

Figure 5 Shows significant negative correlation between AECA level (ng/ml) and PaO2 (mmHg) in COPD patients without corpulmonale.

Figure 6 Highly significant positive correlation between AECA level (ng/ml) and RVSP (mmHg) in COPD patients with corpulmonale.

Figure 7 Highly significant negative correlation between AECA level (ng/ml) and FEV1% of predicted in COPD patients with corpulmonale.

Figure 8 Significant negative correlation between AECA level (ng/ml) and PaO2 (mmHg) in COPD patients with corpulmonale.
and levels of AECA in patients with COPD, than in a reference population [17].

Antiendothelial cell antibodies (AECA) are auto antibodies capable of reacting with different endothelial cell (EC) structures [19]. Recently Arends et al. [29] had reported the presence of IgM and IgG AECA specifically targeting cell surface antigens in the majority of patients with connective tissue disease (CTD) – associated PH and in idiopathic pulmonary arterial hypertension (iPAH). In the current study there were higher levels of AECA in COPD patients with corpulmonale than those without corpulmonale with highly significant difference. This finding is in accordance with Tamby et al. [21,30] who demonstrated the presence of circulating auto antibodies against ECs and fibroblasts in iPAH and CTD – associated PH patients with higher prevalence than in healthy control subjects and in CTD-patient group without PH. Several recent studies highlighted the role of “EC” dysfunction in the pathogenesis of PH in COPD. [31–33] The significantly higher level of AECA in COPD patients with PH and corpulmonale indicate that they might have a role in the pathogenesis of PH in some COPD patients. Their presence could be initiated by smoking induced inflammation and hypoxemia causing “EC” dysfunction with expression of cellular components identified as non-self (i.e. auto antigens). Previous studies [27,28] have shown that tobacco smoking may promote immune dysregulation through modulation of death pathways of immune suppression cells or indirectly by exposing anatomically sequestrated intracellular antigens to the immune system.

In patients with COPD and PH neither the target autoantigen(s) for AECA nor the mechanisms of induction of EC injury have been identified yet. However, in other diseases, especially connective tissue diseases and vasculitides, several autoantigens for AECA [34–36] and mediators [29] had been identified. The pathogenicity of AECA could include cytotoxicity on ECs [37–39] induction of coagulation [40,41] and apoptosis [42,43].

In the present study COPD patients were matched regarding the grade of severity, and 8 patients with moderate to severe COPD, were found to have corpulmonale. This finding is consistent with several studies which revealed that some patients with moderate to severe disease (FEV$_1$ ~ 50%) of predicted can develop PH and corpulmonale [44–46].

<table>
<thead>
<tr>
<th>Groups</th>
<th>RVSP (mmHg)</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD without corpulmonale</td>
<td></td>
<td>18.0</td>
<td>25.00</td>
<td>24.13</td>
</tr>
<tr>
<td>COPD with corpulmonale</td>
<td></td>
<td>32.0</td>
<td>92.00</td>
<td>58.37</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>22.0</td>
<td>34.00</td>
<td>20.17</td>
</tr>
</tbody>
</table>

F – ANOVA test; p-value < 0.01 highly significant.

The mean RVSP was 20.17 ± 2.65 mmHg among control group, 24.13 ± 0.97 mmHg among COPD without corpulmonale group and 58.37 ± 16.78 mmHg among COPD with corpulmonale group.

and levels of AECA in patients with COPD, than in a reference population [17].

<table>
<thead>
<tr>
<th>Groups</th>
<th>AECA level(ng/ml)</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD without corpulmonale</td>
<td></td>
<td>55.40</td>
<td>91.20</td>
<td>64.24</td>
</tr>
<tr>
<td>COPD with corpulmonale</td>
<td></td>
<td>85.90</td>
<td>312.90</td>
<td>163.66</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>18.60</td>
<td>50.10</td>
<td>33.96</td>
</tr>
</tbody>
</table>

F – ANOVA test; p-value < 0.01 highly significant.
We found also that there was significant negative correlation of AECA level with FEV\textsubscript{1}, PaO\textsubscript{2} and SapO\textsubscript{2} in patient groups but not in controls, a finding consistent with other studies [17,47]. The present study disclosed that AECA level was elevated in COPD patients but not in the control subjects, even who smoke with positive correlation with the smoking index. These findings are in agreement with others [27–28] who suggested that some constituents of cigarette smoke are potentially immunogenic capable of inducing auto antigens in the lungs of some smokers.
To our knowledge this is the first study to evaluate the level of AECA quantitatively in COPD patients who develop PH and corpulmonale. Future studies on larger population samples are needed to support our findings and to confirm the role of AECA in the pathogenesis of PH in COPD, if any, so that novel therapeutic interventions manipulating these autoantibodies might help to prevent or to stop progression of pulmonary hypertension complicating COPD.

In summary we found that the AECA level was significantly higher in COPD patients with corpulmonale compared to patients without corpulmonale, with positive correlation with the level of pulmonary artery systolic pressure, suggesting a role for AECA in the pathogenesis of PH and development of corpulmonale in these patients.

Conflict of interest

None declared.

References


