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Full Length Research Paper

Elevated Cardiac Troponin T in Patients with COPD

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Cardiovascular disease is common in patients with COPD. It has been found that a considerable number of patients who are hospitalized for AECOPD have elevated cardiac troponin, suggests there is subclinical myocardial damage in AECOPD, but little is known in stable COPD patients. Hence, the aims of the study were to compare troponin T among patients with stable COPD and AECOPD with healthy controls and assess the association between pulmonary function and plasma troponin T level. Samples were obtained from 68 stable COPD and 72 AECOPD patients and 48 healthy controls. Plasma concentrations of troponin T were measured by ELISA. Pulmonary function testing was performed in all patients and healthy controls. We found that troponin T levels were significantly higher in both stable COPD and AECOPD patients as compared with healthy controls [19.7±1.3 and 27.6±3.4, 4.3±0.5μg/L, P<0.01]. The troponin T levels were also elevated associated with the severity of disease. Our data indicate that low-grade myocardial damage seems to be present not only in AECOPD but also in stable COPD patients. We need to understand the pathogenic mechanisms in COPD and its comorbidities in order to be able to develop new strategies for the prevention and treatment of this condition.

Key words: COPD, ELISA, pulmonary function, troponin T, plasma.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major public health problem and a major cause of death worldwide (Halpern et al., 2003; Chapman et al., 2006). The natural course of COPD is characterized by a progressive decline in pulmonary function and recurrent exacerbations requiring hospitalization. Acute exacerbation of COPD (AECOPD) is associated with both excessive short (in-hospital) and long-term (following discharge) mortality rates (Miravitlles et al., 2000; Almagro et al., 2002; Groenewegen et al., 2003).

Cardiovascular disease is common in patients with COPD and is associated with poorer prognosis in COPD exacerbations (Holguin et al., 2005; Sin et al., 2006). There is increasing awareness that ischemic heart disease (IHD) and cardiac co-morbidities are major contributors to mortality in patients with mild to moderate COPD, many of whom are current or former smokers with increased risk for atherosclerosis and IHD (Hansell et al., 2003; Sin et al., 2006; Sin et al., 2008). The degree to which cardiac disease contributes to mortality during exacerbations of COPD is unknown, but accumulating evidence suggests that this may be substantial. Severe hypoxaemia, pulmonary hypertension and systemic inflammation due to exacerbations of COPD may impact on cardiac function, but the interplay of these factors and their cardiovascular effects in COPD is incompletely understood (McGhan et al., 2007; Ruiz-Gonzalez et al., 2008).

It has been found that a considerable number of patients who are hospitalized for AECOPD have elevated cardiac troponin (Baillard et al., 2003; Harvey et al., 2004; Brekke et al., 2008). Troponin is a protein that is bound to the actin filaments of myocytes (Babuin et al., 2005; Omland, 2010). Troponin can be divided into three subclasses: troponin C, I and T. Troponin I and T that are specific for the cardiac myocytes and are often referred to as cardiac troponin, whereas troponin C is found in skeletal muscles. Cardiac troponins are established markers of myocardial damage, and were included in the diagnostic criteria for myocardial infarction (MI) in 2000 (Eur Heart J, 2000). As measured by elevated levels of cardiac-specific troponin T and I, is a cornerstone in the diagnosis of MI (Thygesen et al, 2007). Thus, elevated levels of cardiac troponin T or cardiac troponin I in peripheral blood are regarded as a marker of myocardial

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injury, including MI. However, elevated troponin T (or cardiac troponin I) has been observed in several other settings than acute MI, a range of cardiac and non-cardiac conditions may all lead to elevated troponin. Elevated levels of troponin are associated with increased mortality in pulmonary embolism, renal failure, ischaemic stroke and sepsis (Korff et al., 2006; Omland, 2010). In these settings, it is well documented that elevated circulating levels of troponins are associated with poor prognosis, regardless of underlying disease. Troponin elevations in these conditions probably reflect general myocardial injury rather than coronary arterial occlusion.

It is, however, not known if the troponin level is associated with COPD or any other index of the severity of the disease. Hence, the aims of the present study were therefore to compare the distribution of troponin T among patients with stable COPD and AECOPD patients with healthy controls and assess the association between pulmonary function and plasma troponin T level among patients.

SUBJECTS AND METHODS

Study Subjects

We enrolled 68 patients with stable COPD and 72 patients with AECOPD who met our entry criteria. The diagnosis and severity of COPD was established in accordance to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report (Rabe et al., 2007). AECOPD was defined by the presence of an increase in at least two of three symptoms—dyspnea, cough, and sputum purulence - severe enough to warrant hospital admission without concomitant evidence of pneumonia. Patients with significant comorbidities, including tuberculosis or other lung disease except from COPD, apparent congestive heart failure (CHF), MI, angina pectoris, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) , renal or liver impairment or failure, diabetes mellitus, history of cancer in any site, metabolic syndrome, collagen and vascular disorders were excluded. The healthy controls consisted of 48 healthy volunteers without symptoms or signs of COPD and any of the above exclusion criteria with normal pulmonary function. Information about smoking habits, respiratory symptoms and other diseases, such as cardiovascular diseases, were obtained using a detailed questionnaire. Characteristics of the three groups are shown in table 1. The study was approved by the Ethics Committee of the China-Japan Union Hospital of Ji Lin University and informed consent was obtained from all participating subjects.

Pulmonary Function Testing

Pulmonary function testing were performed in all control subjects and patients with reversibility using standardized methods according to the American Thoracic Society guidelines, assessed by use of a short-acting β2-agonist, equivalent to 200 mg salbutamol by a metered-dose inhaler (Minato Auto Pal Spirometry, Osaka, Japan). Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were measured and expressed as percentages of the predicted normal reference values (Laszlo, 2006). The predicted normal reference values were obtained from our local population.

Blood Sampling and Analysis

Venous blood samples were taken from all subjects in the morning at 7:00 to 8:00 AM after an overnight fast. The blood was centrifuged immediately at 4°C and stored at -70°C. Plasma troponin T was measured by commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems Inc, Minneapolis, MN, USA) according to the prescription by the producer.

BMI Calculated

Body weight and height were measured and body mass index (BMI) was calculated as weight/height2 (kg/m2) in both groups. Body height was measured to the nearest 0.1 cm. Body weight was assessed by using an electronic beam scale with digital readout to the nearest 0.1 kg after emptying the bladder and with the subjects standing barefoot and wearing light indoor clothing. The normal weight patients BMI was between 21.0 kg/m2 and 25.0 kg/m2.

STATISTICAL ANALYSES

Data were analyzed using the SPSS® statistical package, version 11.5 (SPSS Inc, Chicago, IL, USA) for Windows®. Data of the subjects are presented as mean ± SE, comparisons between healthy control subjects and COPD patients were made using Mann–Whitney rank-sum test, as appropriate. A P-value <0.05 was considered to be statistically significant. The relationships between the data were examined by the Spearman rank correlation coefficient. Correlations with both $R \geq 0.4$ and $P < 0.05$ were considered relevant.

RESULTS

Characteristics of subjects

Clinical characteristics of COPD patients and healthy controls are summarized in Table 1. There was no difference in age or BMI or smoking status among the COPD patients and healthy controls.

Table 1. Characteristics of COPD patients and healthy controls.

	Stable COPD (n=68)	AECOPD (n=72)	healthy controls (n=48)
Age (years)	69.8±7.2	67.4±8.3	71.3±6.7
Male/Female	32/36	35/37	22/26
BMI (kg/m^2)	23.3±0.8	22.5±0.4	24.9±0.5
FEV_1 %	73.2±21.9	68.2±18.5	92.7±14.7
FEV_1/FVC %	56.7±11.6	42.9±10.3	85.6±7.2
Smoking status (pack years)	42±4	39±2	41±3

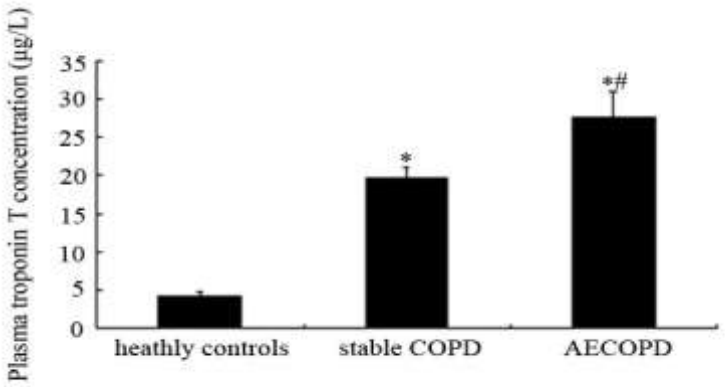

Figure 1: Plasma troponin T concentrations in COPD patients and healthy controls. *Troponin T levels were significantly higher in COPD patients as compared with healthy controls. #AECOPD patients compared with stable COPD.

Plasma Troponin T Level in Copd

Troponin T levels were significantly higher in both stable COPD and AECOPD patients as compared with healthy controls [19.7±1.3 and 27.6±3.4, 4.3±0.5 μg/L, respectively, P<0.01]. The troponin T levels were also elevated associated with the severity of disease, the difference also significant, P<0.05. (Figure 1).

Relationship between plasma troponin t level and pulmonary function in patients with copd

There was no correlation between plasma troponin T level and FEV1, FEV1/FVC in both stable COPD and AECOPD patients.

DISCUSSION

Cardiac troponins are established markers of myocardial damage, and were included in the diagnostic criteria for myocardial infarction (MI) in 2000. However, elevated troponin T (or cardiac troponin I) has been observed in several other settings than acute MI, a range of cardiac and non-cardiac conditions may all lead to elevated troponin. Elevated levels of troponin are associated with

increased mortality in pulmonary embolism, renal failure, ischaemic stroke and sepsis. In order to avoid the influence of these diseases, in our study patients with apparent congestive heart failure (CHF), MI, angina pectoris, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), renal or liver impairment or failure, diabetes mellitus, history of cancer in any site, metabolic syndrome, collagen and vascular disorders were excluded.

The important new information derived from the present study is that both stable and AECOPD patients without a history of coronary heart disease have higher circulating levels of troponin T than a reference population drawn randomly from the general population and the troponin T levels were also elevated associated with the severity of disease.

COPD is predicted to become the sixth leading cause of disability and the third most common cause of death by 2020. Even in mild to moderate COPD patients succumb to cardiovascular disease rather than respiratory failure although the causative mechanism is unknown (Stone et al., 2012). Over the past decade it has become apparent that during an exacerbation of COPD, classically defined by the combination of worsening dyspnoea with increased sputum volume and/or purulence, there is subclinical myocardial damage typified by an increase in troponin level and other biomarkers which predict mortality, but little is known about it in stable COPD patients (Baillard et al., 2003; Chang et al., 2011; Marcun et al., 2012). Various theories have been proposed to explain the rise in troponin during exacerbation of COPD. At least four mechanisms should be considered when explaining troponin elevation in AECOPD: first, increased pressure in the pulmonary circulation leads to increased right ventricle after load, which may promote cardiomyocyte damage or death. AECOPD due to concomitant pulmonary embolism may be included in this category. Secondly, a considerable proportion of patients with COPD may have undiagnosed coronary heart disease and suffer a type 1 MI (Buajordet et al., 2001; Brekke et al., 2008). Thirdly, patients with COPD may have left heart failure accompanied by troponin elevation, and exacerbation of their heart failure may trigger an AECOPD. Fourthly, hypoxia and tachycardia may result in imbalance between oxygen demand and delivery, causing a type 2 MI. A substantial proportion of these myocardial infarctions are likely to have developed secondary to increased myocardial demand/reduced oxygen supply. Under the Universal Definition for Myocardial Infarction, such events, usually resulting in subendocardial rather than transmural infarction, are termed type 2 MI (Thygesen et al., 2007). Another mechanism contributing to troponin elevation in COPD may be increased inflammatory activity. Elevated troponin levels are frequently found in acute disease with a major inflammatory component, such as sepsis (Rosjo et al., 2011). Previous studies suggest that IL-6 might play a salient role in the inflammatory responses in COPD as well as in cardiovascular disease (Biasucci et al., 1996; Sin et al., 2008). In an experiment conducted by Neukamm et al also found that stable COPD patients associated with elevated cardiac troponin T levels, and the troponin T levels increase with the severity of airflow limitation. Higher troponin T levels are associated with higher IL-6 concentrations and pathological Q waves, suggesting that inflammatory activity, as well as unrecognized MI, may contribute to higher troponin T concentrations in stable COPD (Neukamm et al, 2013). This mechanism may explain our results that why troponin T levels were significantly higher in COPD patients as compared with healthy controls and also elevated associated with the severity of disease.

Association studies between plasma troponin T concentrations and lung function is very few. Only Soyseth et al found that higher troponin T levels were associated with decreasing FEV1 (Søyseth et al, 2013). We did not find there was a correlation between plasma troponin T level and FEV1, FEV1/FVC in COPD patients. Probably, the first reason is that in our study the absence of correlation between pulmonary function and plasma level of troponin T can be explained that all patients with COPD were with mild and moderate bronchial obstruction, the second reason may be due to small sample size.

Our study has several limitations. First, we carried out the measurements in plasma, which reflects only systemic changes and may not adequately reflect the local concentrations in the lungs. Further studies involving biological samples such as bronchoalveolar lavage, induced sputum and exhaled breath condensate might shed more light locally. Second, since our study population is limited, and there are only a few related studies in the literature, the precise mechanism and significance of the associations between troponin T and lung disease at the current stage is confusing and frankly paradoxical in places, the value of troponin T in COPD patients should be confirmed by further studies.

In conclusion, plasma troponin T levels were significantly higher in COPD patients as compared with healthy controls. The troponin T levels were also elevated associated with the severity of disease. There was no correlation between plasma troponin T level and lung function. The fact that low-grade myocardial damage seems to be present not only in AECOPD but also in stable COPD patients. We need to understand the pathogenic mechanisms in COPD and its comorbidities in order to be able to develop new strategies for the prevention and treatment of this condition.

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