Evaluation of serum troponin I in patients with acute exacerbations of chronic obstructive pulmonary disease

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Introduction Chronic obstructive pulmonary disease is a common, preventable, and treatable disease. Troponin I is a component of the contractile proteins present in all muscles. The amino acid sequence of cardiac troponin I (cTnI) contains a section that is unique to cardiac muscle.

Aim The aim of the study was to evaluate the incidence of cTnI elevation in patients with acute exacerbation of chronic obstructive pulmonary diseases (AECOPDs) and study the possible association of the level of cTnI with the severity of AECOPD, need for assisted ventilation, and length of hospital stay.

Patients and methods This study was performed on 30 patients with AECOPD admitted to the Chest Department and Respiratory ICU at Benha University Hospital. On admission, all patients were subjected to full medical history taking and full clinical examination. We examined the patients for signs and symptoms of right ventricular (RV) failure. Echocardiography was performed for every patient. Serum troponin I levels (upon admission and 24 h later) were evaluated.

Results The study showed 21 (70%) of 30 patients with positive troponin I versus nine (30%) with negative troponin I. There was a nonsignificant statistical difference among all studied AECOPD patients as regards smoking habits, as 89% of troponin I-negative patients were smokers versus 81% of troponin I-positive patients. When assessed on the basis of pulmonary function tests, 75% of troponin I-negative patients were found to be in moderate stage, 53% of troponin I-positive patients were in severe stage, and 33% of

troponin I-positive patients were in very severe stage. There was a significant statistical difference in troponin elevation as regards pulmonary hypertension (71% of cTnI-positive patients vs. 11% of cTnI-negative patients), RV strain (90% of cTnI-positive patients vs. 33% of cTnI-negative patients), and tricuspid regurge (52% of cTnI-positive patients) but a nonsignificant difference as regards left ventricular dysfunction among all studied AECOPD patients.

Conclusion cTnI in AECOPD patients is mostly positive in tachypneic, tachycardiac, hypoxemic, and hypercapnic patients with more severe pulmonary hypertension and RV dysfunction.

Positive cTnI in AECOPD patients may suggest exacerbation severity, the need for mechanical ventilation (MV), and longer duration of hospitalization. *Egypt J Broncho* 2015 9:14–19
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Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease 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. COPD is the fourth leading cause of death in the world [1].

Exacerbation of COPD is an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum beyond day-to-day variability sufficient to warrant a change in management [2]. Exacerbations affect the quality of life and prognosis of patients with COPD. Hospital mortality of patients admitted for a hypercarbic COPD

exacerbation is ~10%, and the long-term outcome is poor. Mortality reaches 40% at 1 year in those needing mechanical support, and all-cause mortality is even higher (up to 49%) 3 years after hospitalization for a COPD exacerbation [3].

The spectrum of cardiovascular complications associated with COPD is clearly broad. Right ventricular (RV) dysfunction and pulmonary vascular disease are common in COPD and progress with time. Other cardiac diseases found frequently in patients with COPD, including coronary artery disease and arrhythmias, present a unique challenge for clinicians, as the combination of both pulmonary and cardiac disease appears to be additive with regard to morbidity and mortality [4].

The cardiovascular alterations are extremely complex. During an episode of acute exacerbation, the increased

work and oxygen cost of breathing, the increase in left ventricular afterload related to the more negative intrathoracic pressure, the worsening of pulmonary hypertension, and the presence of hypoxemia and hypercapnia may all contribute to the development of cardiac injury [5].

Cardiac biomarkers, such as cardiac troponins, were initially developed for the evaluation of patients with myocardial ischemia and congestive heart failure. The elevated levels of serum cardiac troponins have also been documented in RV dysfunction. In RV failure, cardiac troponins are suspected to be elevated secondary to RV ischemia or microinfarction resulting from increased wall tension, metabolic demand, and reduced coronary perfusion with or without atherosclerosis [6–8]. The release of cardiac troponin from the myocyte to the blood can be due to reversible or irreversible cell damage [9].

Troponin I is a component of the contractile proteins present in all muscles. The amino acid sequence of cardiac troponin I (cTnI) contains a section that is unique to cardiac muscle. The cTnI assay measures these cardiospecific components to provide a highly specific marker for cardiac muscle cell injury. It has no cross-reactivity with the two skeletal muscle isoforms. cTnI is a highly sensitive and long-lasting marker of cardiac injury. Measurements of cTnI concentrations in renal failure, in myopathic states, and after acute skeletal muscle injury have shown normal concentrations in the absence of cardiac injury [10].

Aim

The aim of the study was to evaluate the incidence of cTnI elevation in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and study the possible association of the level of cTnI with severity of AECOPD, need for assisted ventilation, and length of hospital stay.

Patients and methods

This study was performed on 30 patients with AECOPD admitted to the Chest Department and Respiratory ICU at Banha University Hospital.

COPD and AECOPD were diagnosed according to the global initiative for chronic obstructive lung disease 2011 (GOLD, 2011) [1].

Exclusion criteria [11]

Patients were excluded from the study if they had concomitant diseases such as:

(1) Ischemic heart disease, previous myocardial infarction, heart trauma (including contusion,

ablation, pacing, implantable cardioverter defibrillator firings including atrial defibrillators, cardioversion, endomyocardial biopsy, and cardiac surgery.
(2) Aortic valve disease and hypertrophic obstructive cardiomyopathy with significant left ventricular hypertrophy.
(3) Malignant hypertension.
(4) Postoperative noncardiac surgery patients.
(5) Renal impairment (patients with elevated creatinine>2 mg/dl are excluded).
(6) Hypothyroidism and hyperthyroidism.
(7) Infiltrative diseases, including amyloidosis, hemochromatosis, sarcoidosis, and scleroderma.
(8) Acute neurological disease, including cerebrovascular accident and subarachnoid bleeding.

Methods

On admission, the following examinations were carried out on all patients:

(1) Full medical history from the patient (if possible) or his relatives: history of smoking (current, ex, or nonsmoking), history of chest symptoms (cough, expectoration, dyspnea, and wheeze), history of previous intubation and/or ventilator support, prior evidence of cor pulmonale with or without congestive heart failure, comorbidities, and drug therapy.
(2) Full clinical examination (general and local).
(3) Plain chest and heart radiography (posteroanterior, anteroposterior, and/or lateral).

We searched for any of the following to detect RV failure [12]:

(a) Dilatation of the proximal pulmonary arteries with abrupt tapering of the distal branches.
(b) Filling of the retrosternal space secondary to RV enlargement.
(c) Inferior vena cava and azygous vein dilatation.
(d) Increased curvature of the right-heart border secondary to right atrial dilatation seen on anteroposterior or posteroanterior view.

(4) Pulmonary function test:

Measurements of forced expiratory volume in the first second (FEV_1) for assessment of severity of disease were obtained from previous recorded measurements from chest outpatient clinics before admission or from their hospital records; seven patients out of all studied patients had no record for pulmonary functions.

Patients were classified according to their postbronchodilator FEV_1 into mild ($FEV_1 \geq 80\%$

predicted), moderate (50%≤FEV$_1$<80% predicted), severe (30%≤FEV$_1$<50% predicted), and very severe (FEV$_1$<30% predicted) [9].

(5) Echocardiography (ECHO):

ECHO findings associated with RV failure were the following [12]:

(a) RV dilatation and hypokinesis.
(b) RV hypertrophy.
(c) Change to a more concentric RV morphology.
(d) Paradoxical septal motion.
(e) Impaired LV diastolic function.
(f) Right atrial enlargement.
(g) Tricuspid regurgitation.
(h) Pulmonary artery hypertension as estimated by the modified Bernoulli equation.
(i) Pulmonary artery dilatation.
(j) Lack of inspiratory collapse of the inferior vena cava.
(k) Pericardial effusions.

(6) Laboratory investigations:

(a) Complete blood count.
(b) Serum electrolytes (Na, K).
(c) Serum troponin I (upon admission and 24 h later).

Results
The results of this study showed the following:

(1) There was a nonsignificant statistical difference among all studied AECOPD patients as regards age, as the mean age in the troponin I-positive group was 55 versus 52 years in the troponin I-negative group. Also there was no significant statistical difference as regards sex, as the study included two female patients.
(2) It was found that smoking does not affect cTnI, irrespective of the degree of smoking (Table 1).
(3) With respect to the relationship between FEV$_1$ and troponin, 33% of cTnI-positive patients were in very severe stage, 53% were in severe stage, and 14% were in moderate stage, revealing significant statistical difference in cTnI elevation among all studied patients with respect to the severity of disease (Table 2 and Fig. 1).
(4) The current work revealed significant positive correlation as regards pCO$_2$, significant negative correlation as regards pO$_2$, SO$_2$%, and pH, and nonsignificant correlation as regards HCO$_3$ (Table 3).
(5) P-pulmonale, RV strain, pulmonary hypertension, and tricuspid regurge were considerably affected upon cTnI positivity (Table 4).

Table 1 Relationship between smoking habit and troponin level (ng/ml) among all studied acute exacerbation of chronic obstructive pulmonary disease patients at admission

Smoking	Troponin [n (%)] (ng/ml)		Test of significance	P-value
	<0.01 (n = 9)	≥0.01 (n = 21)		
None (n = 2)	1 (11.1)	1 (4.8)	1.614	0.572 (NS)
Ex-smokers (n = 3)	0 (0.0)	3 (14.2)		
Smokers (n = 25)	8 (88.9)	17 (81.0)		
Moderate smokers (n = 9)	4 (50.0)	5 (29.4)	1.307	0.394 (NS)
Heavy smokers (n = 19)	4 (50.0)	12 (70.6)		

Table 2 Severity of disease (FEV$_1$%) and its impact upon troponin level (ng/ml) among acute exacerbation of chronic obstructive pulmonary disease patients at admission

Severity of disease by PFTs	Troponin [n (%)] (ng/ml)		Test of significance	P-value
	<0.01 (n = 8)	≥0.01 (n = 15)		
Moderate (n = 8)	6 (75.0)	2 (13.3)	Fisher exact test = 9.33	0.009 (HS)
Severe (n = 10)	2 (25.0)	8 (53.3)		
Very severe (n = 5)	0 (0.0)	5 (33.4)		

FEV$_1$, forced expiratory volume in the first second; HS, highly significant; PFT, pulmonary function test.

Table 3 Arterial blood gases parameters among all studied acute exacerbation of chronic obstructive pulmonary disease patients and its impact upon troponin level (ng/ml) at admission

Parameters	Troponin (mean ± SD) (ng/ml)		Test of significance	P-value
	<0.01 (n = 9)	≥0.01 (n = 21)		
pH	7.39 ± 0.03	7.29 ± 0.05	5.53	0.001 (HS)
pCO$_2$	49.78 ± 6.83	62.05 ± 6.54	4.65	0.001 (HS)
pO$_2$	80.33 ± 5.63	61.98 ± 6.98	6.96	0.001 (HS)
SO$_2$	89.89 ± 2.15	83.57 ± 4.04	4.40	0.001 (HS)
HCO$_3$	29.22 ± 1.99	28.33 ± 3.86	0.65	0.521 (NS)

Fig. 1
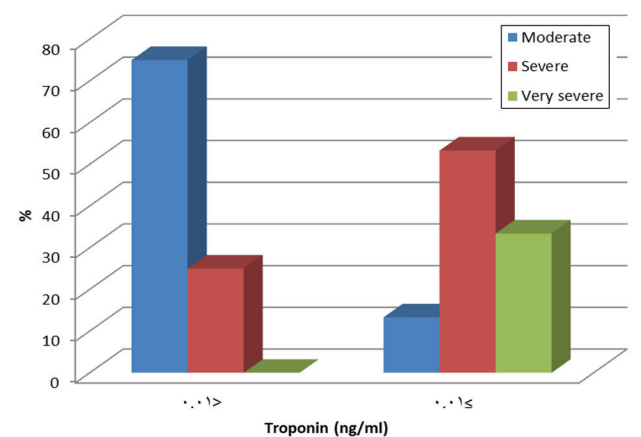
Severity of disease (FEV$_1$%) and its impact upon troponin level (ng/ml) among acute exacerbation of chronic obstructive pulmonary disease patients at admission. FEV$_1$, forced expiratory volume in the first second.

(6) As regards the need for MV, cTnI positivity was more prominent among patients who were ventilated rather than among those who not need MV (Table 5).

(7) As longer the duration of hospitalization the greater the severity of the disease and exacerbation, duration of hospitalization was significantly different among cTnI-positive patients (13.9 ± 4.87) and cTnI-negative patients (7.89 ± 2.67) (Table 6).

Discussion

In the present study, the mean age of patients with positive cTnI was 55.57 ± 7.36 years and the mean age of patients with negative cTnI was 52.56 ± 6.52 years, with no significant difference. This is in agreement with the results of Baillard *et al.* [5] who found no

Table 4 Cardiac changes on echocardiography in acute exacerbation of chronic obstructive pulmonary disease patients and its impact on troponin level (ng/ml) at admission

Parameters	Troponin [n (%)] (ng/ml)		Fisher exact test	P-value
	<0.01 (n = 9)	≥0.01 (n = 21)		
Right ventricular strain				
+ (n = 22)	3 (33.3)	19 (90.5)	18.31	0.003 (HS)
− (n = 8)	6 (66.7)	2 (9.5)		
Left ventricular dysfunction				
+ (n = 1)	0 (0.0)	1 (4.8)	0.443	1.0 (NS)
− (n = 29)	9 (100)	20 (95.2)		
TR				
+ (n = 11)	0 (0.0)	11 (52.4)	5.36	0.02 (S)
− (n = 19)	9 (100)	10 (47.6)		
Pulmonary HTN				
+ (n = 16)	1 (11.1)	15 (71.4)	16.15	0.004 (HS)
− (n = 14)	8 (88.9)	6 (28.6)		

HS, highly significant; HTN, hypertension; S, significant; TR, tricuspid regurge.

Table 5 Need for MV and its relation to troponin level (ng/ml) among acute exacerbation of chronic obstructive pulmonary disease patients at admission

Parameters	Troponin [n (%)] (ng/ml)		Test of significance	P-value
	<0.01 (n = 9)	≥0.01 (n = 21)		
MV				
+ (n = 9)	0 (0.0)	9 (42.9)	9.17	0.029 (S)
− (n = 21)	9 (100.0)	12 (57.1)		

S, significant.

Table 6 Relationship between duration of hospitalization and troponin level (ng/ml) at admission in all studied acute exacerbation of chronic obstructive pulmonary disease patients

Parameters	Troponin (mean ± SD) (ng/ml)		Test of significance	P-value
	<0.01 (n = 9)	≥0.01 (n = 21)		
Duration of hospitalization in days	7.89 ± 2.67	13.9 ± 4.87	3.47	0.002 (HS)

HS, highly significant.

significant difference between positive and negative cTnI patients as regards age in their study.

In contrast, Harvey and Hancox [13] reported a significant difference in the mean age of cTnI-positive patients compared with cTnI-negative patients.

Also in our study there was no significant statistical difference among AECOPD patients as regards sex. This is in agreement with the results of Harvey and Hancox [13] and Deveci *et al.* [14].

Aksay *et al.* [15], however, reported contrasting findings. They found a significant difference in sex among AECOPD patients. This finding could be attributed to the large number of female patients included in their study (59%), with most of them being diagnosed with pulmonary embolism (PE).

As regards smoking habit, there was no significant statistical difference in cTnI elevation among nonsmokers and smokers (Table 1). This may be due to the number of nonsmokers included in the study (two patients). This is in agreement with the studies by Baillard *et al.* [5] and Deveci *et al.* [14], who excluded the effect of smoking on cTnI levels among all studied patients. These results suggest that smoking has no effect on cTnI level in AECOPD patients.

As regards the severity of disease on the basis of FEV_1 (Table 2 and Fig. 1), there was a significant statistical difference in troponin levels among all studied AECOPD patients when evaluated with pulmonary function tests, as 75% of troponin I-negative patients were in moderate stage, 53% of troponin I-positive patients were in severe stage, and 33% of troponin I-positive patients were in very severe stage.

In our study arterial blood gases parameters showed a significant statistical difference in troponin positivity in relation to pH, pCO_2, pO_2, and SO_2, but no significant difference in relation to HCO_3 (Table 3). Baillard *et al.* [5] reported a significant statistical difference in troponin positivity in relation to pCO_2, pO_2, and SO_2, but no significant difference in relation to pH and HCO_3. Harvey and Hancox [13] demonstrated a significant role of O_2 saturation, pCO_2, and pH on cTnI positivity. This could be attributed to the differences in the criteria of selection, the number of patients included, and the severity of AECOPD. Aksay *et al.* [15] agreed as regards oxygen saturation.

ECHO findings showed a significant statistical difference as regards RV strain (90% of cTnI-positive patients vs. 33% of cTnI-negative patients), pulmonary hypertension (71% of cTnI-positive patients vs. 11% of cTnI-negative patients), and tricuspid regurge (52%

of cTnI-positive patients) (Table 4). These findings are in agreement with those of Aksay et al. [15] who revealed a significant effect of RV dysfunction on cTnI elevation, and those of Harvey and Hancox [13], who suggested that the severity of acute exacerbation may lead to cardiac damage and troponin release. Potential mechanisms of cardiac injury include the following: acute elevation of pulmonary arterial pressure secondary to hypoxemic vasoconstriction with subsequent RV distension (similar to the proposed mechanism of cTnI release in pulmonary embolism), tachyarrhythmia such as atrial fibrillation, and cardiac damage mediated by sepsis and/or metabolic stress due to hypoxia and acidosis. Seyhan et al. [16] found a strong correlation between RV dysfunction and cTnI in a group of AECOPD patients.

Baillard et al. [5] did not report a significant effect of either RV dysfunction upon cTnI or cor pulmonale. They stated that the reason for cTnI elevation is difficult to determine, because the cardiovascular alterations are complex. During episodes of exacerbation, the increased work and oxygen cost of breathing, the increase in left ventricular afterload related to the more negative intrathoracic pressure, the worsening of pulmonary hypertension, and the presence of hypoxemia and hypercapnia may all contribute to the development of cardiac injury.

In our study it was found that there was no significant statistical difference between patients with left ventricular dysfunction and patients without left ventricular dysfunction with respect to cTnI positivity. In contrast, Render et al. [17] and Connors et al. [18] reported left ventricular dysfunction in 30% of patients admitted for AECOPD.

In addition, MacIntyre and Huang [19] found that elevation of troponins (especially troponin I) was associated with increased severity of exacerbation. However, troponin T and pro-brain natriuretic peptide are elevated in patients with acute left heart failure and may be used to exclude left ventricular dysfunction as the cause of AECOPD.

As regards the need for MV, cTnI positivity was more prominent among patients who were ventilated versus those who did not need MV (Table 5). This finding is in agreement with those of Aksay et al. [15] who reported that there was a significant statistical difference in cTnI positivity between patients who needed mechanical ventilation and those who did not.

As regards the duration of hospitalization (Table 6), a significant difference was seen in cTnI positivity in relation to duration of hospitalization: cTnI positivity was more prominent in patients with longer duration of hospitalization. This could be attributed to the greater severity of the disease, exacerbation, the need for ICU admission, and the need for MV.

These findings are in agreement with those of Harvey and Hancox [13] who found that patients with greater number of hospital days were more cTnI-positive compared with those with shorter duration. The same findings were made by King et al. [20], who found a significant effect of length of hospitalization on cTnI elevation, and by Martins et al. [21] who found a significant effect of hospital length of stay upon cTnI elevation.

Conclusion

(1) cTnI in AECOPD patients is mostly positive in tachypneic, tachycardiac, hypoxemic, and hypercapnic patients with more severe pulmonary hypertension and RV dysfunction.

(2) Positive cTnI in AECOPD patients may suggest exacerbation severity, the need for MV, and longer duration of hospitalization.

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