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Research Article

Is Heart-type Fatty Acid Binding Protein a Marker of Cardiac Damage in Patient with Exacerbated Chronic Obstructive Pulmonary Disease?

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Abstract

Background: It is aimed to detect the possible cardiac damage in patients with acute exacerbation of COPD via h-fabp, which is a highly specific and sensitive marker for myocardial ischemia.

Methods: Patients who were referred to the Emergency Department of our hospital due to COPD exacerbation were included in the study (n = 30). Patients with a history of comorbid diseases and patients in need of intensive care unit were excluded from the study. Control group consisted of healthy volunteers who did not have any disease history (n = 20). Blood samples were taken to examine arterial blood gases and h-fabp levels at the time of the attack from all patients. Electrocardiography was performed after the first treatment. Respiratory function tests were performed within the next 24 hours after the admission to the hospital.

Results: A total of 50 patients (20 female, 30 male) were included in the study. The patient group consisted of 30 patients. The mean age of the patients was 58.5 ± 8.5. There was no statistically significant difference in h-fabp levels between the patient and the control group ($p > 0.05$). However, there was a moderately significant correlation between the h-fabp levels and the partial oxygen pressure (PO2) in a negative way in the patient group ($r = 0,471$ $p = 0,03$).

Conclusion: Given the normal levels of h-fabp and significant correlation between h-fabp levels and PO2 in patients with acute exacerbations of COPD; it is suggested that extracardiac causes and non-hypoxic mechanisms must be further elaborated to explain elevated cardiac enzyme levels in patients with acute exacerbation of COPD.

Keywords: *Chronic Obstructive Pulmonary Disease; Fatty Acid-Binding Proteins; Myocardial Ischemia*

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases [1]. Comorbidities are common in all stages of COPD. Cardiovascular diseases, especially ischemic heart disease, are the most important comorbidities associated with COPD [2]. Even the modest decreases in expiratory flow rates cause 2 to 3 times more increase in the risk of ischemic heart disease, stroke, and sudden cardiac death [3,4]. In at least 1/3 of the patients with COPD, the disease progresses with recurrent exacerbations [5]. COPD exacerbations are associated with poor prognosis and increased mortality. It is not known which cardiac diseases contribute to increased mortality during the acute exacerbation of COPD. Severe hypoxemia, pulmo-

nary hypertension, and systemic inflammation may affect cardiac functions, but the interactions of these factors and the cardiovascular effects of COPD are not fully understood [6,7]. Cardiac co-morbidities are common in patients hospitalized for acute exacerbations of COPD [8]. In the studies that were made until today, cardiac troponins (Troponin I (TnI) and Troponin T (TnT)) were examined first to assess cardiac damage associated with acute exacerbation of COPD. As a result, it was determined that early and late mortality was increased in patients with high cardiac troponin T levels during the exacerbations [9-12]. Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-ProBNP) levels were also studied in the COPD acute episodes and increased NT-pro BNP levels were associated with increased mortality in patients with COPD acute episodes [13].

Nowadays, a new marker for myocardial ischemia is defined that is superior to other cardiac enzymes in terms of specificity and sensitivity [14]. Although the heart-type fatty acid binding protein (h-fabp) is a small, cytoplasmic protein and is present in high concentrations in the heart; it is present in very low levels in the peripheral muscle tissue [14,15]. In the case of acute myocardial ischemia, it is rapidly released into the circulation, reaching detectable levels in the plasma within 1.5 hours, peaking at 6 hours and returning to normal values after 24 hours [15].

In the light of these data, it is aimed to detect the possible cardiac damage in patients with acute exacerbation of COPD via h-fabp which is a highly specific and sensitive marker for myocardial ischemia.

Materials and Methods

Patients who were referred to the Emergency Department of our hospital due to COPD were included in the study. Medical histories were taken for all patients and physical examinations were performed. Patients who were diagnosed with COPD acute exacerbation according to the criteria of GOLD (global initiative for chronic obstructive lung disease) and who had an indication for admission to the hospital but did not need follow up and treatment in ICU were included in the study [16]. Patients with a history of comorbid diseases (cardiac, renal, immunologic, malignant and other systemic diseases) and drug use due to any disease in their medical history; with chest x-ray showing pneumonic infiltration, pleural mass, pneumothorax, suspicious mass appearance; and patients in need of intensive care unit were excluded from the study. In addition, all patients underwent Wells scoring to assess pulmonary thromboembolism risk. Patients with score 2 and above were also excluded from the study. Control group consisted of healthy volunteers who did not have any disease history. Blood samples were taken to study arterial blood gases and h-fabp levels at the time of the attack from all patients. Electrocardiography was performed after the first treatment. Respiratory function tests were performed within the next 24 hours after the admission to the hospital.

Respiratory function test: The procedure was performed by the same technician with the Jaeger branded device.

Arterial blood gas: Evaluated with ABL 555 device.

H-fabp: Solid phase enzyme-linked immunosorbent assay (ELISA) method was used.

An informed consent form was obtained from all the patients included in the study and the institutional ethics committee approval was obtained for the study (2008/2).

Statistical analysis

Analysis of the data was done in the SPSS 11.5 package program. Continuously measured variables were expressed as mean ± SD and categorical variables as the number of observations (%). The Shapiro-Wilks test was used to investigate if continuous variables showed parametric distribution, and the Student's t test or the Mann-Whitney test were utilized to assess if there was a significant difference between groups in terms of measured characteristics. The results were considered statistically significant for the value of $p < 0.05$. The significance of the linear correlation between continuous variables was evaluated with the Spearman correlation test.

Results and Discussion

A total of 50 patients, 20 females and 30 male were included in the study. The patient group consisted of 30 patients and the control group had 20 patients. The mean age of the patients was 58.5 ± 8.5. There were 46.5 ± 32.8 pack/year cigarettes usage in the patient group. Eight patients were still active smokers. There was no statistically significant difference between the control group and the patient group in terms of age and gender ($p > 0.05$). However, smoking was significantly higher in the COPD group than in the control group ($p = 0.01$). None of the patients had any additional systemic disease except COPD. Demographic characteristics are shown in table 1.

Age (year)	58.5 ± 8.5
Male gender (%)	60.6
Smoking (p/y)	46.5 ± 32.8
Current smoker (%)	26.6
Duration of treatment (year)	11.2 ± 5.1

Table 1: *Demographic characteristics.*

Data is depicted as mean ± SD or number (percentage).

Patients were receiving treatment for COPD for 11.2 ± 5.1 years. When medications of the patients were questioned, it was determined that B2 agonist use was 100%, methylxanthine use was 80%, anticholinergic use was 70%, inhaler steroid use was 70% and systemic steroid use was 40%. 50% of patients had nebulizers and 40% had home oxygen concentrators at home. 20% of the patients had both oxygen concentrators and nebulizers. The duration of hospitalization was found as 4.6 ± 2.1 days. Respiratory function test and arterial blood gas values of the patient group are shown in table 2. Respiratory function test results of all cases included in the control group were within normal limits. In terms of respiratory function test, the difference between the control group and the patient group was statistically significant ($p > 0.001$). When electrocardiographic findings were evaluated, no significant ECG changes suggesting acute myocardial injury were detected in any of the patients.

FEV_1 (%)	33.6 ± 7.6
FEV_1/FVC (%)	54.8 ± 6.7
pH	7.39 ± 0.04
PO_2 (mmHg)	52.2 ± 6.5
PCO_2 (mmHg)	49.9 ± 11.2
SaO_2 (%)	82.2 ± 8.3

Table 2: *Respiratory function test and arterial blood gas values of the patient group.*

FEV1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; SaO_2: Oxygen Saturation.

Data is depicted as mean ± SD.

There was no statistically significant difference in h-fabp levels between the patient and control group ($p > 0.05$). However, there was a moderately significant correlation between the h-fabp levels and the partial oxygen pressure (PO_2) in a negative way in the patient group ($r = 0,471$ $p = 0,03$) (Figure 1). There was no significant relationship between forced expiratory volume in one second (FEV_1) and h-fabp levels ($p > 0.05$).

In this study, there was no significant increase in h-fabp levels in patients with acute exacerbations of COPD when compared to the control group, but there was a negative and significant correlation between h-fabp levels and arterial PO_2 levels. This study is the only

prospective study showing these two important findings in the literature. In the other two studies in which h-fabp levels were studied during COPD exacerbation, patients with COPD were grouped within themselves and the effect on adverse outcomes was assessed.

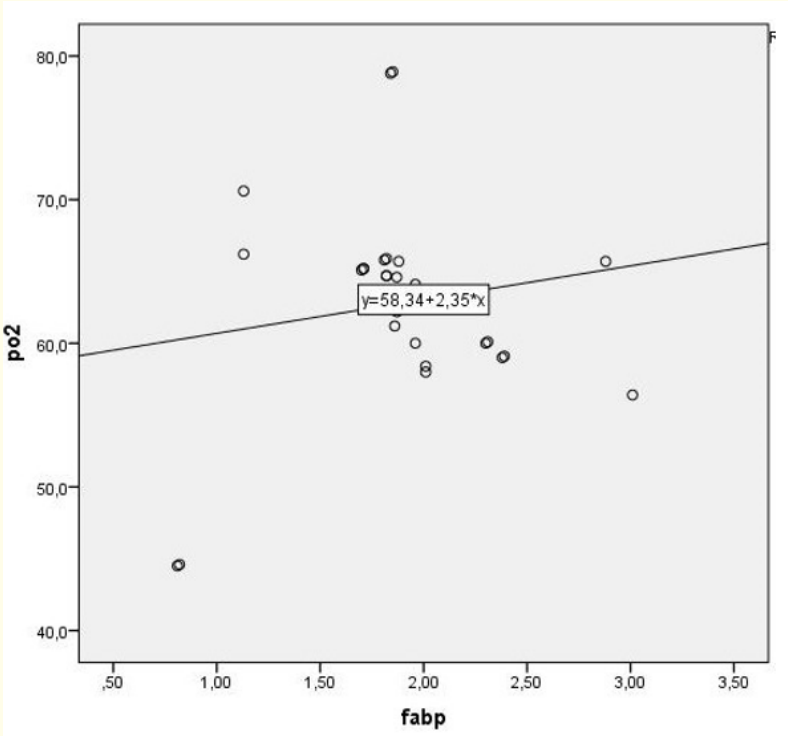

Figure 1: *The xy scatter graph and Spearman correlation analysis shows a moderate negative correlation between pO2 levels and FABP levels (n = 50, r = 0.471, p = 0.03).*

In the study conducted by Miyoung Kim., *et al.* ninety-seven patients with COPD exacerbation were included in the study and allocated into an adverse outcome (n = 10) or a control (n = 87) group. The aim of this study was to investigate whether serum levels of GDF-15 and h-fabp predict an adverse outcome for COPD exacerbation. An adverse outcome was defined as a composite endpoint of 30-day mortality or the need for endotracheal intubation or inotropic support. Serum GDF-15 elevation was more common in the adverse outcome group (80% vs. 43%, p = 0.041). However, serum h-fabp level and frequency of serum h-fabp elevation did not differ between the two groups [17]. Circulating levels of GDF-15 are elevated in acute coronary syndrome, chronic heart failure, acute pulmonary embolism, and idiopathic pulmonary arterial hypertension [18-20].

Another case-control study was conducted to assess whether h-fabp can predict clinical outcomes among patients with COPD exacerbations. This was a retrospective study. 66 patients with COPD exacerbation whose serum h-fabp levels at admission were available were included in this study. The patients were divided into two groups based on the outcomes as the unimproved group and the improved group. The two groups included 12 and 54 subjects, respectively. Cardiac co-morbidities and pneumonia were not exclusion criteria for this study. In this study, it was demonstrated that the level of serum h-fabp was significantly higher in the unimproved group when compared to the improved group [21].

COPD is a multisystemic disease that is not confined to the lungs only, and systemic inflammation is thought to play a major role in the development of systemic effects [22,23]. Among the systemic effects of COPD cardiovascular diseases are shown to be the major cause leading to mortality [24].

In the present study, it was aimed to determine the cardiac damage that may accompany acute exacerbations of COPD using h-fabp. However, unlike other cardiac markers, on the contrary to our expectation no statistically significant difference was observed between the h-fabp level of acute exacerbated COPD patients and the control group of healthy volunteers. In the cases of acute exacerbations of COPD, the cause of the elevated cardiac enzymes without accompanying symptoms and findings of myocardial infarction was not fully understood. In patients with severe COPD attacks, hypoxia and pulmonary vasoconstriction may cause pulmonary hypertension and right ventricular dysfunction. Tachycardia, ventilation-perfusion imbalance, respiratory muscle fatigue and dynamic hyperinflammation and increased left ventricular rhythm may cause increased cardiac stress [13,25]. Although patients do not have obvious coronary artery disease, systemic inflammation-related endothelial dysfunction, and pro-coagulant process-related cardiac damage could develop [26]. Coronary ischemia may become more prominent during acute attack [27]. The presence of underlying silent coronary artery disease may cause cardiac enzymes to elevate with attacks in this group [28]. Although there are many hypotheses put forward, there is no clear explanation yet to explain the elevation of cardiac enzymes. However, the question of whether this increase is related to which cardiac condition or noncardiac cause is still present. There are many factors that affect the release and control of cardiac enzymes during an acute attack of COPD. Age, creatinine clearance, arterial hypertension, tachycardia, non-invasive mechanical ventilation, long-term oxygen therapy history, mechanical ventilation and low hemoglobin level are among the main factors [29].

Similar to the study conducted by Miyun Kim., *et al*. h-fabp, whose specificity and sensitivity for myocardial ischemia is higher than cardiac troponins, was found to be at normal levels in acute exacerbation patients with COPD. This data allows for a different interpretation of the relationship between COPD acute exacerbation and elevated cardiac enzymes. It was thought that the elevation of the cardiac enzyme detected in the previous studies was due to the presumed cardiac damage developed by the attack, but the subjective data for this association could not be reached. H-fabp can be detected at high concentrations in plasma, except acute myocardial ischemia, in the condition of myocardial hypertrophy and reperfusion injury after thrombolytic treatment [15,30]. In addition, it has prognostic value in pulmonary thromboembolism [31]. Extracardiac causes of the troponin elevation such as muscle disease, HIV positivity, and pneumonia are not currently defined in terms of h-fabp. In addition, we found a significant relationship between h-fabp levels and partial oxygen pressures in patients with acute exacerbations of COPD. In the study which NT-pro-BNP elevation was detected; there was no relationship between NT-pro-BNP levels and hypoxemia and disease severity [13]. Similar results were available for cardiac troponins. In a study with the aim of evaluating whether the hypoxic process occurring during the night caused cardiac damage in patients with obstructive sleep apnea syndrome, h-fabp was used; and there was a statistically significant difference between post-sleep measures and pre-sleep measures [32]. This result shows that h-fabp is a highly sensitive marker to hypoxia. This data does not support the hypothesis suggesting that the enzymes increase due to the increased hypoxia and concomitant cardiac damage caused by the COPD attack. In this circumstance, should the factors which cause cardiac stress with extracardiac and non-hypoxic mechanisms be questioned more carefully?

Given all this information and the normal levels of h-fabp detected in patients with acute exacerbations of COPD; it is suggested that extracardiac causes and non-hypoxic mechanisms must be further elaborated to explain elevated cardiac enzyme levels in patients with acute exacerbation of COPD.

However, some limitations of our study should also be mentioned. The fact that our patient numbers are low and cardiac troponin levels have not been studied, are the most important limitations of our study. In addition, only the low-risk group of patients who were not excluded by pulmonary thromboembolic imaging but who were clinically scored were included in the study.

Conclusion

H-fabp does not appear to be a suitable marker for the detection of possible cardiac damage that may accompany acute exacerbation of COPD. Normal levels of h-fabp during COPD exacerbations can present a new insight into the interpretation of the elevated cardiac enzymes in the acute exacerbations of COPD without accompanying symptoms and findings of myocardial infarction. It must be considered that this relation may exist for unexplained extracardiac causes. The mechanisms that may cause non-hypoxic cardiac stress should be assessed. Future prospective studies are still needed to explain the underlying potential mechanisms.

Conflicts of Interest

All authors have no conflicts of interest.

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