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Effects of obesity on respiratory mechanics at rest and during exercise

Amr Shoukri

Obesity is a major health problem worldwide. The prevalence of obesity is increasing and its association with multiple comorbidities is now firmly established. It is considered as an independent risk factor for reduced survival. Obesity directly affects respiratory mechanics at rest and during exercise. Obese individuals usually show changes in certain lung volumes, respiratory compliance and ventilatory behaviour. Dyspnoea is the limiting symptom usually experienced by these individuals.

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Keywords: dyspnoea, obesity, pulmonary functions

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Introduction

Obesity is a chronic disease characterized by the excessive accumulation of body fat that is harmful to the individuals [1]. Usually, body fat above 25% in men and body fat above 30% in women is considered to be obese; therefore, on the basis of this definition, obesity should be determined by measuring body fat. Unfortunately, measures of body composition are not universally and readily available in all clinical settings and therefore most data on the effects of obesity on health rely on the relationship of weight to height, such as the BMI, which is generally useful for describing different magnitudes of obesity. On the basis of BMI, obesity can be classified into mild/class I (30–34.99 kg/m^2), moderate/class II (35–39.99 kg/m^2) and morbid/class III (>40 kg/m^2) [2]. In addition to the degree of obesity, the distribution of excess fat affects the health risks of obesity. A waist-to-hip ratio greater than 1.0 in men and greater than 0.85 in women identify individuals with abdominal fat accumulation and also indicates increased risk for cardiovascular and metabolic disturbances [3].

Obesity and respiratory mechanics at rest

Obesity can profoundly alter pulmonary function and diminish exercise capacity by its adverse effects on respiratory mechanics, resistance within the respiratory system, respiratory muscle function, lung volumes, work and energy cost of breathing. The mass loading effects of excess adipose tissue on the chest wall and abdomen results in reduced compliance of the respiratory system. This is partially caused by a fall in lung compliance, which is decreased by ~25% in simple obesity and 40% in severe obesity [4,5]. Increased pulmonary blood volume [6], as well as increased closure of dependent airways [7], probably contributes to this decreased lung compliance.

Airway, chest wall and respiratory system resistances are elevated in simple obesity and are higher with more elevated BMI. The primary mechanism for increased lung and total respiratory system resistance is likely related to increased resistance at the level of the small, rather than large, airways (due to reduced lung volume) [8].

Maximal inspiratory and expiratory pressures (PI_{max} and PE_{max}, respectively), measured to test respiratory muscle strength, are normal in eucapnic mild-to-moderate obese individuals, but diminished in morbid obesity [9]. Given the elevated total respiratory resistance, decreased compliance and increased inspiratory threshold load associated with obesity, it is not surprising that the mechanical work and oxygen cost of breathing are increased [10]. The work of breathing is three to four times higher in moderate obesity compared with that in normal-weight individuals [11].

The effect of obesity on spirometry and lung volumes is complex and influenced by the degree of obesity, age and type of body fat distribution (central or peripheral). The most frequent pulmonary function test abnormality associated with obesity is decreased expiratory reserve volume, most probably due to displacement of the diaphragm into the chest by the obese abdomen [1]. There is an exponential relationship between increasing BMI and decreasing expiratory reserve volume in a healthy population [1]. The impact of obesity on other lung volumes is modest. Total lung capacity (TLC) may slightly decline with morbid obesity [12]. Residual

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volume (RV) and vital capacity are usually within the normal limits, and forced vital capacity (FVC) is usually in the lower limits of normal. RV/TLC may be increased in obesity, reflecting air-trapping secondary to increased volume-dependent airway closure [1]. The inspiratory capacity (IC) at rest increases about 0.35–0.55 l [13], and the IC/TLC ratio increases with increasing BMI [14]. Forced expiratory volume in 1 s (FEV_1) is usually in the lower range of normal. The FEV_1/FVC ratio is generally normal or slightly elevated, indicating the absence of airway obstruction associated with obesity [15,16]. However, obstruction of the small airways may be detected on the flow volume loop in obese individuals [17]. Table 1 summarizes the effects of obesity on pulmonary functions at rest.

Obesity and respiratory mechanics during exercise

During exercise, there is an increase in ventilatory requirements, reflecting the higher metabolic cost of external work with the increase in oxygen consumption (VO_2) and carbon dioxide production (VCO_2) [18,19].

Obese individuals show different operational lung volumes (Fig. 1) and different breathing pattern responses to incremental cycle exercise, which is more shallow and rapid, compared with that in normal-weight individuals [18]. The larger resting IC and inspiratory reserve volume indicate that obese individuals can increase their end expiratory lung volume without end-inspiratory lung volume prematurely encroaching on the TLC. Thus, there is no mechanical limitation in tidal volume during exercise compared with that in normal weight individuals. This ventilatory behaviour with a more rapid and shallow breathing during exercise may be simply a compensatory adaptation to decrease the elastic work of breathing [20]. The pulmonary dynamic hyperinflation that can be detected in obese patients during exercise is potentially a cause of decreased maximal performance, but it was demonstrated that it has no direct impact on breathlessness in those patients. The presence of higher operational lung volumes in obese patients during exercise, with higher IC, works as a mechanism of adaptation [21].

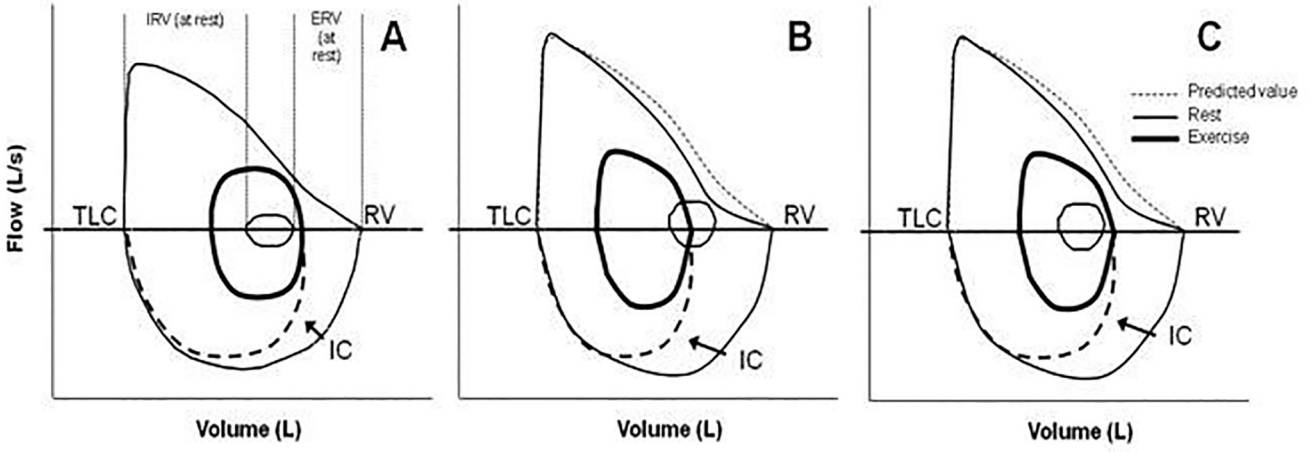
Exertional dyspnoea is a common complaint among obese individuals, but the mechanisms that drive breathlessness are not well defined. In severely obese individuals, it was demonstrated that, even during maximal exercise on a cycle ergometer, they were able to increase their ventilation enough to avoid hypercapnia [11]. There was no difference in peak exercise capacity, in terms of both peak work rate and oxygen consumption, and is normal in healthy obese individuals with and without exertional breathlessness. However, breathlessness was associated with increased ventilatory demand and greater increase in the oxygen cost of breathing during exercise. Breathlessness at rest may also be reported by obese individuals [11].

Table 1 Effects of obesity on pulmonary functions at rest

Respiratory compliance	↓
Small airway resistance	↑
Work of breathing	↑
Respiratory muscle strength	↓ ou ← →↔
FEV_1/FVC	↑ ou ← →
FEV_1	↓ ou ← →
FRC	↓
ERV	↓
TLC	↓ ou ← →
IC	↑

ERV, expiratory reserve volume; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; TLC, total lung capacity.

Fig. 1



Flow volume curves in healthy and obese individuals and summary of the effects of obesity on pulmonary functions.

The respiratory mechanical factors related to obesity do not contribute to breathlessness in obese individuals. When obese and normal-weight women were compared during cycle exercise, it was found that, although oxygen consumption and minute ventilation were greater in obese individuals at all work rates, the relationships between breathlessness scores and both oxygen consumption and minute ventilation were no different in the obese and normal-weight individuals [18].

Conclusion

Obesity results in decreased compliance and increased resistance of the respiratory system and in pulmonary dynamic hyperinflation secondary to small airway obstruction. These mechanical effects increase with the increase in BMI. The work of breathing is increased in obese patients, and the ventilatory requirements are higher during exercise due to higher metabolic cost. Certain mechanisms of adaptation help in decreasing the consequences of these mechanical effects; the higher IC at rest and the modification of the ventilatory behaviour lead to decrease in the elastic work of the respiratory muscles. However, obesity and especially severe obesity remain an important potential cause of dyspnoea, which is essentially associated with increased ventilatory demand during exercise.

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Conflicts of interest

There are no conflicts of interest.

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Chronic obstructive pulmonary disease among women using biomass fuels in some rural areas of Fayoum governorate

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Context Chronic obstructive pulmonary disease (COPD) is an important health problem; it represents an important health challenge in terms of both prevention and treatment. Although smoking is recognized as the most important risk factor for COPD, rural women in developing countries have a greater risk not as a result of smoking, as smoking is uncommon there, but due to smoke from domestic biomass fuel combustion, which is another potential risk factor.

Aims The aim of this study was to investigate exposure to biomass fuel as a potential risk factor for COPD among women in the rural areas of Fayoum governorate in whom cigarette smoking was not the risk factor.

Materials and methods This study included 100 nonsmoker women who used biomass fuels and 100 women who had not used biomass throughout their life who served as controls. All groups in the study were subjected to questionnaire on respiratory symptoms, clinical examination, and were investigated using spirometer.

Statistical analysis Data were analyzed using SPSS, version 11. Quantitative data were analyzed using the χ^2-test, whereas the *t*-test was used for comparison between groups as regards quantitative data.

Results Biomass fuel is an important risk factor for development of COPD among rural nonsmoker women who use biomass. The decline in forced expiratory volume in first second and forced expiratory flow 25–75% is significantly related to the duration of exposure to biomass fuels.

Conclusion It was detected that biomass fuel is an important risk factor for development of COPD. Biomass fuels affect pulmonary functions and this is strongly related to the duration of biomass use. *Egypt J Broncho* 2015 9:227–230

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Keywords: biomass, chronic obstructive pulmonary disease, Fayoum, rural

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Introduction

Chronic obstructive pulmonary disease (COPD) is an important public health problem; it represents an important health challenge in terms of both prevention and treatment [1,2].

COPD is a major cause of chronic morbidity and mortality as many people suffer from this disease, with the prevalence ranging from 3 to 17% in developed countries; however, in developing countries the prevalence rates are higher, ranging from 13 to 27% (with a few exceptions) [3].

Although smoking is recognized as the most important risk factor for COPD, rural women in developing countries are at a greater risk not as a result of smoking, as smoking is uncommon among women in rural areas, but due to smoke from domestic biomass fuel combustion, which is another potential risk factor for the development of COPD [2].

About half the world's population, mostly in developing countries, use solid fuels (biomass and coal) as their main energy source, resulting in potentially harmful exposures [4]. Most of these people live in the rural areas of developing countries, where about 80% of households rely on biomass fuels as their major or the only source of domestic energy for cooking and sometimes space heating [5].

The aim of this study was to investigate exposure to biomass fuel as a potential risk factor for COPD among women in some rural areas in Fayoum governorate in whom cigarette smoking is not the risk factor.

Materials and methods

Study design

This study included 100 nonsmoker women who used biomass and 100 women who did not use biomass selected from the surgical and the gynecology outpatient clinics as controls. This group was matched with cases as regards age, occupation, level of education, and social standard.

All patients and controls were subjected to the following:

(1) History taking.
(2) Thorough clinical examination.
(3) Routine laboratory investigations.
(4) Chest radiographiy (posteroanterior and lateral views).
(5) Simple spirometric study before and after bronchodilator (the apparatus used was Winspiro PRO spirometry [MIR Spirodoc Oxi Diagnostic Spirometer/Winspiro PC software. Intermedics supply, Inc, Miami, USA]).
(6) Arterial blood gas analysis at room air if SpO_2 is less than 92%.

Inclusion criteria

(1) Age 40–60 years.
(2) Female sex.
(3) History of nonsmoking.
(4) History of biomass exposure.

Exclusion criteria

(1) Age less than 40 and more than 60 years.
(2) Male sex.
(3) Absent history of biomass exposure.
(4) Individuals with medical history of bronchial asthma, chronic heart diseases, chronic liver diseases, chronic renal diseases, or occupational lung diseases.

Statistical analysis

Data were computed and analyzed using SPSS, version 11 (Statistical Package for Social Sciences (SPSS)/IBM company/SAGE UK, London). Quantitative data were analyzed using the χ^2-test, whereas the *t*-test was used for comparison between groups as regards quantitative data. A multivariate analysis was used to identify the most relevant factors affecting COPD.

Ethical consideration

This study was reviewed by the Faculty of Medicine Research Ethical Committee. The participants were informed about the objectives of the study, the examination, and the investigation that would be carried out. Confidentiality of their information was assured and the participants had the right to refuse to participate in the study. All patients gave their formal consent. The protocol was approved the Ethical Committee of the Fayoum University.

Results

The study was carried on 200 women attending our chest clinic in Fayoum University Hospital. The age of the women enrolled in this study ranged between 40 years as a minimum age and 60 years as a maximum age, with a mean age of 50.64 ± 6.34 years.

The control group had normal forced expiratory volume in first second/forced volume capacity (FEV_1/FVC) ratio, whereas the case group was classified as follows: 23 women had normal ratio, 13 had obstructive abnormality, and 64 had restrictive abnormality, with statistically significant difference between the case and control groups ($P = 0.000$) (Table 1).

The case group was classified as follows: 22 cases had normal FEV_1, 49 cases had mild affection, 24 cases had moderate affection, and five cases had severe affection, with statistically significant difference between the case and control groups ($P = 0.000$) (Table 2).

The case group was classified as follows: 29% of cases had normal forced expiratory flow (FEF), 23% had mild affection, and 20% had moderate affection (Table 3). However, 11% of cases had severe affection and 17% of them had very severe affection of FEF, with a statistically significant difference between the case and control groups ($P = 0.000$).

Among cases with the duration of biomass usage of 10–20 years, seven were considered normal, one as obstructive, and 13 as restrictive (Table 4). Among cases with the duration

Table 1 Relation between FEV_1/FVC ratios and the case and control groups

FEV_1/FVC ratio	Cases = 100 [*N.* (%)]	Control = 100 [*N.* (%)]	Total = 200 [*N.* (%)]	*P* value
Normal	23 (23.0)	100 (100)	123 (61.5)	0.000*
Obstructive	13 (13.0)	0 (0)	13 (6.5)	
Restrictive	64 (64.0)	0 (0)	64 (32.0)	

FEV_1, forced expiratory volume in first second; FVC, forced volume capacity; *Significant.

Table 2 Classification of the studied group on the basis of the value of FEV_1

FEV_1	Cases = 100 [*N.* (%)]	Control = 100 [*N.* (%)]	Total = 200 [*N.* (%)]	*P* value
+80	22 (22.0)	100 (100)	122 (61.0)	0.000*
+50–80	49 (49.0)	0 (0)	49 (24.5)	
+30–50	24 (24.0)	0 (0)	24 (12.0)	
<30	5 (5.0)	0 (0)	5 (2.5)	
Total	100 (100)	100 (100)	200 (100)	

FEV_1, forced expiratory volume in first second; *Significant.

Table 3 Relation between FEF25–75% and the case and control groups

FEF25–75%	Cases = 100 [*N.* (%)]	Control = 100 [*N.* (%)]	Total = 200 [*N.* (%)]	*P* value
Normal	29 (29.0)	100 (100)	129 (64.5)	0.000*
Mild	23 (23.0)	0 (0)	23 (11.5)	
Moderate	20 (20.0)	0 (0)	20 (10.0)	
Severe	11 (11.0)	0 (0)	11 (5.5)	
Very severe	17 (17.0)	0 (0)	17 (8.5)	

FEF25–75%, forced expiratory flow rate at 25–75% of flow-volume curve; *Significant.

Table 4 Relation between duration of biomass use and FEV_1/FVC ratios

FEV_1/FVC ratio	No uses [*N.* (%)]	10–20 [*N.* (%)]	+20–30 [*N.* (%)]	+30 [*N.* (%)]	Total [*N.* (%)]	*P* value
Normal	100 (50)	7 (3.5)	16 (8.0)	0 (0)	123 (61.5)	0.000*
Obstructive	0 (0)	1 (0.5)	6 (3)	6 (3)	13 (6.5)	
Restrictive	0 (0)	13 (6.5)	41 (20.5)	10 (5.0)	64 (32.0)	
Total	100 (50)	21 (10.5)	63 (31.5)	16 (8.0)	200 (100)	

FEV_1, forced expiratory volume in first second; FVC, forced volume capacity; *Significant.

of biomass usage for more than 20–30 years, there were 16 normal, six obstructive, and 41 restrictive cases. Cases using biomass for more than 30 years had no normal ratio, had six obstructive abnormality, and 10 restrictive abnormality, with statistically significant difference between the case and control groups ($P = 0.000$).

Discussion

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing [1]. Although smoking remains the predominant risk factor for COPD [6], it needs to be emphasized that the prevalence of COPD in nonsmokers suggests the existence of other risk factors such as passive smoking, occupational exposure, and indoor air pollution [7]. In recent times, exposure to biomass smoke resulting from household combustion of solid fuels has been identified as an important risk factor for COPD, with rural women in developing countries being more exposed to disease [8]. In addition to respirable particulate matter, biomass combustion results in high levels of pollutants such as carbon monoxide, oxides of nitrogen and sulfur, formaldehyde, and benzene that are a major source of respiratory irritants in the etiopathogenesis of COPD [9].

In our study, 200 women were recruited from the rural areas of Fayoum governorate. Women aged between 40 and 60 years, with the mean age 50.64 ± 6.34 years, were included in the study. Our study showed a strong relationship between biomass fuel use and prevalence of COPD in rural nonsmoker women, as well as presence of a significant percentage of restrictive patterns, denoting association of biomass with other restrictive lung diseases. The decline in FEV_1 and FEF25–75% is significantly related to duration of exposure to biomass fuels.

Similar to our study were those performed by, Shengming *et al.* [10], Kurmi *et al.* [11], Priscilla *et al.* [12], Justino *et al.* [13], Kiraz *et al.* [14], Liu *et al.* [15], Mejza *et al.* [16] and Ekicia *et al.* [17] were performed. Shengming *et al.* [10] reported a higher prevalence of COPD in the whole population and subpopulation of nonsmoking women in rural areas compared with urban areas of south China (12 vs. 7.4%) despite a higher incidence of smoking in urban women compared with rural women (7.2 vs. 2.5%). This suggests that other important factors might have contributed to COPD. In contrast to our study, in this study, the relation between biomass duration and FEV_1 and FVC and FEF25–75% was not ascertained. Kurmi *et al.* [11] showed that the prevalence of airflow obstruction was higher in individuals exposed to biomass smoke in rural Nepal compared with nonexposed participants (8.1 vs. 3.6%). However, in this study, postbronchodilator lung function was not measured. The study showed significant reduction in FEV_1 and FEF25–75% in populations using biomass across all age groups, but there was no significant association between FVC and biomass use. Despite significant decline in FEF25–75%, they stated that FEF25–75% is not recommended in clinical practice for the diagnosis of small airway obstruction, although its deficit provides additional evidence for the presence of airflow obstruction. These results are similar to those reported in our study on significant reduction in FEV_1 and FEF25–75% in relation to biomass use. Kiraz *et al.* [14] showed higher prevalence of COPD in rural than in urban women from Turkey (12.4 vs. 3.9%). The study showed that values of FEV_1 were relatively low in rural than in urban women. This was in agreement with our results in which values of FEV_1 were low in women who used biomass fuel compared with those who did not use biomass fuel. Liu *et al.* [15] showed that the total prevalence of COPD in the studied population was 19.4%, with higher prevalence in rural than in urban areas of Guangdong Province in China (12 vs. 7.4%). Priscilla *et al.* [12], in contrast to our study, reported no statistically significant results in the detection of COPD in rural women of Tamil Nadu, but they showed that higher COPD was detected in biomass fuel users than in clean fuel users. Justino *et al.* [13] showed that 13% of nonsmoking women had FEV_1/FVC less than 70%, with a slight increase in women using biomass fuel compared with those using gas stoves (82.8 vs. 79.9%) in rural Mexico. The study revealed that most of the cases using biomass had moderate decline in FEV_1 similar to that reported in our study, in which 47% of cases had moderate decline in FEV_1 (50–80%). There was a small significant difference in FEV_1 and FVC between women using biomass and those using gas stoves. Ekicia *et al.* [17] suggested that biomass smoke was an important contributing factor to the development

of COPD in nonsmoking women living in rural areas. Mejza *et al.* [16] showed an independent relationship of farming, in addition to biomass use, with lower FEV_1/FVC values, as well as increased COPD risk, in a random population sample of Malopolska inhabitants. The study showed significant reduction in lung function in individuals using biomass. Filip *et al.* [18] showed significantly low FEV_1/FVC ratio in individuals exposed to biomass combustion and occupational exposures among Malopolska inhabitants, with 26.6% having a ratio less than 70%. The study showed significant decrease in lung function in individuals using biomass with stage 2 or higher COPD (FEV_1 50–80%).

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Conflicts of interest

None declared.

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Risk factors for hospital mortality among mechanically ventilated patients in respiratory ICU

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Background The possible factors affecting hospital mortality among mechanically ventilated patients in respiratory ICU is still not fully studied.

Objective The aim of this study was to identify the predictors of hospital mortality among mechanically ventilated patients in respiratory ICU.

Patients and methods In a prospective descriptive study, all eligible patients of Assiut Chest Department who were mechanically ventilated for more than 1 day (247 patients) during the period from April 2010 to March 2012 were included in this study. Different clinical and laboratory variables were recorded at the time of admission and followed until hospital discharge and were compared between survivors (146 patients) and nonsurvivors (101 patients).

Results A total of 247 patients were included in the study. The mean age was 57.6 ± 13.3 years. Male patients represented 65.6% of the study cohort. The hospital mortality was 40.9%. On multivariate analysis, risk factors for hospital mortality were as follows: patients diagnosed with adult respiratory distress syndrome, interstitial lung diseases, and pulmonary embolism [odds ratio (OR) = 14.2 95% confidence interval (CI), $P = 0.031$]; hospital complications (OR = 9.17 95% CI, $P = 0.000$); reintubation (OR = 8.56 95% CI, $P = 0.000$); use of sedatives for 24 h or more (OR = 3.72 95% CI, $P = 0.04$); and comorbidity burden (OR = 2.36 95% CI, $P = 0.006$).

Conclusion The major independent risk factor for hospital mortality was patients diagnosed with adult respiratory distress syndrome, interstitial lung diseases, and pulmonary embolism. In addition, patients suffering from more comorbidities or hospital complications and patients requiring longer use of sedation (≥24 h) should be monitored closely in ICU because of their high risk for hospital nonsurvival. *Egypt J Broncho* 2015 9:231–237

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Keywords: hospital mortality, mechanical ventilation, respiratory ICU, risk factors

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Introduction

Mechanical ventilation (MV) is an essential life support for the survival of a significant percentage of patients admitted to the ICUs. Patients admitted in the ICUs in the developing world are substantially different from those in developed countries [1].

Mortality associated with MV has been amply described, with widely varied results. Mortality may be set at around 40%, although it depends on different factors [2]. The aim of the clinical practice is to decrease the mortality rate in ICUs. Determination of the risk factors for mortality may provide useful guidance for intensive care patients. Predicting outcomes is an important issue during the management of critically ill patients [3].

Variables that have been commonly linked to an increased risk for in-hospital mortality in mechanically ventilated patients include age, comorbidities, Simplified Acute Physiology Score (SAPS) III, severe adult respiratory distress syndrome (ARDS), deep sedation, duration of MV, and ICU complications [4–7]. However, there is a wide variation in the prognostic variables between studies, which may be related to differences in the characteristics of patient cohorts, clinical variables recorded, and the geographical setting of different studies [8].

ICU survivors who receive MV for any duration have a substantially higher mortality rate compared with nonventilated ICU patients [9]. It is important to identify patients who are likely to have poor outcome at the time of admission, so that such patients can be managed aggressively [10].

The aim of the study was to identify predictors of death in critically ill adult patients under MV in respiratory ICU.

Patients and methods

Study design and ethics

The present prospective descriptive study was conducted in the respiratory ICU (RICU), Chest Department, Faculty of Medicine, Assiut University Hospital, during the period from April 2010 to March 2012. The study design was approved by the Scientific Ethics Committee of Faculty of Medicine of Assiut University. Informed consent was obtained from the patient or from a surrogate decision maker.

Patients

Among 595 patients who were admitted to the RICU during this period (and supported by either invasive and/or noninvasive ventilation), only 247 patients were intubated and fulfilled the inclusion criteria. Patients were eligible for enrollment (247 patients) if they were admitted to the respiratory ICU with respiratory disorders and required MV for more than 1 day. Exclusion criteria included the following: patients who received noninvasive ventilation without subsequent intubation; age below 18 years; and patients with postarrest encephalopathy.

Baseline patient data

Full history was taken from the patient or their relatives. Full clinical examination was also carried out on the day of ICU admission. Chest radiography, daily assessment of arterial blood gases, and full laboratory assessment were performed. Illness severity and expected mortality were measured on the day of ICU admission with Acute Physiology and Chronic Health Evaluation (APACHE) II score [11] and the SAPS II [12]. Reasons for ICU admission based on a predefined list of medical diagnoses, such as amount of sputum, endotracheal tube diameter, duration of hospitalization before ICU admission, and use of sedative and its duration, were also recorded.

Procedures

All included patients (247 patients) were intubated using endotracheal tubes (ETTs) of size 7.0–8.0 mm. Ventilation was performed with the Puritan-Bennett 840 ventilator (Nellcor Puritan-Bennett 840 ventilator, USA). Patients were adjusted on synchronized intermittent mandatory ventilation, volume-controlled mode, except patients with severe asthma and ARDS, who were adjusted on pressure-controlled mode as a lung protective strategy. The procedure of weaning from MV was considered as early as possible. Weaning was conducted in 166 patients on the basis of the prevailing criteria of ERS, ATS, ESICM, SCCM, and SRLF [13]. The spontaneous breathing trial was performed with either pressure support ventilation (in 88 patients) or automatic tube compensation (in 78 patients).

Other data

Comorbidities were also evaluated on the day of ICU admission. Patients were identified on the basis of the international classification of diseases (ICD-10). Comorbidities included diabetes mellitus, hypertension, moderate-to-severe renal dysfunction (creatinine>3 mg or renal failure), hepatic dysfunction (viral hepatitis, liver cirrhosis, and hepatic failure), ischemic heart disease, heart failure, anemia (HGB < 10 g/dl, which may be the level that affects weaning process), polycythemia (HCT>56% or HGB = 17 and/or 15 g/dl in male and female patients, respectively), thrombocytopenia (PLT<100 kU/l), obesity (BMI > 30 kg/l^2), and history of drug addiction. Comorbidity burden was measured as a sum of comorbidities [14].

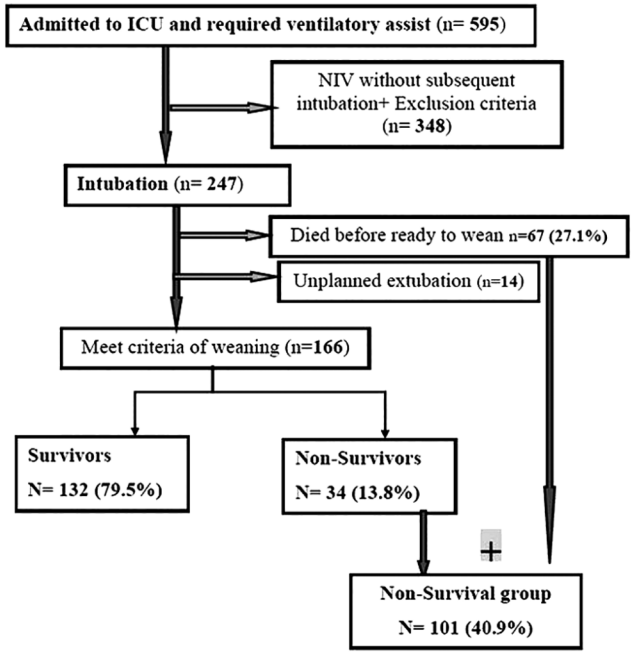
Moreover, prospectively collected data included duration of MV, length of ICU stay, length of hospital stay, reintubation rate, and occurrence of complications arising during the course of the MV and ICU stay (including pneumonia, ARDS, shock, sepsis, barotrauma, major arrhythmia, renal failure, electrolyte disturbance, deep venous thrombosis, and stress ulcer). Hospital mortality was considered as the primary outcome. The course and outcome are summarized in Fig. 1.

Statistical analysis

Data were analyzed using SPSS (Statistical Package for Social Science), version 21 (IBM Inc., Armonk, New York, USA). Data were presented as mean ± SD for quantitative variables and as frequencies, percentage, median, and range for qualitative variables. *P*-values were determined for both the survival and nonsurvival groups, and a value less than 0.05 was considered significant. Nonparametric tests were used in the current study, such as the Mann–Whitney test (equivalent to independent Student's *t*-test in parametric tests) and χ^2-test.

Multivariate logistic regression with backward stepwise selection was performed to evaluate risk factors for hospital mortality. Variables with a *P*-value less than 0.05 in the univariate analysis were entered in the multivariable analysis.

Fig. 1



Flowchart of the study.

Results

During the study period, 247 patients were intubated and fulfilled the inclusion criteria. Distribution of patients based on the clinical diagnosis is shown in Table 1. The study included 52 patients with acute respiratory failure and 195 patients with chronic respiratory failure. Hospital mortality was 40.9% (101 patients).

Table 1 Distribution of patients based on clinical diagnosis

Patient diagnosis	Number of patients
Group I (ARF)	52 (21.1)
Asthma	17 (6.9)
ARDS	23 (9.3)
Pulmonary embolism	12 (4.9)
Group II (CRF)	195 (78.9)
COPD	148 (59.9)
CRF non-COPD	47 (19)
Post-TB sequelae	15 (6)
ILDs	14 (5.7)
OHS	13 (5.3)
Kyphoscoliosis	2 (0.8)
Alveolar microlithiasis	2 (0.8)
PPH	1 (0.4)
Total	247 (100)

Data are expressed as *n* (%). ARDS, adult respiratory distress syndrome; ARF, acute respiratory failure; COPD, chronic obstructive pulmonary disease; CRF, chronic respiratory failure; ILD, interstitial lung disease; OHS, obesity hypoventilation syndrome; PPH, primary pulmonary hypertension.

Demographic data and patient characteristics of both groups are shown in Table 2. The number of male patients was 162 (65.6%), whereas the number of female patients was 85 (34.4%). Male patients were significantly predominant among survivors (73.3%) versus nonsurvivors (54.5%), whereas the proportion of female survivors and nonsurvivors was 26.7 and 45.5%, respectively. The mean age was 57.6 ± 13.3 years. The mean age of patients who survived was 56.5 ± 12.7 years, which was nonsignificantly lower compared with patients who died (58.9 ± 14.2 years). The mean BMI was about 26 in total and both groups. There was no significant difference between the two groups as regards BMI, smoking index, the Glasgow Coma scale, and amount of endotracheal secretion. Patients with oliguria at first day of ICU were significantly increased among nonsurvivors.

The importance of early ICU admission was also evaluated. Critically ill patients admitted to the emergency room or hospitalized in the ward for 24 h or more before ICU admission were significantly increased in the nonsurvivor group.

The mean APACHE II score in all patients was 23.75 ± 5.32, with a mean expected mortality of about 45%. Nonsurvivors had significantly higher APACHE II. The mean SAPS II score in all patients

Table 2 Demographic data and patient characteristics of the studied groups

Parameters	Total (*n* = 247)	Survival group (A) (*n* = 146) (59%)	Nonsurvival group (B) (*n* = 101) (41%)	*P*-value
Sex				
Male	162 (65.6)	107 (73.3)	55 (54.5)	0.002*
Female	85 (34.4)	39 (26.7)	46 (45.5)	
Age (years)				
Mean ± SD	57.63 ± 13.32	56.52 ± 12.72	58.94 ± 14.2	0.36
Median (range)	60 (20–86)			
BMI (kg/m^2)	26.59 ± 4.57	26.74 ± 4.42	26.39 ± 4.81	0.55
Smoking index (pack/year)	31.99 ± 12.6	31.6 ± 12.03	32.6 ± 13.01	0.66
Hospitalization before ICU admission (h)				
<24	119 (48.2)	96 (65.8)	23 (22.8)	0.000*
≥24	128 (51.8)	50 (34.2)	78 (77.2)	
GCS before intubation	10.02 ± 3.51	10.54 ± 3.04	9.43 ± 4.06	0.071
At ICU admission				
Urine output <500 ml	20 (8.1)	3 (2.1)	17 (16.8)	0.000*
Abundant secretion	137 (55.5)	76 (52.1)	61 (60.4)	0.2
APACHE II	23.75 ± 5.32	22 ± 4.78	26.29 ± 5.04	0.000*
Expected mortality %	45.3 ± 16.47	39.86 ± 14.94	53.13 ± 15.43	0.000*
SAPS II	43.18 ± 12.06	37.71 ± 8.91	51.09 ± 11.56	0.000*
Expected mortality %	34.19 ± 22.02	23.94 ± 15.17	49.02 ± 21.99	0.000*
First tracheal aspirate culture				
Sterile	81 (32.8)	55 (37.6)	26 (25.7)	0.05*
Isolation of pathogens	166 (67.2)	93 (62.4)	73 (74.3)	
Comorbidity burden	2.35 ± 1.39	2.09 ± 1.39	2.74 ± 1.38	0.000*
Use of sedative >1 day	132 (53.4)	50 (34.2)	82 (81.2)	0.000*

Data are presented as mean ± SD, median (range), or *n* (%). APACHE II, Acute Physiology and Chronic Health Evaluation; GCS, Glasgow Coma scale; SAPS II, Simplified Acute Physiology Score. *P*-value is evaluated for both the survival and nonsurvival groups. *Significant difference.

was 43.18 ± 12.06, with a mean expected mortality of about 34%. Nonsurvivors had significantly higher SAPS II score compared with survivors. Certainly, expected mortality calculated by both scores was significantly higher in the nonsurvival group.

Sterile cultures obtained from tracheal aspirate cultures taken on admission were significantly associated with the survival group. However, isolation of pathogenic organisms were significantly associated with hospital mortality.

Moreover, the impact of comorbidities and sedation duration on outcome was evaluated. The comorbidity burden (number of comorbidities) and the use of sedative for more than 24 h were significantly increased among patients who died compared with those who survived.

Table 3 shows standardized mortality ratio (SMR), which is defined as the ratio between the actual and predicted hospital mortality. SMR with APACHE II (90.3%) showed a lower number of death than is expected (APACHE II overestimated the mortality to a lower extent). However, SMR with SAPS II (119.6%) showed a higher number of death than is expected (SAPS II underestimated the mortality to a higher extent).

Table 3 SMR based on APACHE II and SAPS II

Parameters	Actual hospital mortality [*n* (%)]	Expected mortality (%)	Standardized mortality ratio (%)
APACHE II	101 (40.9)	45.3	90.3
SAPS II		34.19	119.6

APACHE II, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; SMR, standardized mortality ratio.

In Table 4, the mean duration of hospital stay in all patients was 11.37 ± 8.28 days, whereas for ICU stay it was 7.03 ± 6.62 days. The mean duration of MV was 3.86 ± 2.75 days. Moreover, 34 (13.8%) patients required reintubation and 11 (4.5%) patients required tracheostomy. The differences were statistically significant between the two groups as regards duration of MV, hospital length of stay, reintubation, and tracheostomy rate.

Results for ICU and hospital complications are presented in Table 5. There was statistically significant difference between the two groups as regards the percentage of patients who suffered from barotraumas, hospital acquired pneumonia, ARDS, shock, sepsis, arrhythmia, renal failure, and electrolyte disturbance. The total number of complications was significantly increased in the nonsurvivor group.

The variables related to hospital mortality are shown in Table 5, taking hospital survival as a reference. Multivariate logistic regression identified patients diagnosed with ARDS, interstitial lung diseases (ILDs),

Table 4 Length of stay, duration of MV, and outcome

Parameters	Total (*n* = 247)	Survival group (A) (*n* = 146) (59%)	Nonsurvival group (B) (*n* = 101) (41%)	*P*-value (A vs. B)
Hospital stay (days)	11.37 ± 8.28	13.01 ± 7.27	8.99 ± 8.06	0.000*
ICU stay (days)	7.03 ± 6.62	6.92 ± 5.091	7.19 ± 6.38	0.78
Duration of MV (days)	3.86 ± 2.75	3.51 ± 2.19	4.35 ± 3.37	0.05*
Reintubation rate [*n* (%)]	34 (13.8)	9 (6.2)	25 (24.8)	0.000*
Tracheostomy rate [*n* (%)]	11 (4.5)	2 (1.4)	9 (8.9)	0.006*

MV, mechanical ventilation; *Significant difference.

Table 5 ICU and hospital complications among 247 patients

Complications	Total (*n* = 247)	Survival group (A) (*n* = 146) (59%)	Nonsurvival group (B) (*n* = 101) (41%)	*P*-value (A vs. B)
Barotrauma	6 (2.4)	1 (0.7)	5 (5)	0.043*
HAP	44 (17.8)	6 (4.1)	38 (37.6)	0.000*
ARDS	28 (11.3)	2 (1.4)	26 (25.7)	0.000*
Shock	93 (37.7)	4 (2.7)	89 (88.1)	0.000*
Sepsis	65 (26.3)	3 (2.1)	62 (61.4)	0.000*
AF or V. arrhythmia	66 (26.7)	17 (11.6)	49 (48.5)	0.000*
Renal failure	46 (18.6)	2 (1.4)	44 (43.6)	0.000*
Hepatic failure	5 (2)	2 (1.4)	3 (3)	0.33
Electrolyte disturbance	148 (59.9)	79 (54.1)	69 (68.3)	0.017*
Others	60 (24.3)	28 (19.2)	32 (31.7)	0.023*
Number of complications	2.27 ± 2.01	0.98 ± 0.97	4.12 ± 1.4	0.000*

Others include deep venous thrombosis (DVT), bed sores, hematemesis, hemoptysis and psychological disturbance. AF, atrial fibrillation; ARDS, adult respiratory distress syndrome; HAP, hospital-acquired pneumonia; V. arrhythmia, ventricular arrhythmia; *Significant difference.

and pulmonary embolism as a major independent risk factor for hospital mortality [odds ratio (OR) = 14.2]. To a lesser extent, patients who suffered from more ICU and hospital complications and reintubation were more likely to not survive (OR = 9.2 and 8.6, respectively). Moreover, patients who required sedation for more than 24 h had a significant trend to hospital mortality (OR = 3.7). Finally, patients with higher comorbidity burden were more likely to not survive (OR = 2.4). However, other variables cannot be considered as independent risk factors for hospital mortality (Table 6).

Discussion

The present study included 148 patients diagnosed with chronic obstructive pulmonary disease (COPD) (59.9%); 47 patients suffered from chronic respiratory failure other than COPD (20.1%) and 52 patients from acute respiratory failure (19%). Sellares *et al.* reported that COPD patients represented 51.9% and chronic respiratory diseases represented 20.4% in a study conducted in the respiratory ICU [15].

As regards demographic data of studied patients, the mean age was ~57.6 years (survivors 56.5 vs. nonsurvivors 58.9 years), with male patients representing ~66%. These results were compatible with those reported by Tonnelier *et al.* [16] and Mansoura *et al.* [17]. Nonsurvivors characterized by nonsignificant older age than those who survived (58.9 years vs. 56.5 years, respectively). The same finding was also reported by Ucgun *et al.* [4]. Female patients were significantly increased in the nonsurvival than in the survival group (45.5 vs. 26.7%). There was an apparent discrepancy with a study by Cheng *et al.* [18], who reported significant increase in age and nonsignificant increase in female patients in the nonsurvival group. This can be explained by the relatively younger age and female predominance in patients diagnosed with ARDS, ILDs, and pulmonary embolism who had the highest mortality in our study.

Table 6 Variables associated with hospital mortality in multiple logistic regression

Parameters	*P*-value	OR	95.0% CI	
			Lower	Upper
Sex	0.764	1.009	0.952	1.069
BMI	0.093	0.883	0.764	1.021
Hospitalization ≥ 24 h before ICU admission	0.630	1.411	0.347	5.745
ARDS/ILD/PE	0.031*	14.185	1.272	158.216
Abundant secretion	0.297	0.478	0.119	1.916
Urine output <500 ml	0.111	0.079	0.003	1.797
Isolation of pathogenic organism	0.093	0.883	0.764	1.021
APACHE II	0.216	1.156	0.919	1.454
SAPS II	0.299	0.945	0.851	1.051
Comorbidity burden	0.006*	2.364	1.281	4.363
Use of sedative >24 h	0.040*	3.720	0.816	16.956
Duration of MV	0.959	1.012	0.648	1.580
Reintubation	0.000*	8.556	2.749	19.743
Number of complications	0.000*	9.167	4.170	20.152

APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, adult respiratory distress syndrome; CI, confidence interval; ILD, interstitial lung disease; MV, mechanical ventilation; OR, odds ratio; SAPS, Simplified Acute Physiology Score; *Significant difference.

No significant difference existed between the survival and nonsurvival groups in terms of BMI and smoking index. The same finding was also reported by Bakr *et al.* [19]. In addition, Macedo *et al.* [20] documented that 10% of ICU patients had oliguria for 24 h. They concluded that oliguria is an early predictor of higher mortality in critically ill patients.

In the present work, 55% of mechanically ventilated patients had abundant tracheal secretion on the first day of ICU admission (depending upon the frequency and amount of tracheal suction) without significant difference between the two groups. Khamiees *et al.* [21] observed that 48% of patients had abundant secretion and 49% had frequent suction (every less than 2 h).

We also found that 51.8% of patients were hospitalized for more than 24 h before being transferred to ICU. The usual cause for the delay in ICU admission was the lack of ICU bed availability. A significant increase in patients hospitalized for more than 24 h was observed in the nonsurvival group. Bing-Hua [22] found that 31.2% of patients were immediately admitted, whereas 68.8% of patients had delayed ICU admission. He concluded that prolonged waiting hours in the ICU because of bed shortage was associated with higher ICU mortality among critically ill surgical patients. Cardoso *et al.* [23] reported the same results in ICU patients.

As regards ICU scores, we found that the average APACHE II score was 23.8 ± 5.3, with a significant difference between the two groups (survivors 22 ± 5 vs. nonsurvivors 26 ± 5). Likewise, we found that the average SAPS II score was 43.2 ± 12.1, with a significant difference between the two groups (survivors 38 ± 9 vs. nonsurvivors 51 ± 12). Cohen *et al.* [24] reported similar results (mean APACHE II 22 ± 8). Anzueto *et al.* [25] found a mean SAPS II of 43 ± 18, which is compatible with our results. Mohan *et al.* [5] and Timmers *et al.* [26] posted that APACHE II and SAPS II were significantly associated with hospital mortality, which is consistent with our results. In contrast, Madkour and Adly [27] reported no significant difference as regards SAPS II between survivors and nonsurvivors.

In our study, the expected mortality with APACHE II was 45.3 versus 34.2% with SAPS II. This means that APACHE II score overestimated mortality, whereas SAPS II underestimated mortality. The ratio between the actual and predicted hospital mortality was 90.3% for APACHE II and 119.6% for SAPS II. Therefore, we documented that APACHE II was better than SAPS II in estimating hospital mortality. Del Bufalo *et al.* [28] concluded that the APACHE II score was a good predictor of hospital outcome and better than SAPS II, with the ratio between the actual and predicted hospital mortality being 86% for APACHE II and 83% for SAPS II. However, the APACHE II score is neither very sensitive nor specific in terms of mortality prediction. The major limitation of this scoring system is that many patients have several comorbid conditions, and selecting only one principal diagnostic category may be very difficult. In addition, the physiological variables are all dynamic and can be influenced by multiple factors. All these factors can lead to a risk of overestimation of predicted mortality [29].

The first tracheal aspirate cultures were sterile in 32.8%. Khalil *et al.* [30] reported that up to 61.5% of admission cultures were sterile. A significant increase in sterile cultures in the survival group was observed; however, isolation of pathogenic organisms was significantly increased in the nonsurvival group. Mohan *et al.* [5] reported similar finding. The elevated percentage of sterile cultures may be related to the use of conventional culture, which did not discover viral or atypical organisms, and the use of the first tracheal culture only.

Comorbidity burden was 2.1 ± 1.4 among nonsurvivors versus 2.7 ± 1.4 among survivors, with significant difference between the two groups. Ucgun *et al.* [4] posted that the presence of comorbidities was significantly increased in the nonsurvival group. Mukhopadhyay *et al.* [31] reported that 37% of patients had more than three comorbidities and were associated with hospital mortality. Moreover, Cheng *et al.* [32] demonstrated that comorbidity burden significantly increased among nonsurvivors.

We found a significant increase in the use of sedative drugs for more than 24 h in the nonsurvival group. Shehabi *et al.* [33] documented that longer and deep sedation was significantly associated with hospital mortality.

Kahn *et al.* [34] reported that a mean duration of MV of 3.1 ± 4.6 days, mean ICU length of stay of 6.6 ± 6.9 days, and mean hospital length of stay of 12.5 ± 12.2 days. Approximately 15% of patients in whom MV is discontinued require reintubation within 48 h [35]. These results are consistent with our results.

We found a significant increase in the duration of MV, reintubation rate, and tracheostomy rate among patients who died compared with patients who survived. Cheng *et al.* [18] reported that the duration of MV and reintubation significantly increased among nonsurvivors. Moreover, Khalil *et al.* [36] reported that the duration of MV and tracheostomy rate significantly increased in the nonsurvival group. These results are compatible with our results.

In our study, no significant difference was observed in ICU length of stay. However, hospital length of stay was significantly increased in the survival group. Tanaka *et al.* [7] reported similar results. Moreover, several ICU and hospital-related complications were encountered and associated with morbidity and mortality. They included barotraumas, hospital-acquired pneumonia, shock, ARS, sepsis, arrhythmia, electrolyte disturbance, and renal and hepatic failure. We also found a significant increase in complications among nonsurvivors. Ucgun *et al.* [4] and Khalil *et al.* [36] reported similar results.

For in-hospital mortality, multivariate logistic regression was performed to evaluate predictors of hospital mortality. We identified patients diagnosed with ARDS, ILDs, and pulmonary embolism as a major risk factor for hospital mortality (OR = 14.2, P = 0.031). We also found that ICU and hospital complications, reintubation, and comorbidity burden were significantly associated with nonsurvival. Moreover, we found that patients who required longer sedation (>24 h) were at increased risk of ICU and hospital death.

Several studies evaluated risk factors for hospital mortality among critically ill patients. Ucgun *et al.* [4] reported that ICU complications and comorbidities could be considered as factors affecting mortality in COPD patients. Mohan *et al.* [5] reported that duration of MV was significantly associated with hospital mortality. Feng *et al.* [6] concluded that age and duration of MV were strongly associated with mortality in critically ill patients. Mansoura *et al.* [17] stated that APACHE II and SAPS II were not associated with hospital mortality in logistic regression analysis and that only the SOFA score was an independent predictor of mortality among the respiratory ICU patients. Bing-Hua [22] documented that significant association between early ICU admission and survival rates existed. Cheng *et al.* [32] reported that the number of comorbidities could be considered as a risk factor for death. Tanaka *et al.* [7] identified age, Charlson comorbidity index >2, SAPS III, severe ARDS, and the deep sedation as major factors associated with hospital mortality in mechanically ventilated patients.

Conclusion

In a respiratory ICU population, ARDS, ILD, and pulmonary embolism patients were at a higher risk for hospital mortality. The present results identified that ICU and hospital complications, reintubation, comorbidity burden, and longer sedation (>24 h) as risk factors associated with hospital mortality among mechanically ventilated patients.

Acknowledgements

Conflicts of interest

None declared.

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Impact of C-reactive protein and BMI on patient outcome in respiratory ICU in Abbassia Chest Hospital

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Introduction C-reactive protein (CRP) is the most widely used biomarker of infection in critically ill patients and some data are available on the morbidity and mortality in obese patients in the medical intensive care setting, but it is widely held that their outcomes are poor.

Aim of the work This study aimed to evaluate the impact of CRP and BMI on the outcome of patients admitted in the respiratory ICU (RICU) in Abbassia Chest Hospital.

Materials and methods This prospective study was carried out on 71 patients admitted to the RICU at Abbassia Chest Hospital from January 2011 to July 2011. A full assessment of history, a thorough clinical examination, length of stay (LOS), and need for mechanical ventilation were assessed, and BMI and CRP were measured.

Results There was a highly significant correlation between BMI categories and outcome in which the mortality rate was high among underweight patients; there was also a significant correlation with complications, wherein septicemia was more common in underweight patients. Complications of mechanical ventilation were more common in morbidly obese patients and nosocomial infection was more common in obese patients. The results showed an insignificant correlation between smoking, need for mechanical ventilation, duration of MV, LOS in ICU, and outcome in terms of the CRP level.

Conclusion The study concluded that CRP exerted an independent effect on the duration of mechanical ventilation (MV) and LOS in RICU. The mortality rate was high in underweight patients, but not in overweight, obese, or severely obese patients. *Egypt J Broncho* 2015 9:238–244

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Keywords: BMI, C-reactive protein, length of stay, respiratory ICU

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Introduction

C-reactive protein (CRP) is a marker of inflammation that has been used to monitor the course of infection and inflammatory diseases. CRP has been considered not only as a biochemical marker of inflammation but also as an active modulator of the inflammatory response [1].

Numerous studies have reported increased CRP levels in patients with sepsis [2], but their relation to multiple organ dysfunctions and failure has not been well evaluated. Some studies have suggested that CRP may be an indicator of organ failure [3].

Serum CRP level began to be used as a diagnostic tool useful in determining the degree of activity and as a therapeutic guide for a number of conditions that commonly lead to marked changes in the plasma concentrations of acute-phase proteins [4].

The impact of obesity on outcome in critically ill patients has not been well studied. There are only a few comprehensive reviews that detail the management of obese critically ill patients. Hospitalized obese patients are at an increased risk of developing respiratory and other complications [5].

During the last decade, the increase in the incidence of obesity in the general population has led to a higher number of obese patients being hospitalized in ICUs. However, the direct influence of excessive body weight on ICU mortality remains controversial. Few data are available on morbidity and mortality in obese patients in the medical intensive care setting, but it is widely held that their outcomes are poor [6].

Problems in obese patients in the ICU may include difficulties with airway maintenance, disordered ventilation and gas exchange, impaired circulation, and altered drug pharmacokinetics. Procedures are more challenging, whether nonoperative (e.g. airway intubation, vascular access, neural blocks, urinary catheterization) or operative. Safe transport, repositioning, image acquisition, and mobilization can be major challenges requiring careful planning and execution. Of the many effects of obesity on various organ systems, we have chosen to focus on the following obesity-related disorders encountered commonly in the ICU that indicate the diverse effects through which obesity increases morbidity and complicates management [6].

All previously published studies of impact of CRP and BMI on patient outcome in critically ill patients have

addressed this relation in either medical, surgical, or trauma ICUs, but never in a specialized respiratory ICU (RICU). We hypothesized that there would be a relation between BMI, CRP, and the patient outcome in the RICU.

Aim of the work

The aim of our study is to evaluate the impact of CRP and BMI on the outcomes of patients admitted in the RICU in Abbassia Chest Hospital.

Material and methods

This prospective study was carried out on 71 patients admitted to the RICU at Abbassia Chest Hospital from January 2011 to July 2011.

Inclusion criteria

Patients older than 20 years of age.

Patients' first admission in the ICU who stay more than 24 h.

Exclusion criteria

Patients younger than 20 years of age.

Patients whose body weight cannot be measured (because of loss of consciousness or because they are bedridden).

All the patients were subjected to the following:

(1) Full assessment of history either from the patient or his/her relative.
(2) Thorough clinical examination.
(3) Investigations: These included the following:
    (a) Plain chest radiograph.
    (b) Arterial blood gas analysis.
    (c) Laboratory investigations; these included the following: blood sugar, liver profile, renal profile, complete blood count, and electrolytes.
    (d) CRP assay using (Rapid Tex CRP Latex Test).
    (e) Height and weight measurements in the first 2 h of admission.

The BMI was calculated as follows [7]:
Weight in kilograms/(height in meter)^2.
Patients were classified as follows:
Underweight: <18.5; normal weight: 18.5–24.9; overweight: 25–29.9; obese: 30–39.9; morbidly obese: ≥40.

    (f) ECG 7 – Special investigations were performed according to the clinical condition, for example, echocardiography, ultrasonography, and computed tomography scan if needed.
(4) Length of stay (LOS), requirement of mechanical ventilation, or oxygen therapy.

Expected values

Normal adult levels of CRP are reported to be less than 12 mg/l. The CRP levels in patients with strongly positive CRP reactions had been detected to be as high as 330 mg/l [8].

Statistical analysis

The collected data were revised, coded, tabulated, and entered in a PC using the Statistical Package for Social Science. Data were presented and suitable analysis was carried out according to the type of data obtained for each parameter.

Results

This study included 71 patients admitted to Abbassia Chest Hospital in the ICU from January 2011 to July 2011.

This study included 44 men and 27 women, mean age 51.9 ± 15.2 years; the mean BMI was 26.65 ± 8.12 and the mean CRP was 19.39 ± 8.25.

Forty-two patients were mechanically ventilated; the mean duration of mechanical ventilation was 7.12 ± 7.23, the mean LOS in the ICU was 11.07 ± 8.5 days, and the mortality rate was 46.5%.

The relationship between the CRP result and mechanical ventilation among the study participants showed an insignificant correlation between the CRP result and mechanical ventilation, although increased CRP with mechanical ventilation (Table 1).

The relationships between the CRP result and outcome among the study participants are shown in Table 2 and Fig. 1 shows insignificant correlations between the CRP result and outcome, although mortality was high in patients with elevated CRP.

There was an insignificant correlation between the CRP result and length of ICU stay as shown in Table 3.

There was an insignificant correlation between the CRP result and the duration of mechanical ventilation as shown in Table 4 and Fig. 2.

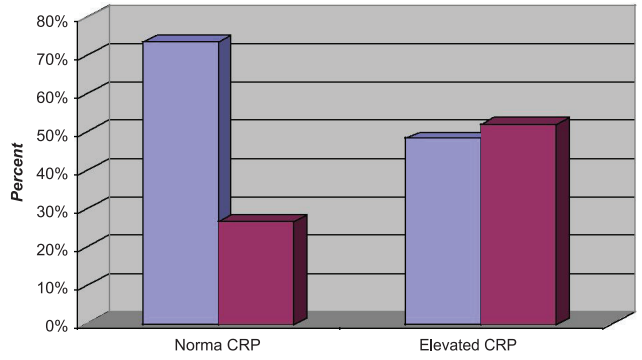
There was an insignificant correlation between sex, smoking, different BMI groups, mechanical ventilation,

Table 1 Relationship between C-reactive protein result and mechanical ventilation among the study patients

CRP	Mechanical ventilation [*N* (%)]		*P*	Significance
	Yes	No		
Elevated	33 (78.6)	23 (79.3)	0.940	NS
Normal	9 (21.4)	6 (20.7)		

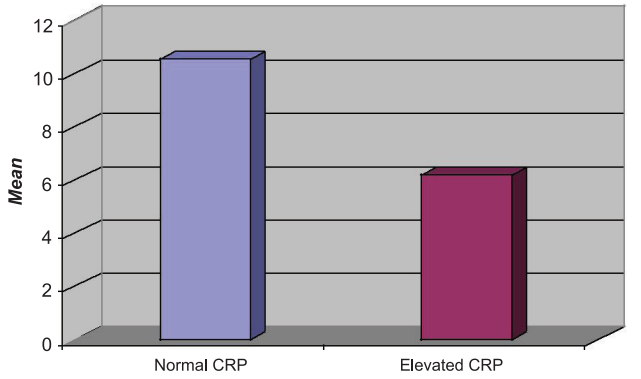
CRP, C-reactive protein.

Fig. 1



Relationship between C-reactive protein (CRP) result and outcome among the study patients.

Fig. 2



Relationship between C-reactive protein (CRP) result and duration of MV among the study patients.

Table 2 Relationship between C-reactive protein results and outcome among the patients studied

Patients outcome	CRP [*N* (%)]		*P*	Significance
	Normal	Elevated		
Lived	11 (73.3)	27 (48.2)	0.083	NS
Died	4 (26.7)	29 (51.8)		

CRP, C-reactive protein.

Table 3 Relationship between C-reactive protein result and length of stay in ICU among the studied patients who survived

CRP	Length of ICU stay (mean ± SD)	*P*	Significance
Elevated	10.37 ± 5.02	0.651	NS
Normal	11.55 ± 9.17		

CRP, C-reactive protein.

Table 4 Relationship between C-reactive protein result and duration of mechanical ventilation among the study patients

CRP	Duration of MV (mean ± SD)	*P*	Significance
Elevated	6.18 ± 5.84	0.284	NS
Normal	10.56 ± 10.71		

CRP, C-reactive protein.

complications, and outcome among patients with normal and elevated CRP as shown in Table 5.

There was an insignificant correlation between BMI groups in terms of age, serum CRP level, duration of mechanical ventilation, and LOS in ICU as shown in Table 6.

There was an insignificant correlation between BMI groups in relation to sex, smoking, serum CRP level, and need for mechanical ventilation; however, there was a significant correlation in terms of complications. Septicemia was more common in underweight patients. Complications of mechanical ventilation were more common in morbidly obese patients, nosocomial infection was more common in obese patients, whereas there was a highly significant correlation of outcome with the mortality rate, which

Table 5 Description and relations between sex, smoking, different BMI categories, MV, complications, and outcome among patients with normal and elevated C-reactive protein

Patient data	CRP [*N* (%)]		*P*	Significance
	Normal	Elevated		
Sex				
Male	8 (53.4)	36 (64.2)	0.634	NS
Female	7 (46.6)	20 (35.8)		
Smoking				
Ex-smoker	3 (20)	9 (16.1)	0.317	NS
Nonsmoker	8 (53.4)	20 (35.7)		
Smoker	4 (26.6)	27 (48.2)		
BMI				
Underweight	2 (13.3)	11 (19.6)	0.574	NS
Normal	2 (13.3)	16 (28.6)		
Overweight	5 (33.4)	12 (21.4)		
Obese	4 (26.6)	13 (23.2)		
Morbidly obese	2 (13.3)	4 (7.2)		
MV				
Yes	9 (60)	33 (58.9)	0.825	NS
No	6 (40)	23 (41.1)		
Complications				
Nosocomial infections	2 (13.3)	10 (17.9)	0.516	NS
ARDS	2 (13.3)	3 (5.3)		
Septicemia	1 (6.7)	11 (19.6)		
MV complications	2 (13.3)	4 (7.2)		
None	8 (53.4)	28 (50)		
Outcome				
Lived	11 (73.4)	27 (48.2)	0.083	NS
Died	4 (26.6)	29 (51.8)		

CRP, C-reactive protein.

was higher in the underweight group as shown in Table 7.

There was a highly significant correlation between the patients who died and those who survived in terms of complications; the most common cause of death was ARDS and septicemia as shown in Table 8.

Table 9 shows a highly significant correlation between the patients who died and those who survived in terms

of diagnosis, and those diagnosed with malignancy had a poor outcome.

There was a highly significant correlation between patients with and without nosocomial infections in terms of LOS and duration of MV; patients with nosocomial infection had longer stay in ICU and the duration of MV was prolonged as shown in Table 10.

Discussion

During the last decade, the increase in the incidence of obesity in the general population has led to a higher number of obese patients being hospitalized in ICUs. However, the direct influence of obesity on ICU mortality remains controversial. Some data are available on morbidity and mortality in obese patients in the medical ICUs, but it is widely held that their outcomes are poor [6].

In the present study, there were 56 patients with elevated CRP; of those, 27 (48.2%) patients were smokers and 20 (35.7%) patients were nonsmokers, whereas nine (16.1%) patients were ex-smokers. We found that 33 (59%) patients needed mechanical ventilation, whereas 23 (41%) patients did not. Also, estimated 27 (48.2%) patients survived, whereas 29 (51.8%) patients died.

Table 6 Comparison between patients with different BMIs in terms of age, C-reactive protein, duration of mechanical ventilation, and length of ICU stay

	BMI group (mean ± SD)					*P*	Significance
	Normal	Underweight	Overweight	Obese	Morbidly obese		
Age (years)	49.56 ± 12.66	43.54 ± 19.39	52.94 ± 17.02	58.65 ± 12.46	55.33 ± 3.27	0.085	NS
CRP level (mg/l)	19.87 ± 8.69	17.45 ± 7.80	19.50 ± 10.59	19.85 ± 7.09	21.00 ± 6.00	0.936	NS
Duration of MV (days)	6.40 ± 8.24	7.55 ± 6.70	7.57 ± 8.87	7.11 ± 7.75	7.00 ± 5.57	0.997	NS
Length of hospital stay	11.89 ± 11.28	10.15 ± 8.15	10.06 ± 7.47	11.82 ± 6.00	11.33 ± 10.17	0.954	NS

CRP, C-reactive protein.

Table 7 Description and relations between sex, smoking, C-reactive protein, mechanical ventilation, complications, and outcome among patients with different BMIs

	BMI group [*N* (%)]					*P*	Significance
	Normal	Underweight	Overweight	Obese	Morbidly obese		
Sex							
Male	15 (83.3)	7 (53.8)	9 (52.9)	10 (58.8)	3 (50.0)	0.300	NS
Female	3 (16.7)	6 (46.2)	8 (47.1)	7 (41.2)	3 (50.0)		
Smoking							
Nonsmoker	5 (27.8)	5 (38.5)	8 (47.1)	7 (41.2)	3 (50.0)	0.115	NS
Ex-smoker	4 (22.2)	1 (7.7)	0 (0.0)	4 (23.5)	3 (50.0)		
Smoker	9 (50.0)	7 (53.8)	9 (52.9)	6 (35.3)	0 (0.0)		
CRP							
Normal	2 (11.1)	2 (15.4)	5 (29.4)	4 (23.5)	2 (33.3)	0.620	NS
Elevated	16 (88.9)	11 (84.6)	12 (70.6)	13 (76.5)	4 (66.7)		
Mechanical ventilation							
Yes	10 (55.6)	11 (84.6)	7 (41.2)	9 (52.9)	5 (83.3)	0.108	NS
No	8 (44.4)	2 (15.4)	10 (58.8)	8 (47.1)	1 (16.7)		
Complications							
None	9 (50.0)	1 (7.7)	11 (64.7)	12 (70.6)	2 (33.3)	0.020	S
Nosocomial Infections	1 (5.6)	3 (23.1)	2 (11.8)	3 (17.6)	1 (16.7)		
ARDS	2 (11.1)	1 (7.7)	2 (11.8)	1 (5.9)	0 (0.0)		
Septicemia	3 (16.7)	7 (53.8)	0 (0.0)	1 (5.9)	1 (16.7)		
MV complications	3 (16.7)	1 (7.7)	2 (11.8)	0 (0.0)	2 (33.3)		
Outcome							
Lived	8 (44.4)	1 (7.7)	12 (70.6)	14 (82.4)	3 (50.0)	0.001	HS
Died	10 (55.6)	12 (92.3)	5 (29.4)	3 (17.6)	3 (50.0)		

CRP, C-reactive protein.

Table 8 Comparison between the patients who died and those who survived in terms of complications

	Complications [*N* (%)]					*P*	Significance
	None	Hospital-acquired infections	ARDS	Septicemia	Complications of MV		
Outcome							
Lived	32 (91.4)	4 (40.0)	0 (0.0)	0 (0.0)	2 (28.5)	0.001	HS
Died	3 (8.6)	6 (60.0)	6 (100.0)	11 (100.0)	5 (71.5)		

Table 9 Comparison between patients who died and those who survived in terms of diagnosis

	Diagnosis [*N* (%)]				*P*	Significance
	Infections	COPD/asthma	ILD	Malignancy		
Outcome						
Lived	9 (34.6)	20 (80.0)	4 (50.0)	0 (0.0)	0.001	HS
Died	17 (65.4)	5 (20.0)	4 (50.0)	6 (100.0)		

COPD, chronic obstructive pulmonary disease.

Table 10 Comparison between patients with and without nosocomial infection in terms of length of hospital stay and duration of mechanical ventilation

	Nosocomial infection (mean ± SD)		*P*	Significance
	No	Yes		
Length of ICU stay (days)	9.19 ± 6.49	20.33 ± 10.93	0.0001	HS
Duration of MV (days)	4.34 ± 4.83	16.00 ± 6.55	0.0001	HS

The mean ± SD LOS among patients with elevated CRP was 10.37 ± 5.02 days, compared with patients with normal CRP, which was 11.55 ± 9.17 days, and the duration of MV among patients with elevated CRP was 6.18 ± 5.84 days, compared with those with normal CRP, which was 10.56 ± 10.71.

This study found that there was an insignificant correlation between CRP in terms of smoking, need for MV and duration of MV, outcome, and LOS in ICU.

These results are not in agreement with those of Lobo *et al*. [9], who found that increased CRP concentrations were associated with organ failure, prolonged ICU stay, and high infection and mortality rates; the difference in the results between this study and our study was because of the different numbers of patients, different age groups, and the fact that the study was not carried out in the RICU.

The present study is in agreement with Wang *et al*. [10], who found an independent association between CRP level and ICU mortality.

This current study found that there was an insignificant correlation between CRP and need for mechanical ventilation, and this is not in agreement with Schuetz *et al*. [11]; these differences may have been because of the inclusion of patients with different diseases in our study, whereas the study of Schuetz *et al*. [11] was carried out only on H1N1 patients.

The present study showed that there was an insignificant correlation between the CRP results and the duration of MV, but Zimmerman *et al*. [12] showed that both BMI and CRP can be used to estimate the risk of prolonged MV in critically ill trauma patients and concluded that BMI less than 23.3 kg/m^2 or CRP greater than 10 mg/l at the time of discontinuation of MV were independent predictors of more than 7 days' duration of MV.

The present study found an insignificant correlation in the LOS and CRP level and this is not in agreement with Bhattacharya *et al*. [13], who found that higher CRP levels result in longer duration of hospital stay and poor clinical and radiological recovery in patients with community-acquired pneumonia.

For BMI, in the present study, we found that 38 (53.5%) patients survived and 33 (46.5%) patients died; the patients who died were categorized in terms of BMI as follows: 10 (55.6%) patients were normal weight, 12 (92.3%) patients were underweight, five (29.4%) patients were overweight, three (17.6%) patients were obese, and three (50.0%) patients were morbidly obese.

The present study reported that there was high significance between different BMI categories and outcome, wherein the mortality rate was high among underweight patients, but this result was not in agreement with that of Lobo *et al*. [9], who found an increased risk of morbidity and mortality for morbidly obese patients, and critically ill morbidly obese patients had higher ICU mortality compared with nonobese patients. Because missing data were not detected because of the retrospective design of the study, it was difficult to draw a conclusion on the exact influence of BMI on mortality in this study; also, Honarmand and Safavi [14] showed that obese patients had a mortality rate that was 3.9 times greater than that of the normal-weight group. In addition, Lissner *et al*. [15] found that obesity defined as BMI greater than 27 was associated with a higher mortality rate among ICU patients. Also, Goulenok *et al*. [16] reported that, after they controlled for comorbidities, obesity was not associated with increased mortality in 'seriously ill' hospitalized patients, whereas Galanos *et al*. [17] showed that abnormal BMI had no significant influence on ICU mortality. In contrast to previous reports, the obese group showed a trend toward reduced mortality and reduced duration of ICU care and hospital stay compared with the underweight and normal groups.

The data of the present study are in agreement with those of Lim *et al*. [18], who found increased mortality in the underweight patients in the medical and emergent surgical groups, but not in the elective surgical group, and also El-Solh *et al*. [6] in agreement with the present study as he found that low BMI was associated with increased mortality and worsened hospital discharge.

Obese patients have higher levels of leptin. Bornstein *et al*. [19] reported a positive association between leptin concentrations and survival of septic patients, suggesting that leptin could play a role in the adaptive response to critical illness. Also, Tremblay and colleagues [20,21] found increased mortality associated with underweight and obese patients, particularly in patients with higher levels of obesity, relative to the normal-weight category.

In addition, this study found that there was an insignificant correlation between different BMI categories in terms of LOS and duration of MV, and this was agreement with Peake *et al*. [22], who reported that there were no significant differences in the ventilation rate or weaning difficulties across the BMI categories. This was also in agreement with O'Brien *et al*. [23], who proved that obesity was not associated with increased length of ventilation and LOS. Moreover, the ICU readmission rate was similar across the BMI categories [14].

In the present study, there was an insignificant correlation between the outcome of different BMI categories in terms of age and this result was not in agreement with the study of Flegal *et al*. [24], who found excess mortality in younger patients that decreased considerably with age in all degrees of obesity, and also with Landi *et al*. [25], who reported that the mortality rate among elderly patients was greatest at the lowest BMI.

In the current study, complications of mechanical ventilation were more common in morbidly obese patients; this was in agreement with the main results of Allison *et al*. [26], who reported an increased incidence of specific complications in obese patients, including VAP.

Furthermore, in the current study, nosocomial infection was more common in obese patients, which was in agreement with Calle *et al*. [27], who found that the incidence and severity of nosocomial complications, particularly infections, and hospital mortality were higher in obese patients compared with lean patients.

In the present study, there was a highly significant correlation between patients who developed nosocomial infection and duration of MV and LOS. This is in agreement with Valencia and Torres [28], who found a significant increase in LOS and duration of MV. In terms of the outcome attributable to nosocomial infections, Fagon and colleagues [29,30] reported excess mortality, prolonged ICU stay, higher antibiotic consumption, and increased therapeutic activity, which led to considerable cost overruns.

Moreover, mortality was significantly higher among patients acquiring more than one nosocomial infection than in paired controls. The same results have been reported by Gendall *et al*. [31].

Conclusion

The study concluded that:

(1) CRP is not a good marker of morbidity and mortality in RICU patients.
(2) CRP exerted an independent effect on duration of MV and LOS in RICU.
(3) Mortality rate was high in underweight patients, but not in overweight, obese, or severely obese patients.
(4) BMI exerted no effect on duration of mechanical ventilation and LOS in the RICU.

Acknowledgements

Conflicts of interest

None declared.

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The prognostic value of the dead-space fraction and other physiological parameters in the weaning process of mechanical ventilation in patients with obstructive air flow

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Background Patients with obstructive air flow including chronic obstructive lung diseases and bronchial asthma use a substantial proportion of mechanical ventilation (MV) in the ICU, and their overall mortality with ventilator support can be significant. From the pathophysiological standpoint, they have increased airway resistance, pulmonary hyperinflation, and high pulmonary dead space, leading to an increased work of breathing. MV is an integral part of the treatment for acute respiratory failure.

Aim of the work The present study aimed to demonstrate the prognostic value of ventilatory parameters including that of the dead-space fraction (DSF), end-tidal carbon dioxide ($ETCO_2$), lung mechanics, and gas exchange during the application of MV.

Patients and methods Forty consecutive patients admitted to the ICU with acute respiratory failure due to chronic obstructive lung diseases and acute severe asthma were enrolled in the study. Lung mechanics (compliance and airway resistance), DSF, $ETCO_2$, and arterial blood gases were measured at the following times: on admission to the ICU, initially, and finally before extubation.

Results Successfully weaned and survivors represent 60% (n = 24) of all patients included in this study. They had a lower MV duration at a mean of 3.75 days ±1.8 SD. Logistic regression analysis revealed a significant association between the MV duration, pH more than 7.32, and dynamic compliance on the one hand and extubation failure on the other, but no significant association was found between the DSF and extubation failure, with odds ratio equal to 2.08 (95% confidence interval: 0.05–85.78, P = 0.7).

Conclusion We concluded that DSF is not an influential predictor of extubation failure in patients with obstructive air flow, whereas dynamic compliance plays a strong prognostic role in the weaning process.

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Keywords: bronchial asthma, chronic obstructive lung diseases, dead-space fraction, lung mechanics, mechanical ventilation

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Introduction

Chronic obstructive airway disease includes not only chronic obstructive lung diseases (COPD) and chronic asthma, but also disorders such as bronchiectasis, pneumoconiosis, and post-tuberculosis lung disease. COPD is a major health and economical problem of growing prevalence; in the year 1990, it represented the sixth most common cause of deaths worldwide, and by 2020, the disease is expected to become the third most common cause of death. The mortality associated with asthma is also considerable, with an estimated one to eight deaths per 100 000 inhabitants/year. Adequate triage or screening for admission to the ICU is therefore essential among patients at risk [1].

Although the lung mechanics are similar under both conditions (asthma and COPD), there are some physiopathological differences that should be mentioned. In effect, COPD is characterized by greater airway collapse and a loss of elastic rebound of the lungs [2], whereas asthma is characterized by hypertrophy of the airway walls secondary to inflammation, lesser airway collapse despite the considerable decrease in airway caliber (central involvement vs. peripheral involvement in COPD), and a generally reversible obstruction that can be minimal or lacking in long-evolving asthma [3].

If the ventilator demand exceeds the capacity of the respiratory muscles, acute respiratory failure results [4]. Although a general indication for almost all conditions, patients of this kind should not receive invasive mechanical ventilatory support, because the mortality increases significantly as a result. However, the failure of noninvasive mechanical ventilation (MV) (effective in at least 75% of the cases, particularly in COPD) can lead to a fatal outcome [5].

Measurements of respiratory mechanics are simple to perform and provide useful and relevant information for severity assessment and ventilator management.

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They are really reliable only under passive conditions of ventilation, in which plateau pressure (Pplat) monitoring is essential for adequate ventilatory management [6]. Resistance of the airways is described as an obstruction to airflow provided by the conducting airways, resulting mainly from the larger airways (down to division 6–7). Airway resistance to flow is present during both inspiration and expiration and the energy required to overcome it represents the actual work of breathing [7].

The expiratory capnogram provides qualitative information on the wave form patterns associated with MV and quantitative estimation of the end-tidal carbon dioxide ($ETCO_2$). Dead-space fraction (DSF) can be calculated easily from the Enghoff modified caution of the Bohr equation using the arterial partial pressure of carbon dioxide ($PaCO_2$) with the assumption that $PaCO_2$ is similar to alveolar PCO_2. DSF is increased in COPD, pulmonary embolism, decreased cardiac output, and hypovolemia. A high DSF represents an impaired ability to excrete CO_2 because of any kind of V/Q mismatch [6,8].

Few studies have been conducted to assess the value of physiological factors as a weaning predictor. The present work aimed to study the ventilatory parameters including of $ETCO_2$, lung mechanics, DSF, and gas exchange in COPD, and bronchial asthma patients during the application of MV to assess whether the length of MV in these patients can be predicted by the measurement of these parameters.

Patients and methods

Patients

The present study included 40 patients aged between 45 and 78 years, who were admitted to the ICU in El-Minia University Hospital during a period from July 2012 to August 2013 for the management of acute respiratory failure due to COPD and acute severe asthma.

The protocol was approved by the institutional ethics committee, and informed consent was obtained from the patients or their next of kin. Exclusion criteria were the association of pulmonary edema, hemodynamic instability, and the presence of intrathoracic drainage. Data were collected in all patients requiring MV; criteria used were similar to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the ATS guidelines for intubations [9]. The following data were recorded: age, sex, smoking history, comorbidity, and pulmonary function tests.

Study protocol

All patients were sedated and mechanically ventilated using a Puritan Bennett 840 microprocessor ventilator (Germany). Initially, the patients were placed on volume-control constant flow mode and ventilated with a tidal volume (Vt) ranging from 6 to 8 ml/kg body weight and a respiratory rate from 10 to 12/min supplied by volume control mode (controlled mandatory ventilation), and initial inspired fraction (FiO_2) 1.0 (100%). The extrinsic best positive end-expiratory pressure (PEEP) is the maximum amount of PEEP that can be applied without increasing the peak airway pressure during volume preset MV [10]. For all patients, the started parameters were usually changed, according to each situation after the first arterial blood gases (ABGs) analysis. All patients were under cardiac and respiratory monitoring (heart rate, respiratory rate, O_2 saturation, and $ETCO_2$). When passive ventilation was obtained and respiratory muscle activity was resumed (i.e. spontaneous breathing trial), the patient started to trigger the ventilator at his or her usual rate. Then, a spontaneous breathing trial using a T tube was performed during a 30-min period. Criteria for passing the spontaneous breathing trial were those defined by the Sixth International Consensus Conference on Intensive Care Medicine [11]. Weaning was decided when the following weaning criteria were met [11–13].

(1) Reversal of the cause of MV.
(2) Hemodynamic stability: that is, no clinically important hypotension and no requirement for vasopressors or a requirement only for low-dose vasopressor therapy (e.g. dopamine or dobutamine <5 l/kg/min).
(3) Patient capable of initiating an inspiratory effort.
(4) No electrolyte disturbances and no sedation or narcotics.
(5) Good nutritional status and no clinically evident myopathy or neuropathy.
(6) Corrected reversible causes of weaning failure such as sepsis or heart failure.

The patients were assessed for the following outcomes:

(1) Weaning success was defined as an absence of tachypnea more than 35, tachycardia more than 120, PaO_2/FiO_2 more than 150, FiO_2 less than 0.4–0.5, pH more than 7.32, and the patient is not reintubated and ventilated within 48 h of extubation, rapid shallow breathing index (respiratory rate/Vt) less than 105 [11].
(2) Days of MV.
(3) The length of ICU stay.

Extubation failure was defined as reintubation or noninvasive ventilation within 48 h after extubation [14].

The arterial sample was analyzed immediately in the blood gas analyzer ALB 30 (Radiometer, Copenhagen, Denmark) present in the respiratory ICU. ABG was performed initially and before extubation. Follow-up by ABGs after MV was carried out till the discharge of the patient.

The $ETCO_2$ was measured using the noninvasive cardiac output monitor (DS5000A Patient Monitor; Digital Science Technology, 2535 W. 237th Street, Suite 108, Torrance, CA 90505, USA) on the expiratory side of the circuit's endotracheal tube connector. After proper calibration and an equilibration time of 20 min with stable hemodynamic and respiratory variables, $ETCO_2$ were determined and the highest reading was recorded.

Estimation of the alveolar DSF using arterial and $ETCO_2$: $PaCO_2$-$ETCO_2$/$PaCO_2$ was ~59.5% of VD alv/Vt alv (Bohr–Fowler) [15–17].

Lung mechanics (resistance and elastance) were measured by the technique of rapid airway (end-inspiratory and end-expiratory) occlusion using standard formulas [18].

This produces a rapid decrease in the peak pressure, and after 3–5 s, the pressures at the ventilator and the alveoli equilibrate at which point the pressure curve plateaus off. The difference between the peak pressure and the Pplat yields the total resistance of the respiratory tract.

Measuring of airway resistance

The resistance to airflow during inspiration was determined by dividing the peak inspiratory flow rate (Vinsp) into the pressure needed to overcome the resistance to airflow (PIP–Pplat). Rinsp = PIP–Pplat/Vinsp, where Rinsp is the airway resistance during inspiration and Vinsp is the peak inspiratory flow rate.

This resistance represents the summed resistance of the connector tubing, the tracheal tube, and the airways. However, changes in Rinsp should represent changes in the airway resistance as long as the inspiratory flow rate and the size of the tracheal tube and the connector tubing are constant.

Measurement of compliance during MV

Compliance was calculated during MV by dividing the volume of air delivered to the patient through the ventilator by the obtained pressure.

Static compliance is easily calculated as the ratio between Vt and the Pplat minus PEEP. Elastance is the reverse of compliance (how much pressure we need for a given volume). A low compliance-high elastance reflects mainly a small aerated lung available for ventilation [6].

The Vt delivered had to be corrected by the subtraction of the noncompressible volume of the tubing system that connects the patient to the mechanical ventilator. We can assess auto-PEEP by airway occlusion at end expiration. PEEP, whether external applied or auto-PEEP, should be subtracted from the pressure obtained by the manometer.

$$\text{Cst} = \frac{\text{Vt} - 3(\text{PIP})}{\text{Pplat} - \text{total PEEP}},$$

$$\text{Cdyn} = \frac{\text{Vt} - 3(\text{PIP})}{\text{PIP} - \text{total PEEP}},$$

where PIP is the peak inspiratory pressure, Pplat is the plateau pressure, total PEEP = (auto-PEEP+applied PEEP), Cdyn is the dynamic compliance

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using statistical package for social sciences program, software version 20 (SPSS, Inc., Chicago, IL).

Descriptive statistics were performed for numerical data by mean, SD, and minimum and maximum of the range, whereas they were carried out for categorical data by the number and percentage. Analyses were performed for quantitative variables using the independent sample *t*-test for parametric data between the two groups and the Mann–Whitney *U*-test for nonparametric data between the two groups

The χ^2-test was used for qualitative data between groups when the cell contains more than 5 and the Fisher exact test when the cell contains less than 5.

Correlation between two variables determined using Pearson's correlation coefficient was as follows: weak (r = 0–0.24), fair (r = 0.25–0.49), moderate (r = 0.5–0.74), and strong (r = 0.75–1)

Simple logistic regression analysis was performed for the calculation of the odds ratio.

The level of significance was taken at P value 0.05 or less.

Results

Clinical and biochemical parameters of the 40 mechanically ventilated patients with COPD exacerbation and severe acute asthma on admission are illustrated in Table 1. The age of the patients was 63.15 ± 9.09 years. Men represented 40% of all patients

included in this study. In this work, 45% of the patients were smokers. Causes of acute respiratory failure were acute exacerbation of COPD in 77.5% of the patients and acute severe asthma in 22.5% of the patients (Table 1).

Table 1 Demographic and clinical criteria on admission in all studied patients

Variables	Range (mean ± SD)
Age (years)	45–78 (63.15 ± 9.09)
Sex [*N* (%)]	
Male	16 (40)
Female	24 (60)
Smoking [*N* (%)]	
No	22 (55)
Yes	18 (45)
Cause of acute respiratory failure [*N* (%)]	
Acute exacerbation of COPD	31 (77.5)
Acute severe asthma	9 (22.5)
MV duration (days)	2–16 (5.67 ± 4.25)
ICU duration (days)	3–21 (8.05 ± 5.23)
ABGs (before MV)	
pH	7–7.42 (7.22 ± 0.07)
PCO_2 (mmHg)	52.6–149 (98.22 ± 24.34)
PO_2 (mmHg)	30.6–87.7 (55.45 ± 14.58)
HI	61.2–175.4 (109.9 ± 28.9)
Lung mechanics	
DSF	0.03–0.7 (0.43 ± 0.15)
Cst (ml/cmH_2O)	6.1–42.9 (20.98 ± 9.5)
Cdyn (ml/cmH_2O)	4.5–38.6 (13.85 ± 7.29)
Raw (cmH_2O/l/s)	1.2–31.8 (15.68 ± 7.82)
$ETCO_2$ (mmHg)	13.7–65.3 (39.87 ± 15.76)

Cdyn, dynamic compliance; COPD, chronic obstructive lung diseases; Cst, static compliance; DSF, dead-space fraction; $ETCO_2$, end-tidal carbon dioxide; HI, hypoxia index; MV, mechanical ventilation; PCO_2, partial pressure of carbon dioxide.

About 60% of all the patients (n = 24) were weaned successfully and survived. They were with a significantly lower age (60.71 ± 8.95), had a heart rate less than 120, a lower MV duration (3.75 ± 1.8 days), and a higher pH more than 7.32. They showed significant improvement in Cdyn (22.47 ± 8.21) and had a lower Raw (10.99 ± 18.7). Otherwise, there were no significant differences with regard to $ETCO_2$, DSF, and static compliance (Table 2).

A significant correlation was observed between the final $ETCO_2$ and Cdyn. However, no correlation was found between the final $ETCO_2$ and other physiological parameters (Table 3 and Fig. 1).

In Table 4, the logistic regression analysis showed a significant association between failure of weaning and each of age, MV duration, heart rate, pH, rapid shallow breathing index, and Cdyn.

The COPD patients who survived had a significantly higher Raw and lower compliance in comparison with the asthmatic group (Table 5).

Discussion

There are no clearly defined criteria for the start of invasive MV in COPD and asthma. In COPD, the

Table 2 Final outcome measures in both the successful and the failed weaning groups

Variables	Successful weaning (n = 24)	Failed weaning (n = 16)	P value
Age (mean ± SD) (years)	60.71 ± 8.95	66.81 ± 8.26	0.036*
Sex [*N* (%)]			
Males	9 (37.5)	7 (43.8)	0.693
Females	15 (62.5)	9 (56.2)	
Smoking	12 (50)	6 (37.5)	0.436
Cause of ARF [*N* (%)]			
COPD	17 (70.8)	14 (87.5)	0.216
Severe asthma	7 (29.2)	2 (12.5)	
MV duration (mean ± SD) (days)	3.75 ± 1.8	8.56 ± 5.23	0.003*
Weaning success parameters			
Heart rate <120 [*N* (%)]	24 (100)	8 (50)	<0.001*
Respiratory rate <35 [*N* (%)]	23 (95.8)	13 (81.2	0.132
pH >7.32 [*N* (%)]	23 (95.8)	9 (56.2)	0.002*
Hypoxic index >150 [*N* (%)]	24 (100)	14 (87.5)	0.076
RSBI (mean ± SD)	58.21 ± 28.8	120.43 ± 44.01	<0.001*
Lung mechanics (mean ± SD)			
DSF	0.31 ± 0.14	0.33 ± 0.21	0.74
$ETCO_2$ (mmHg)	53.39 ± 19.49	54.69 ± 23.51	0.850
Cst (ml/cmH_2O)	31.03 ± 11.78	25.63 ± 13.41	0.151
Cdyn (ml/cmH_2O)	22.47 ± 8.21	16.62 ± 7.57	0.041*
Raw (cmH_2O/l/s)	10.99 ± 18.7	11.17 ± 6.01	0.036*

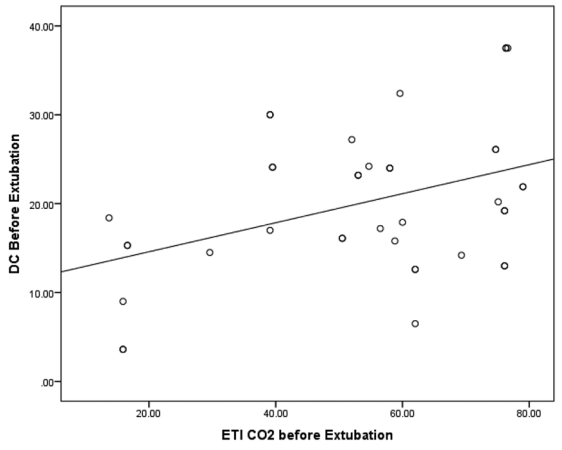
Cdyn, dynamic compliance; COPD, chronic obstructive lung diseases; Cst, static compliance; DSF, dead-space fraction; $ETCO_2$, end-tidal carbon dioxide; RSBI, rapid shallow breathing index; *P < 0.05 = significant.

most widely adopted approach is patient intubation if noninvasive MV fails after 1 h (clinical and/or worsening of blood gas criteria) [5]. In asthma, with early and aggressive management, the majority of the asthma attacks can be managed without the need for intubation and ventilation. In our study, a low percentage of the patients (22.5%) were asthmatic. Progressive exhaustion, respiratory arrest, a decreased level of consciousness, persistent respiratory acidosis (pH < 7.2), and unremitting hypoxemia (O_2 saturation <90) are clear indications for intubation [19,20]. Respiratory acidosis is the best predictor of patient exhaustion [5].

In the present study, arterial blood gas analysis on admission revealed a marked respiratory acidosis and hypoventilation (pH 7.22 ± 0.07, $PaCO_2$ 98.22 ± 24.34), in addition to poor oxygenation as (PaO_2 55.45 ± 14.58) the PaO_2/FiO_2 ratio less than 150 (109.9 ± 28.9) (Table 1). For COPD exacerbation, a Glasgow coma score of less than 11, respiratory rate more than 30, and pH less than 7.25 at admission were associated with a 70% risk of intubation [21]. However, the pH value should not be used as the only deciding factor, but rather should be used in conjunction with other factors such as the patient's mental status, comorbid conditions, patient's code status, etc. [7]. The major physiologic defects in COPD are an increased dead space, severe ventilation–perfusion misdistributions, marked airflow limitation, air trapping, and hyperinflation. Such defects frequently result in poor oxygenation and hypercapnia [22].

In our study, the successfully weaned patients represent 60% (n = 24) of all patients, and 40% (n = 16) of all

Fig. 1



Correlation between the final end-tidal carbon dioxide ($ETCO_2$) and dynamic compliance (Cdyn).

Table 3 Correlation between the final $ETCO_2$ and the DSF and the PH, the $PaCO_2$, the Raw, the Cst, and the Cdyn

Variables	Final $ETCO_2$		Final DSF	
	R	*P* value	*R*	*P* value
pH	0.262	0.102	−0.281	0.079
CO_2	−0.049	0.763	0.091	0.576
Raw (cmH_2O/l/s)	0.018	0.910	−0.224	0.165
Cst (ml/cmH_2O)	0.333	0.035*	−0.289	0.071
Cdyn (ml/cmH_2O)	0.408	0.009*	−0.139	0.393
MV time	0.016	0.921	0.085	0.604

Cdyn, dynamic compliance; Cst, static compliance; DSF, dead-space fraction; $ETCO_2$, end-tidal carbon dioxide; MV, mechanical ventilation; $PaCO_2$, arterial partial pressure of carbon dioxide; *P < 0.05 = significant.

Table 4 The logistic regression analysis, taking failed extubation as the dependent variable and examining the different variables that showed at least a tendency towards statistical significance in the univariate analysis

Variables	Odds ratio	95% CI	*P* value
Age (mean ± SD) (years)	1.09	1.002–1.179	0.045*
Sex			
Male	1.296	0.36–4.69	0.693
Female	0.77	0.21–2.79	0.693
Smoking	0.6	0.16–2.18	0.438
Cause of ARF			
Acute exacerbation of COPD	2.88	0.51–16.15	0.229
Acute severe asthma	0.35	0.06–1.94	0.229
MV duration (days)	1.51	1.1–2.08	0.011*
Weaning success parameters			
Heart rate <120	0.02	0.001–0.39	0.001*
Respiratory rate <35	0.19	0.02–2	0.166
pH >7.32	0.06	0.006–0.52	0.011*
Hypoxic index >150	0.12	0.005–2.64	0.178
Lung mechanics (final) (mean ± SD)			
DSF	2.08	0.05–85.78	0.7
DSF >0.6	2.54	0.37–17.25	0.341
Cst (ml/cmH_2O)	0.96	0.91–1.02	0.188
Cdyn (ml/cmH_2O)	0.91	0.82–0.99	0.04*
Raw (cmH_2O/l/s)	1.001	0.96–1.045	0.97
$ETCO_2$ (mmHg)	1.003	0.97–1.03	0.845
RSBI	1.04	1.02–1.06	0.001*

Cdyn, dynamic compliance; COPD, chronic obstructive lung diseases; Cst, static compliance; DSF, dead-space fraction; $ETCO_2$, end-tidal carbon dioxide; MV, mechanical ventilation; RSBI, rapid shallow breathing index; *P < 0.05 = significant.

Table 5 Changes in lung mechanics before extubation in the survivors of both the COPD and the acute severe asthma groups of patients

Variables	Acute severe asthma (N = 7)	COPD (N = 17)	*P* value
DSF	0.4 ± 0.08	0.43 ± 0.14	0.506
Raw (cmH_2O/l/s)	4.2 ± 0.91	13.78 ± 21.77	0.004*
Cst (ml/cmH_2O)	38.78 ± 14.43	27.82 ± 9.18	0.035*
Cdyn (ml/cmH_2O)	28.02 ± 9.84	20.18 ± 6.45	0.030*
$ETCO_2$	63.9 ± 20.3	49.06 ± 17.95	0.090

Cdyn, dynamic compliance; COPD, chronic obstructive lung diseases; Cst, static compliance; DSF, dead-space fraction; $ETCO_2$, end-tidal carbon dioxide; *P < 0.05 = significant.

patients failed weaning and died. Similar findings were reported in the study and 31% (n = 4) failed weaning trials and finally died.

Our findings revealed that the mortality rate was lower among asthmatic patients (22.5%), whereas it reached 45.1% among the COPD patients. Williams *et al.* [23] has reviewed 28 publications on ventilation in asthma and found a range of mortalities from 0 to 38% (mean 13%). Mortality and morbidity figures seem to be decreasing in recent years with the avocation of controlled hypoventilation [19,20].

Patients with COPD who require MV generally have a greater dependence on ventilators than those with asthma. In addition to an excessive workload and the weakened pressure-generating capacity of the inspiratory muscles [24,25], tracheal obstruction may be an important factor prolonging ventilator dependence [26]. Data from weaning units describe another picture: 42% of the patients with COPD in a weaning unit became partially or completely ventilator dependent and 23% of them died there [25].

In the present study, it was found that logistic regression analysis showed a significant association between weaning failure and an older age. In the study of Ali *et al.* [27], the principal findings are that

(a) Both COPD-related hypercapnic respiratory failure and an inability to clear secretions were the most common causes of extubation failure in the elderly,
(b) The presence of underlying pulmonary disease, the need for MV for more than 4 days, and severe hypoalbuminemia are associated with an increased risk of extubation failure in the elderly, and
(c) Extubation failure carries a higher risk of morbidity and mortality.

Some patients can be weaned successfully from MV within hours, and for others, it may take longer, possibly days or weeks. The MV duration (lower mean ± SD in days) observed in the success group was 3.75 ± 1.8 compared with 8.56 ± 5.23 in the failure group of the current study. Logistic regression analysis also showed a significant association between weaning failure and prolonged MV duration (days) (odds ratio 1.51, P = 0.011) (Table 4). A prolonged MV, especially in COPD exacerbation patients, yields a poor chance for weaning [28,29].

The present study revealed that a heart rate less than 120, a rapid shallow breathing index (<105), and pH more than 7.32 were the most important predictors of successful weaning (Tables 2 and 4)

Physiologic parameters such as minute ventilation (<15 l), respiratory rate (<30), Vt (>325 ml), and maximum inspiratory pressure (<−15) have some utility in predicting the patient's ability to sustain spontaneous ventilation [30–32].

The PaO_2/inspired fraction of oxygen (PaO_2/FiO_2) ratio is still the most frequently used variable for evaluating the severity of lung failure and is included in the current definition of acute lung injury/acute respiratory distress syndrome [33]. From this PaO_2/FiO_2 ratio, the higher the FiO_2, the poorer the prognosis [34]. Despite its limitations, this ratio remains the most commonly used means of assessing the severity of lung disease. Despite this, our findings showed that the hypoxia index is not a dependable parameter for weaning as some of the failed weaning patients had PaO_2/FiO_2 more than 150. The oxygen index [(mean airway pressure ´ FiO_2 × 100)/ PaO_2] accounts better for the influence of ventilator pressures on the oxygenation value [6,35].

Assessment of respiratory mechanics

Because of the lack of physiological monitoring of the respiratory muscle function, the ventilator is set essentially by common practice and the effects of MV on the inspiratory effort and work of breathing are not directly measured [36].

In our study, the survivors had a higher dynamic and static compliance (22.47 ± 8.21 and 31.03 ± 11.78, respectively); also, they had a lower Raw (10.99 ± 18.7) than patients who failed weaning (Cdyn, 16.62 ± 7.57; Raw, 11.17 ± 6.01). Logistic regression analysis also showed that Cdyn is the most important one of the predictable parameters of weaning; this in addition to the significant correlation between Cdyn and $ETCO_2$ (Table 4 and Fig. 1).

Consistent with our results, many studies [30–32] reported that Cdyn more than 22 and static compliance more than 33 were associated with successful weaning. Depending on the tracheal tube size, the resistance may be as great as 10 cmH_2O ± 1 l ± 1 s, whereas compliance may be as small as 0.06 l ± 1.20 cmH_2O [10].

Our findings confirmed that COPD patients who survived had a significantly higher resistance and both lower static and Cdyn than asthmatic patients who survived (Table 5). Patients with COPD have an increased fixed expiratory airflow resistance. Alveolar attachments that normally keep the smaller airways open through radial traction are lost. This leads to airway narrowing and collapse. The greater airway collapse may also be due fundamentally to the destruction of the lung parenchyma (particularly in emphysema) as well as due to a loss of elastic rebound of the lungs [7].

In this study, the aim was to calculate the DSF and to demonstrate whether this parameter can be useful in determining the prognosis. Logistic regression analysis showed no significant association between the DSF and extubation failure, with odds ratio equal to 2.08 (95% confidence interval: 0.05–85.78, $P = 0.7$). We also found no significant correlation between DSF and pH, $PaCO_2$, and lung mechanics parameters. These findings do not contribute to the evaluation of the patient's condition, nor do they enable us to predict the length of artificial ventilation necessary for patients with acute respiratory failure due to chronic air flow obstruction.

Few studies have demonstrated the usefulness of simple biochemical and clinical markers that need only some calculations of the $PETCO_2$ concentration and DSF using a simple equation such as the Bohr used in our study [15,16].

In line with our study, Farah and Makhoul [22] concluded that the evaluation of DSF does not provide a factor in estimating the length of treatment for patients with acute respiratory failure due to COPD exacerbation. No other studies succeeded in utilizing the measurement of DSF in COPD exacerbation patients as a predictor for weaning from MV information [22]. Bousso *et al.* [37] reported that in a pediatric population receiving MV due to a variety of etiologies, the VD/Vt ratio was unable to predict the populations at risk of extubation failure or of reintubation.

In contrast to our findings, many studies demonstrated the utility of DSF measurement at the time of diagnosis in patients with acute respiratory distress syndrome and in patients with pulmonary embolism [15,38]. González-Castro *et al.* [39] found that logistic regression analysis showed a significant association between the VD/Vt and extubation failure, with odds ratio equal to 1.52 (95% confidence interval: 1.11–2.09, $P = 0.008$). More research is necessary to explore the reasons for differing patient management and outcomes.

In contrast, the appropriate use of $ETCO_2$ monitors as a noninvasive direct method of assessing $PaCO_2$ in ventilated patients remains unclear [22]. Through our results, clearly, logistic regression analysis showed no significant association between weaning failure and $ETCO_2$ (Table 4), and no correlation between arterial $PaCO_2$ and $ETCO_2$ (Table 3). However, Adel *et al.* [40] found a significant correlation between $ETCO_2$ and arterial PCO_2 throughout the period of MV in CB and emphysematous patients; hence, monitoring $ETCO_2$ provided a good noninvasive assessment of hypercapnic episodes during weaning from MV. Belpomme *et al.* [41] noticed that there was a wide variation in the gradient between $PaCO_2$ and $ETCO_2$ depending on the patient's condition, and this relationship does not remain constant over time. Many studies [28,41,42] concluded that $ETCO_2$ is a less accurate measure of $PaCO_2$ with Vt breathing and in patients with pulmonary disease.

Conclusion

Mechanical ventilatory support plays a crucial role in the management of severe airflow obstruction, especially when patients confront life-threatening respiratory failure.

$PaCO_2$-$ETCO_2/PaCO_2$ may be a useful serial measurement in the critically ill patient because all the necessary data are easily obtained and calculation is significantly simpler than for VD alv/Vt alv (Bohr–Fowler).

Weaning failure is commonly multifactorial in origin, and thus an index that assesses a single physiologic function may not be optimal. Indeed, this was shown by the data in the present and previous studies, which showed that indexes assessing the major determinants of the weaning outcome had limited diagnostic accuracy when used individually.

Also, it was concluded that DSF was unable to predict the populations at risk of extubation failure in patients with obstructive airflow diseases who were mechanically ventilated.

We limited our study population to medical patients, as it is generally more difficult to predict the weaning outcome in these patients than in surgical patients. Second, the technique of making the physiologic measurements needs to be stated clearly. More research is necessary to explore the reasons for differing patient management and outcomes.

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Conflicts of interest

There are no conflicts of interest.

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Automatic tube compensation versus pressure support ventilation as a weaning mode: does it make a difference?

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Background Automatic tube compensation (ATC) is one of the newer weaning modes that seem promising to improve the weaning process.

Objective To evaluate the benefit of ATC in hastening and improving the weaning process.

Patients and methods In a prospective randomized-controlled trial, all eligible patients of Assiut Chest Department who were mechanically ventilated were included during the period from April 2010 to March 2012. They were divided into two groups, 88 patients weaned by pressure support ventilation (PSV) and 78 patients weaned by ATC. The primary outcomes measure was the ability to maintain spontaneous breathing for more than 48 h after extubation and weaning duration.

Results A total of 166 patients were included; the mean age was 58.6 ± 12.3 years; males represented 70%. The weaning duration was shorter in ATC than in PSV (19.7 vs. 29.9 h, respectively). Also, ATC had a higher trend toward successful extubation than PSV (88.5 vs. 78.4%). Patients who underwent weaning by ATC had a nonsignificant trend toward simple weaning. Moreover, hospital mortality was less in ATC (ATC 15.4% vs. PSV 22.7%). However, the difference did not reach significance in all primary and secondary outcomes.

Conclusion In respiratory ICU patients, the weaning process can be usefully performed by ATC (at least as effective as PSV) but without significant hastening of the weaning process. All primary and secondary outcomes were potentially improved (weaning duration, extubation outcome, predictive value of ATC-assisted ratio of respiratory rate and tidal volume, number of spontaneous breathing trials, weaning category, reintubation rate, complications, and hospital mortality). *Egypt J Broncho* 2015 9:253–260

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Keywords: automatic tube compensation, pressure support ventilation, respiratory ICU, weaning

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Introduction

Weaning covers the entire process of liberating the patient from mechanical support and from the endotracheal tube (ETT) [1]. Weaning from mechanical ventilation (MV) is a challenge. Its prolongation is related to increased mortality [2]. Spontaneous breathing trial (SBT) is the major diagnostic test to determine whether patients can be successfully extubated. SBT tolerance is an evidence-based method to predict successful weaning [1]. The question of the most adequate way to perform SBTs is still unanswered [3].

With recent advances in technology, new features on ventilators like automatic tube compensation (ATC) have been developed. Several trials have been performed to evaluate the prediction of weaning outcome using this new feature [4–7].

The working principle of ATC is based on continuous calculations of tracheal pressure, whereby calculation is based on continuously measured flow and airway pressure (at the proximal end of the ETT) and tube-specific coefficients [8]. ATC compensates for the pressure drop across the endotracheal or tracheostomy tube by delivering exactly the amount of pressure necessary to overcome the resistive load imposed by the tube [9]. However, partial tube obstruction as a result of secretions and kinking might result in undercompensated ETT resistance with the ATC mode [8,10].

ATC has been shown to decrease the work of breathing (WOB) necessary to overcome ETT resistance more effectively than pressure support ventilation (PSV) or continuous positive airway pressure (CPAP). So, it can simulate spontaneous breathing without ETT, so it has been designated as 'electronic extubation'. Therefore, ATC is ideally suitable for use during the weaning period [11]. It is possible, however, that ATC could allow more marginal patients to tolerate a breathing trial, who then would develop ventilatory failure after extubation. This mode therefore theoretically can decrease the weaning duration and increase the

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probability of successful extubation by decreasing the WOB [12].

The aim of the study was to assess the value of ATC in predicting successful weaning and hastening the weaning process. To do this, we assessed extubation outcome after an SBT with ATC and compared it with PSV.

Patients and methods

Study design and ethics

The present prospective randomized-clinical trial study was conducted in Respiratory Intensive Care Unit (RICU), Chest Department, Faculty of Medicine, Assiut University Hospital, during the period from April 2010 to March 2012. The study design was approved by the Scientific Ethics Committee of Faculty of Medicine of Assiut University. After meeting the inclusion criteria, informed consent was obtained from the patient or the surrogate decision-maker.

Patients

Patients were eligible for enrollment (166 patients) if they admitted to respiratory ICU with respiratory disorders and required MV for more than 1 day. Exclusion criteria include patients who received noninvasive ventilation without subsequent intubation; patients who died before they were ready to wean; patients who experienced unplanned extubation before or during the weaning process; age less than 18 years and patients with postarrest encephalopathy.

Baseline patient data

Full history was taken from the patient or their relatives. Full clinical examination also was observed on the day of ICU admission. Chest radiography, daily arterial blood gases, and full laboratory assessment were carried out. Illness severity and expected mortality were measured on the day of ICU admission by Acute Physiology and Chronic Health Evaluation (APACHE) II score [13] and the Simplified Acute Physiology Score (SAPS) II [14]. Moreover, the prospectively collected data included reasons for ICU admission according to a predefined list of medical diagnoses, amount of sputum, ETT diameter, duration of hospitalization, and use of sedative and its duration.

Procedures

Initiation of mechanical ventilation

All included patients (166 patients) were intubated using ETTs of size 7.0–8.0 mm. Ventilation was performed with the Puritan–Bennett 840 ventilator. Patients were adjusted on synchronized intermittent mandatory ventilation (Nellcor Puritan-Bennett 840 ventilator, Florida, USA), volume controlled mode except for patients with severe asthma and acute respiratory distress syndrome (ARDS), who were adjusted on pressure controlled mode (synchronized intermittent mandatory ventilation, pressure control) as a lung protective strategy.

Weaning from mechanical ventilation procedure

The procedure of weaning from MV was considered as early as possible. Patients who were receiving MV more than 24 h underwent a daily screen of subjective and objective indices for assessment of readiness to wean. Weaning was conducted in 166 patients, according to the current statement of ERS, ATS, ESICM, SCCM, and SRLF [1].

The process of SBT

Usually SBT was conducted early in the morning, when the patient was fully rested and fully conscious. The duration of the trials ranges between 30 and 120 min. Shorter time duration can be recommended for patients on the ventilator for less than 1 week and weaning success is expected, while longer duration trial is for patients who have previously failed weaning [15].

Modes of SBT: The SBT was performed with either PSV or ATC. In both groups, the patients breathed through the ventilator circuit with flow-triggering set at 3 l/min, the peak end expiratory pressure at 0–5 cmH_2O and FiO_2 less than or equal to 0.4. For patients who were weaned by PSV (88 patients), initial positive pressure support (PS) was 15 cmH_2O. Patients were extubated at PS of 8 cmH_2O, which is necessary to overcome increased airway resistance. The first trial was usually conducted by rapid decline of PS, while subsequent trials were conducted by rapid or gradual reduction of support [1]. PS was lowered by 2–4 cmH_2O based on respiratory parameter, circulation, and patient response. In the ATC group (78 patients), the size of the ETT is entered into the ventilator software and the patients breathe through the ventilatory circuit with inspiratory ATC set at 100%. Patients who failed the first SBT underwent all subsequent SBTs with the same SBT method.

Monitoring during SBT

Patients should be subjectively observed for dyspnea, fatigue, anxiety, and distress. The criteria for passing an SBT include good respiratory pattern, adequate gas exchange, hemodynamic stability, and subject comfort [1]. Arterial blood gases were done at the

end of the SBT. Tolerance to SBT was continuously evaluated. Ventilatory data were recorded at the end of the SBT, including tidal volume, respiratory rate, RR/TV (breaths/min/l), and the integrative weaning index (IWI). IWI equals to static compliance of the respiratory system (Cst, rs)×arterial oxygen saturation (SaO_2)/RR/TV ratio [16]. Values were displayed on the ventilator and we used the average of three breaths.

Signs of a low trial tolerance (SBT failure) included spontaneous respiratory rate more than 35/min, heart rate more than 140/min (or ≥20% change), systolic blood pressure more than 180 mmHg or less than 90 mmHg, PaO_2 less than or equal to 60 mmHg or SaO_2 less than 90% on FiO_2 less than or equal to 0.4, pH less than or equal to 7.32 or a decrease in pH more than or equal to 0.07, $PaCO_2$ more than 50 mmHg or an increase in $PaCO_2$ more than 8 mmHg, RR/TV more than 105 breaths/l, worsening of respiratory distress, deterioration of the neurological status, including psychomotor agitation requiring sedation and life-threatening cardiovascular alterations [1].

Fate of SBT

Patients in whom the SBT was successful were then extubated. Patients who passed the first SBT and extubated successfully (n = 89) were considered as simple weaning. If one or more signs of poor procedure tolerance were observed during the trial, the patient was considered difficult-to-wean (n = 59) and full ventilatory support was immediately recommended to allow muscle rest. In such patients, the same procedure of weaning was repeated the next day, if permitted by the patient's clinical condition, following the same protocol. Patients who fail at least three weaning attempts, or require more than 7 days of weaning after the first SBT were considered prolonged weaning (n = 18). If the patient could not be disconnected from MV after several attempts without positive evolution of the weaning process, a tracheostomy (n = 11) was considered. The final decision to extubate or to do tracheostomy was made by the physician in charge.

Weaning procedure was considered successful (138 patients) when the unassisted spontaneous breathing is sustained for 48 consecutive hours without respiratory distress, with pH more than 7.35 and PaO_2 more than 60 mmHg in a patient breathing through a mask at FiO_2 less than or equal to 0.6. The total weaning duration was calculated as the days between the time when a patient was first ready to wean and the time when a patient was successfully weaned for the last time [17].

Weaning failure (inability to tolerate spontaneous breathing without ventilatory support) was defined as:

(a) Failed SBT;
(b) Reintubation and/or resumption of ventilatory support following successful extubation for more than 2 days after weaning; and
(c) Death within 48 h following extubation [18].

Outcome variables

The primary outcome measures are weaning duration and successful extubation. The secondary outcome measures are duration of MV, days ventilated before start of weaning, number of SBT, failure of first SBT, weaning categories, length of ICU stay, length of hospital stay, reintubation rate, need of noninvasive ventilation after extubation and its duration, hospital mortality, occurrence of complication arising during the course of the MV, and ICU stay (including pneumonia, ARDS, shock, sepsis, barotrauma, major arrhythmia, renal failure, electrolyte disturbance, deep venous thrombosis, and stress ulcer). In addition the predictive value of ATC-assisted RR/TV was also evaluated.

Statistical analysis

Data were recorded to statistical package for social science, version 21 (IBM Inc., Armonk, New York, USA). Data were described using mean ± SD or frequencies and percentage accordingly if they are quantitative or qualitative, respectively. A P-value was done between both ATC and PSV group and the value of less than 0.05 was considered significant. Nonparametric tests were used in the current study as the Mann–Whitney test (equivalent to independent Student's t-test in parametric tests) and the χ^2-test.

Results

During the study period, 247 patients were intubated and fulfilled the inclusion criteria. Among them, 166 patients met the criteria of weaning, 88 were weaned from MV by PSV mode (PSV group) and 78 were weaned by ATC mode (ATC group). The course and outcome are summarized in Fig. 1.

No statistically significant difference was found between the groups in terms of sex, age, BMI, ever cigarette smoker, previous hospitalization, APACHE II score, SAPS II score, need for sedation more than 24 h, and size of ETT. The only significant variable between both groups was the type of respiratory failure necessitating intubation and MV. The study included 17 patients with acute respiratory failure (12 asthma, three ARDS, two pulmonary embolism) and 149 patients with chronic respiratory failure (120 chronic obstructive pulmonary disease, 13 post-tuberculosis sequelae,

seven obesity hypoventilation syndrome, five ARDS, and four others). Patients with acute respiratory failure were more in the PSV groups, while patients with chronic respiratory failure were more in the ATC groups (Table 1).

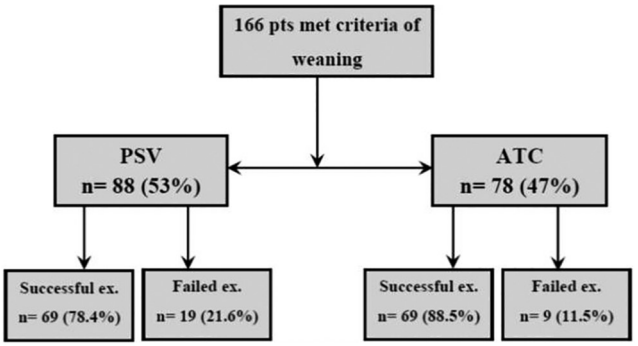
The respiratory and hemodynamic characteristics before the start of weaning according to the method of weaning are shown in Table 2. No statistically significant difference was determined between the groups in terms of vital signs and blood gas parameters.

The characteristics at the end of the first SBT are shown in Table 3. No significant differences were identified between the ATC and PSV groups in any parameter studied at the end of the first SBT. In the ATC group, improvement of exhaled tidal volume (4.96 vs. 4.35 ml/kg), RR/TV (104 vs. 120) and IWI (53 vs. 51) was observed as compared with the PSV group.

We evaluated the role of ATC to improve the predictive value of RR/TV and integrated weaning index in predicting successful outcome as shown in Table 4. Both ATV-assisted RR/TV and IWI were significantly efficient in predicting successful extubation.

Comparison between the groups in terms of weaning outcome is presented in Table 5. Duration of MV, duration of weaning, and the number of SBT were less in ATC than in PSV with no significant difference. In the ATC group, 69 of 78 patients (88.5%) tolerated the breathing trial and underwent successful extubation, compared with 69 of 88 (78.4%) in the PSV group; however, this observed difference was not significant. However,

Fig. 1



The course and outcome of patients in PSV and ATC groups. ATC, automatic tube compensation; PSV, pressure support ventilation.

Table 1 Demographic data and baseline difference between PSV and ATC groups

Parameter	Total (*n* = 166)	PSV group (*n* = 88)	ATC group (*n* = 78)	*P*-value
Sex: male/female	116/50	58/30	58/20	0.24
Age (years)	58.63 ± 12.26	56.86 ± 12.63	60.62 ± 11.58	0.49
BMI (kg/m^2)	26.84 ± 4.53	26.96 ± 4.86	26.71 ± 4.15	0.73
Ever cig. smoker	99 (59.6)	50 (56.8)	49 (62.8)	0.43
Hospitalization last year	0.87 ± 0.88	0.88 ± 0.86	0.86 ± 0.86	0.91
Type for respiratory failure				
ARF	17 (10.2)	13 (14.8)	4 (5.1)	
CRF	149 (89.8)	75 (85.2)	74 (94.9)	0.035*
APACHE II	22.42 ± 4.42	22.14 ± 4.89	22.73 ± 3.84	0.38
SAPS II	38.41 ± 8.84	39.38 ± 9.4	37.33 ± 8.1	0.13
Use of sedative>24 h	67 (40.4)	36 (40.9)	31 (39.7)	0.88
ETT size (mm)	7.49 ± 0.13	7.49 ± 0.14	7.49 ± 0.11	0.72

Continuous data are presented as mean ± SD, whereas categorical variables are presented as frequency and %; APHCHE II, acute physiology and chronic health evaluation; ARF, acute respiratory failure; ATC, automatic tube compensation; CRF, chronic respiratory failure; ETT, endotracheal tube; ever cig. smoker, exsmoker+current smoker; PSV, pressure support ventilation; SAPS II, simplified acute physiology score; *Significant difference.

Table 2 Vital signs and blood gases at the start of weaning trial

Parameter	Total (*n* = 166)	PSV group [*n* = 88 (53%)]	ATC group [*n* = 78 (47%)]	*P*-value
Heart rate (beats/min)	88.46 ± 14.77	90.63 ± 16.43	86.03 ± 12.28	0.075
Mean BP (mmHg)	85.6 ± 19.86	83.19 ± 19.53	88.31 ± 20.01	0.098
Respiratory rate (breaths/min)	25.55 ± 4.39	26.09 ± 4.51	24.94 ± 4.2	0.09
Temperature (°C)	37.15 ± 0.53	37.11 ± 0.52	37.18 ± 0.54	0.12
pH	7.46 ± 0.05	7.46 ± 0.05	7.45 ± 0.06	0.83
$PaCO_2$ (mmHg)	51.8 ± 10.01	51.3 ± 10.73	52.36 ± 9.16	0.49
PaO_2/FiO_2	210.93 ± 49.76	210.85 ± 52.56	211.01 ± 46.75	0.98
SaO_2	95.83 ± 2.27	95.75 ± 2.41	95.91 ± 2.13	0.65

ATC, automatic tube compensation; BP, blood pressure; PSV, pressure support ventilation.

Table 3 Parameters of weaning at the end of first SBT

Parameter	Total (*n* = 166)	PSV group (*n* = 88)	ATC group (*n* = 78)	*P*-value
Heart rate	94.33 ± 16.56	95.48 ± 17.94	93.02 ± 15.21	0.26
Respiratory rate (breaths/min)	29.84 ± 9.5	30.11 ± 7.16	29.53 ± 11.63	0.69
Tidal volume (ml/kg)	4.63 ± 2.9	4.35 ± 1.56	4.96 ± 3.88	0.17
RR/TV	112.2 ± 59.28	119.56 ± 65.25	103.97 ± 50.9	0.09
IWI	52.23 ± 42.27	51.39 ± 45.34	53.17 ± 38.79	0.79
pH	7.42 ± 0.15	7.43 ± 0.07	7.41 ± 0.22	0.45
$PaCO_2$ (mmHg)	56.37 ± 11.36	56.72 ± 12.58	55.97 ± 9.86	0.67
PaO_2 (mmHg)	72.23 ± 15.25	72.82 ± 18.09	71.58 ± 11.3	0.59
PaO_2/FiO_2	179.81 ± 36.26	179.6 ± 42.6	180.04 ± 27.69	0.94
SaO_2	93.21 ± 42.27	92.86 ± 3.88	93.6 ± 2.59	0.15

ATC, automatic tube compensation; IWI, integrated weaning index; PSV, pressure support ventilation; RR/TV, ratio of respiratory rate and tidal volume; SBT, spontaneous breathing trial.

Table 4 Assisted RR/TV and IWI in predicting successful extubation

Parameter	Successful extubation	Failed extubation	*P*-value
PSV-assisted RR/TV	106.54 ± 59.38	166.87 ± 65.143	0.000*
ATC-assisted RR/TV	96.88 ± 46.89	158.33 ± 49.83	0.000*
PSV-assisted IWI	57.74 ± 46.96	28.33 ± 29.78	0.002*
ATC-assisted IWI	57.08 ± 39.49	23.23 ± 9.17	0.000*

ATC, automatic tube compensation; IWI, integrated weaning index; PSV, pressure support ventilation; RR/TV, ratio of respiratory rate and tidal volume; SBT, spontaneous breathing trial, *Significant difference.

31 patients failed their first SBT in ATC compared with 46 patients in PSV. A total of 30 patients (18.1%) required reintubation: 12 (15.4%) in the ATC group and 18 (20.5%) in the PSV group. There is no significant difference between both groups as regard failure of first SBT, successful weaning, and need of noninvasive ventilation after extubation. No significant difference existed between the ATC and PSV groups regarding weaning categories. However, patients who underwent weaning by PSV had a higher trend toward difficult and prolonged weaning, while patients who underwent weaning by ATC had a higher trend toward simple weaning.

Length of stay, complications, and mortality outcome are demonstrated in Table 6. Hospital-acquired pneumonia was less frequent with ATC versus PSV (12.8 vs. 20.8%, respectively). There was no significant difference in terms of occurrence of hospital-acquired pneumonia or number of complications. Patients weaned by ATC had a nonsignificant trend toward lower ICU and hospital mortality.

Discussion

ATC is a newly developed mechanical ventilatory support method to overcome respiratory work produced by endotracheal resistance.

As regards demographic and baseline data, no significant difference between both ATC and PSV groups was found in term of age, sex, BMI, smoking history, previous hospitalization, APACHE II score, SAPS II score, proportion of patients who required sedation for more than 24 h, and size of ETT. Patients weaned with ATC were compared with patients weaned with PSV in terms of heart rate, mean blood pressure, respiratory rate, and axillary temperature, measured at the start of weaning with no significant difference being found. Also, blood gases variables were not significantly different between both groups. However, patients with acute respiratory rate were more weaned by PSV than ATC ($P = 0.035$). However, the determined statistical significance was of minimal clinical importance, since all other parameters had no significant difference between both groups including APACHE II and SAPS II. So, we can propose that there were no significant differences in baseline characteristics between the two groups. This finding suggests that both modes of weaning (ATC vs. PSV) can be conveniently compared with each other in terms of weaning course and outcome and also regarding the fate of extubation, length of stay, the occurrence of complications, and mortality rate [7].

Moreover, no significant difference was observed in terms of characteristics at the end of first SBT between both groups. These results are consistent with Figueroa-Casas and colleagues, who posted that RR/TV ratio and PaO_2/FiO_2 had no significant difference between ATC group and CPAP group. Selek and colleagues reported that there was no significant difference regarding the respiratory rate and SaO_2 over the course of the study period between ATC and T-piece. On the other hand, Haberthur and colleagues stated that there were significant differences between both groups in respiratory rate, tidal volume, and RR/TV ratio. We also found that the predictive value of ATC-assisted RR/TV and IWI was improved in predicting

Table 5 Weaning course and outcome

Parameter	Total (*n* = 166)	PSV group (*n* = 88)	ATC group (*n* = 78)	*P*-value
Duration MV before weaning (days)	3.37 ± 1.92	3.49 ± 2.18	3.23 ± 1.59	0.26
Duration of MV (days)	4.33 ± 2.87	4.6 ± 3.17	4.01 ± 2.48	0.39
Duration of weaning (h)	25.11 ± 38.31	29.93 ± 42.84	19.68 ± 31.85	0.08
Number of SBT	1.76 ± 1.03	1.84 ± 1.08	1.67 ± 0.97	0.28
Failure of first SBT [*n* (%)]	77 (46.4)	46 (52.3)	31 (39.7)	0.07
Successful extubation [*n* (%)]	138 (83.1)	69 (78.4)	69 (88.5)	0.08
Reintubation [*n* (%)]	30 (18.1)	18 (20.5)	12 (15.4)	0.26
Need of NIV after extubation [*n* (%)]	95 (57.2)	46 (52.3)	49 (62.8)	0.17
Duration of NIV (days)	1.28 ± 1.7	1.09 ± 1.55	1.49 ± 1.84	0.13
Weaning category [*n* (%)]				
Simple weaning	89 (53.6)	42 (47.7)	47 (60.2)	0.11
Difficult weaning	59 (35.5)	34 (38.6)	25 (32.1)	0.38
Prolonged weaning	18 (10.8)	12 (13.6)	6 (7.7)	0.16

ATC, automatic tube compensation; MV, mechanical ventilation; NIV, noninvasive ventilation; PSV, pressure support ventilation; SBT, spontaneous breathing trial.

Table 6 Length of stay, complications, and mortality outcome

Parameter	Total (*n* = 166)	PSV group (*n* = 88)	ATC group (*n* = 78)	*P*-value
ICU stay (days)	8.67 ± 7.29	8.94 ± 7.71	8.37 ± 6.82	0.62
Hospital stay (days)	14.23 ± 8.24	13.76 ± 8.56	14.76 ± 7.89	0.44
HAP [*n* (%)]	28 (16.9)	18 (20.5)	10 (12.8)	0.14
Complication number	1.61 ± 1.82	1.8 ± 1.99	1.41 ± 1.58	0.17
ICU mortality [*n* (%)]	26 (15.7)	18 (20.5)	8 (10.3)	0.055
Hospital mortality [*n* (%)]	32 (19.3)	20 (22.7)	12 (15.4)	0.16

ATC, automatic tube compensation; HAP, hospital-acquired pneumonia; PSV, pressure support ventilation.

extubation outcome (P = 0.000 in both). Cohen and colleagues reported similar results.

The duration of MV and duration of MV before weaning were less in ATC than in PSV, but this observed difference did not reach statistical significance (P = 0.26 and 0.39, respectively); these results are consistent with those of Figueroa-Casas and colleagues, who reported similar results. Moreover, weaning duration and weaning trials were less in the ATC than in the PSV group (20 vs. 30 h and 1.7 vs. 1.8 weaning trials). However, this observed difference of about 10 h between the two groups did not also reach statistical significance (P = 0.08). These results are compatible with those of Figueroa-Casas and colleagues, who found similar results. However, Aggarwal and colleagues concluded that the duration of weaning was significantly shorter in the ATC group than in the PSV group in patients with severe neuroparalytic snake envenomation. Also, Selek and colleagues found weaning duration was significantly shorter in ATC versus T-piece (4.96 vs. 7.42 days, respectively); there results could not be evaluated objectively because of limited patient number.

We found a nonsignificant trend toward more failure of the first SBT in the PSV group than ATC (46 vs. 31% P = 0.07); this same finding was also reported in a study of ATC versus T-piece versus PS [8] and in two studies of ATC versus CPAP [5,19]. Moreover, in a similar study of ATC versus PSV of 7 cmH_2O a trend of better SBT tolerance with ATC was found [6].

We did not find a significant difference in extubation outcome between PSV and ATC (successful extubation rate of about 78 vs. 89%, respectively). This was consistent with Haberthur and colleagues, Cohen and colleagues, and Figueroa-Casas and colleagues, who concluded the same result with different numbers. This apparent discrepancy with a study of ATC versus PSV by Cohen and colleagues, which claimed a superior extubation outcome with ATC, merits further consideration. Moreover, we did not find a significant difference in reintubation rate between both groups (PSV 15% vs. ATC 20%). This was also compatible with Cohen and colleagues and Figueroa-Casas and colleagues. Also Selek and colleagues did not find significant differences between ATC and T-piece.

We also evaluated the need of noninvasive ventilation after extubation, either prophylactic or therapeutic, for treatment of postextubation respiratory failure (PSV 52% vs. ATC 63%). Our result demonstrated a nonsignificant difference in both groups in favor

of PSV in the need and duration of noninvasive ventilation. This was more than what was posted by Tallo and colleagues – that between 25 and 40% of patients have a respiratory distress after extubation. That is probably due to the chronic nature of the majority of our study patients. Moreover, patients who underwent weaning by PSV had a nonsignificant trend toward difficult/prolonged weaning, while patients who underwent weaning by ATC had a nonsignificant trend toward simple weaning. These variables were not evaluated between both groups in previous studies. ICU length of stay, complications including hospital-acquired pneumonia, ICU, and hospital mortality outcome demonstrated a nonsignificant difference in both groups in favor of ATC.

Some considerations should be clarified. First, the rate of passing of the first SBT was 53.6%, which is much lower than the range (58–74%) reported by other investigators with various SBT methods [19]. This can be explained by the nature of patients in our study as all patients had primary pulmonary cause of respiratory failure and the majority of patients had chronic respiratory failure (89.8%). COPD appears as an independent risk factor for increased duration of weaning and weaning failure with failure of first SBT rate reaching up to 61% [1]. Second, unsuccessful extubation rates in our study lie within the range 12–24%, as reported in previous studies [20]. Third, the reintubation rate (18%) in our study was slightly higher than the range (10–15%) reported by Thille *et al.* [21] but within the range (6–23%) reported by Ferrer *et al.* [22].

Despite the strong theoretical advantages of ATC, most of the studies published to date did not prove superiority to other SBT methods. For ATC to be superior to other weaning modes, failure would need to frequently result from the imposed WOB rather than other causes. Only 10–20% of extubated patients fail extubation and require reintubation. Many of those result from upper-airway obstruction, excessive secretions, inadequate cough, or abnormal mental status – a combination of factors that compromise the patient's ability to protect the airway and have little to do with the SBT ventilation mode. Of the remainder, it is likely that only a minority can be attributable to excessive or insufficient support by PSV (which proposed to be avoided by ATC). Although the ideal level of PS varies widely, the typically used pressure range of 5–8 cmH_2O may actually prove adequate in most patients; this range may infrequently lead to either excessive or inadequate support [23]. The pressure delivered by ATC depends on the characteristics of the ETT [24]. ETT configuration changes and tracheal secretions can increase ETT resistance and decrease the ability of ATC to compensate for the increased respiratory workload [10]. Although ATC can be considered as a safe procedure, its use in clinical routine yet remains controversial [3].

We agree with Frutos-Vivar and Esteban, who stated that despite the appropriate results obtained in the studies published to date (including our result), more researches are needed, involving larger patient samples and, especially, patients with weaning difficulties, to be able to recommend ATC as the method of choice in performing weaning trial.

Conclusion

In a respiratory ICU population, ATC was safe, reliable, and can be reasonably used for weaning trials. ATC confers a potential benefit in weaning duration, weaning category, number of Ss, failure of first SBT extubation outcome, ICU length of stay, complication, and mortality rate. In addition, ATC improves the predictive value of RR/TV and IWI in predicting weaning success.

Although each variable of primary and secondary outcome was nonsignificantly improved by ATC, the observed differences were efficient and worthy. When we evaluate all these variables collectively, we can state that ATC might improve the weaning process.

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Conflicts of interest

There are no conflicts of interest.

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Evaluation of serum-soluble triggering receptor expressed on myeloid cells-1 as a novel marker in the diagnosis of ventilator-associated pneumonia in adults

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Ventilator-associated pneumonia (VAP) remains the most common nosocomial infection in ICUs. VAP occurs in 10–20% of patients who are mechanically ventilated for more than 48 h. The interval between diagnosis and the availability of microbiological results is the period when clinicians would most benefit from a reliable biomarker that could provide an early indication of poor response. Serum-soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) belongs to the immunoglobin superfamily, and it has the advantage of being increased during infectious processes but not in noninfectious inflammatory conditions. The aim of this study was to assess the value of serum level of sTREM-1 as a diagnostic biomarker for VAP in comparison with commonly used indicators, including procalcitonin (PCT) and C-reactive protein (CRP). This study was carried out on 60 participants. They were divided into two groups: group I included 30 adult patients with clinically suspected VAP, and group II included 30 ICU ventilated patients of the same age group without VAP and free of other infectious diseases who served as the control group. They were selected from the ICUs of Chest and other Departments, Tanta University Hospitals, during the period from January 2014 until September 2014. The present study revealed that serum level of sTREM-1 was significantly higher in patients with VAP in comparison with the control group. It was also concluded that serum level of sTREM-1 was significantly higher in VAP patients with bacterial growth culture results than in VAP patients with no growth culture results. A diagnostic cutoff value greater than 110 pg/ml with a sensitivity of 87.5%, specificity of 83.3%, positive predictive value of 95.5%, and negative predictive value of 62.5% of serum sTREM-1 level could discriminate positive culture results from negative culture results in VAP patients, which were higher than that of serum levels of PCT and CRP. It was concluded that serum level of sTREM-1 was significantly higher in VAP patients in comparison with non-VAP patients and it showed the highest sensitivity and specificity (87.5 and 83.3%, respectively) in differentiating between VAP patients with bacterial growth culture results and VAP patients with no growth culture results compared with PCT and CRP levels, thus rendering serum level of sTREM-1 a novel diagnostic marker for VAP. *Egypt J Broncho* 2015 9:261–268

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Introduction

Ventilator-associated pneumonia (VAP) is a type of nosocomial pneumonia that occurs in patients who receive mechanical ventilation. VAP is usually acquired in the hospital-setting ~48–72 h after mechanical ventilation [1].

It carries a mortality of 10–50%. VAP prolongs patients' mean ICU stay by an estimated 6.1 days and results in high financial costs [2].

The associated organisms and their resistance patterns vary on the basis of the patient group and hospital setting [1]. Most cases of VAP are caused by bacterial pathogens that normally colonize the oropharynx and gut, or that are acquired through transmission from healthcare workers, from environmental surfaces, or from other patients. Common pathogens include *Pseudomonas* spp. and other highly resistant gram-negative Bacilli, Staphylococci, the *Enterobacteriaceae*, Streptococci, and *Haemophilus* spp. [3].

A diagnosis of VAP is suspected when the patient has a new infiltrate on chest radiograph along with fever and raised leukocyte count after 48 h of invasive mechanical ventilation. To diagnose a VAP episode, the presence of clinical signs of pneumonia plus microbiologic confirmation by quantitative cultures is required, and it can be obtained from either tracheal aspirate, bronchoalveolar lavage (BAL) fluid, mini-BAL, or protected brush specimens [4].

Clinical Pulmonary Infection Scoring (CPIS) was introduced to improve the specificity of clinical diagnosis. CPIS combines clinical, radiological, physiological, and microbiological (culture of tracheal

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aspirate) data into a single numerical value. However, recent studies suggest that CPIS has a lower specificity for the diagnosis of VAP compared with quantitative culture of BALF [5].

Quantitative culture of BALF retrieved by means of direct bronchoscopic methods yields the best sensitivity and specificity to diagnose VAP and can differentiate true infection from colonization or inflammation. However, bronchoscopy is an invasive procedure and requires specialized skills [5].

Many biological markers have been studied in an effort to improve the rapidity and performance of current diagnostic procedures in VAP [6].

C-reactive protein (CRP) is used in clinical practice because of its greater availability, but it has limited abilities to distinguish sepsis from other inflammatory conditions [7].

Procalcitonin (PCT), a 116 amino acid propeptide of calcitonin, is a new marker that has been suggested for the diagnosis of invasive bacterial and fungal infections that lead to systemic inflammation. However, the usefulness of this marker in different clinical situations remains uncertain [8].

The triggering receptor expressed on myeloid cells (TREM-1) is a member of the immunoglobulin superfamily. Upon invasion of bacteria or fungi, tissues are infiltrated with neutrophils and monocytes that strongly express TREM-1. A soluble form of TREM-1 (sTREM-1) can be measured in various body fluids, possibly reflecting TREM-1 shed from the membranes of activated phagocytes [9].

Patients and methods

The present study was carried out in the Medical Microbiology & Immunology, Chest and Anesthesia Departments, Faculty of Medicine, Tanta University. It was conducted on 60 adult patients during the period from January 2014 until September 2014.

Patients in this study were divided into two groups

Group I included 30 adult ventilated patients with clinically suspected VAP.

Group II included 30 ventilated patients without VAP and free of other infectious diseases who served as the control group.

Demographic variables such as sex, age, together with patient's clinical data, risk factors for pneumonia, and antibiotic regimen were collected from patient's record after getting patient's consent and approval of the ethical committee.

Inclusion criteria

(1) Age more than 18 years.
(2) Evidence of new infiltrates on chest radiographs after 48–72 h of endotracheal intubation.
(3) Presence of at least two of the following:
    (a) Fever.
    (b) Increased white blood cell (WBC) count.
    (c) Purulent respiratory tract secretions.

Exclusion criteria

(1) Patients with pneumonia on admission or within 48 h of mechanical ventilation.
(2) Patients with acquired immunodeficiency syndrome.
(3) Patients with decrease in polymorphonuclear granulocytes (<500/μl).

Material used for bacteriological study

Clinical specimens

Both BALF and serum samples were taken from enrolled patients.

BALF was tested for possible common bacterial pathogens using the following:

(1) Gram-stained smear.
(2) Culture on different bacteriological media.
(3) Biochemical reactions.

Serum samples

They were taken from controls and clinically suspected patients with VAP under complete aseptic technique and centrifuged. Thereafter, the serum samples obtained were stored until processed. Human sTREM-1 and PCT were measured with enzyme-linked immunosorbent assay (ELISA) kit, whereas CRP was measured using the latex agglutination test.

Media used

In this study, the media used were dehydrated oxoid media. They were prepared and sterilized according to the manufacturer's instructions. The following media were used:

(1) Ordinary nutrient agar.
(2) Blood agar.
(3) Chocolate agar.
(4) MacConkey's agar.

Biochemical reaction tests

(1) Optochin sensitivity test (oxoid).
(2) Catalase test.
(3) Coagulase test.
(4) Oxidase test (oxoid).
(5) Citrate utilization test (oxoid).
(6) Urease test (oxoid).
(7) Indole test.
(8) Vogas, Proskauer reaction.
(9) Methyl-Red test.
(10) Bile solubility test.
(11) Sugar fermentation tests.

Detection of serum level of serum-soluble triggering receptor expressed on myeloid cells-1

The CUSABIO Human sTREM-1 ELISA kit is an in-vitro ELISA for the quantitative determination of human sTREM-1.

This assay used the quantitative sandwich enzyme immunoassay technique. Antibody specific for sTREM-1 had been precoated onto a microplate. Standards and samples were pipetted into the wells, and any sTREM-1 present was bound by the immobilized antibody. After removing any unbound substances, a biotin-conjugated antibody specific for sTREM-1 was added to the wells. After washing, avidin-conjugated horseradish peroxidase was added to the wells. Following a wash to remove any unbound avidin-enzyme reagent, a substrate solution was added to the wells and color developed in proportion to the amount of sTREM-1 bound in the initial step. The color development was stopped and the intensity of the color was measured at 450 nm.

All participants in this study were subjected to the following:

(1) Complete medical history with particular emphasis on the age, sex, underlying disease, chief reason for admission, time of onset of pneumonia, and use of mechanical ventilation during the ICU admission.
(2) Clinical examination and recording of the following: body temperature, tracheal secretions, chest radiograph, WBC counts, and CRP.
(3) Group I patients were subjected to bacteriological study of the BALF specimens to determine the causative organism of infection.
(4) Quantitative measurement of human sTREM-1 and PCT in serum using ELISA kits.

Results

This study was conducted on 60 mechanically ventilated patients. They were divided into two groups:

Group I included 30 adult ventilated patients with clinically suspected VAP [18 male (60%) and 12 female (40%)] with a mean age of 38.5 ± 18.8 years.

Group II included 30 ventilated patients without VAP and free of other infectious diseases who served as the control group [15 male (50%) and 15 female (50%)], with a mean age of 45.2 ± 17.6 years.

There were no significant differences between the two groups as regards age and sex distribution.

The most common causes of admission of the studied cases and controls were cerebral hemorrhage (16 cases, 27%) and fracture base (16 cases, 27%), followed by heart failure (eight cases, 13%), cardiogenic shock (eight cases, 13%), renal failure (six cases, 10%), and hemothorax (six cases, 10%) (Table 1).

Clinical presentation of the patients included in the study is shown in Table 2.

Clinical parameters of CPIS [4]:

Temperature	1 = ≥38.4≤38.9	2 = ≤36 or ≥39
White blood count	1 = < 4000 or >11 000	2 = Plus band forms ≥500
Secretions	1 = Moderate/large	2 = Purulent
Chest radiograph	1 = Diffuse/patchy infiltrate	2 = Localized infiltrate
PaO_2/FiO_2 ratio	0 = >240 without ARDS	2 = <240 without ARDS
Culture	0 = <10 000 bacteria or no growth	1 = >10 000 bacteria
Gram stain of direct smear 1 = Positive gram stain		

The frequency of different micro-organisms isolated from cases of positive culture (24 patients) with microbiologically confirmed VAP showed that the highest percentage of cases (30%) were infected with *MRSA* (nine cases) followed by *Pseudomonas aeruginosa* (six cases, 20%), whereas three cases (10%) were infected with *Escherchia coli*, three cases were infected

Table 1 Distribution of studied cases and controls based on the cause of admission

Cause of admission	Patient [*N* (%)]	Control [*N* (%)]	Total [*N* (%)]
Cerebral hemorrhage	9 (30)	7 (23)	16 (27)
Fracture base	9 (30)	7 (23)	16 (27)
Renal failure	3 (10)	3 (10)	6 (10)
Hemothorax	3 (10)	3 (10)	6 (10)
Heart failure	3 (10)	5 (17)	8 (13)
Cardiogenic shock 3 (10)		5 (17)	8 (13)
Total	30 (100)	30 (100)	60 (100)

with *Staphylococcus aureus* (10%), and three cases were infected with *Candida* (10%) (Table 3).

Serum level of CRP in VAP patients was 40.66 ± 55.5 and it was 29.22 ± 39.02 in the control group. Serum level of CRP had no significant difference between patients with VAP and controls ($t = 0.922$, $P = 0.360$) (Fig. 1).

Comparison of PCT level in the studied groups is shown in Table 4.

Serum level of PCT was found to be significantly higher in patients with VAP in comparison with the control group ($t = 3.25$, $P < 0.01$).

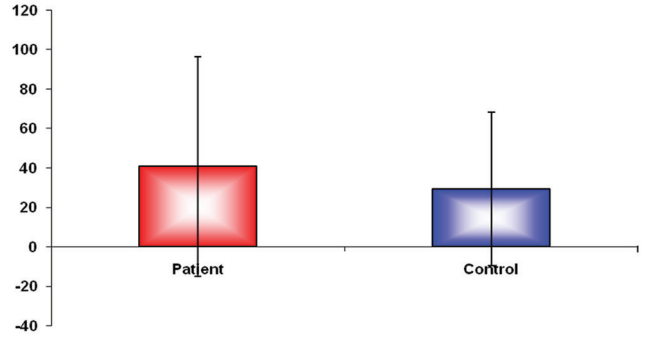
Mean serum level is sTREM-1 in VAP patients was 283.47 ± 187.78 and it was 146.14 ± 177.83 in the control group. Mean serum level is sTREM-1 was found to be significantly higher in patients with VAP in comparison with the control group ($t = 2.9$, $P < 0.01$) (Fig. 2).

There was no significant relation between culture result and serum level of CRP ($P = 0.801$). However, there was a significant relation between culture result and serum level of PCT, with a mean of 55.5 ± 35.5 in no growth result and a mean of 6.66 ± 9.523 in bacterial growth result ($P < 0.001$).

There was also a significant relation between culture result and serum level of sTREM-1, with a mean of 67.532 ± 49.974 in no growth result and a mean of 337.462 ± 169.455 in bacterial growth result ($P < 0.01$) (Table 5).

There was no significant difference between serum level of PCT and the type of causal micro-organism in positive culture results ($P = 0.272$). The highest range of PCT was in *Pseudomonas aeruginosa,* with a mean of 13.002 ± 13.518, and the lowest range of PCT was in *Staphylococcus aureus*, with a mean of 0.980 ± 0.220 (Table 6).

Fig. 1



C-reactive protein (CRP) in the two studied groups.

There was a significant difference between serum level of sTREM-1 and the type of causal micro-organism in culture results ($P < 0.001$). The highest range of sTREM-1 was in *Pseudomonas aeruginosa*, with a mean of 549.677 ± 107.680, and the lowest range of sTREM-1 was in *E. coli*, with a mean of 179.100 ± 6.398 (Table 7).

Table 2 Distribution of clinical parameters of clinical pulmonary infection score in the studied cases of ventilator-associated pneumonia

Items	CPIS	*N* (%)
Temperature	1	13 (43.33)
	2	17 (56.67)
White blood count	1	11 (36.7)
	2	19 (63.3)
Secretion	1	9 (30.00)
	2	21 (70.00)
Chest radiograph	1	24 (80.00)
	2	6 (20.00)
PaO_2/FiO_2 ratio	0	6 (20.00)
	2	24 (80.00)
Culture results	0	6 (20.00)
	1	24 (80.00)
Gram stain	0	15 (50.00)
	1	15 (50.00)

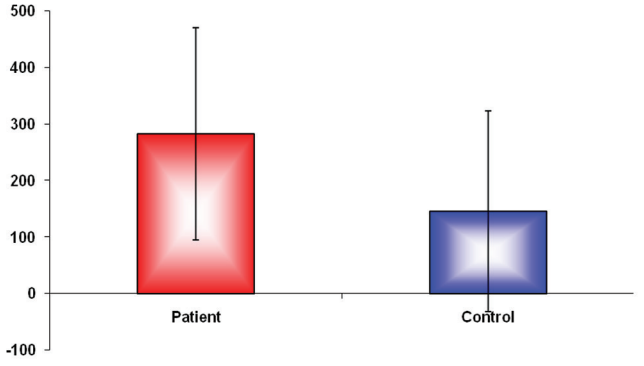
CPIS, clinical pulmonary infection score; PaO_2, arterial oxygen tension, FiO_2, fractional inspired oxygen.

Table 3 Distribution of studied cases based on bacterial culture results

Organism	Culture [*N* (%)]
No growth	6 (20.00)
*MRSA**	9 (30.00)
Pseudomonas aeruginosa	6 (20.00)
*E. coli**	3 (10.00)
Staphylococcus aureus	3 (10.00)
Candida	3 (10.00)
Total	30 (100.00)

*Methicillin resistant staph aureus.

Fig. 2



Serum-soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in the two studied groups.

Table 8 and Figs. 3 and 4 show cutoff point, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of sTREM-1 level to discriminate positive culture result from negative culture result. A diagnostic cutoff value greater than 110 pg/ml was found with a sensitivity of 87.5%, specificity of 83.3%, positive predictive value of 95.5%, and negative predictive value of 62.5%.

Table 9 and Fig. 5 show that sTREM-1 has the highest specificity (83.8%) together with positive predictive value (95.5%), negative predictive value (62.5), and accuracy (0.806) to discriminate positive culture result from negative culture result in cases of VAP.

Table 4 Comparison of serum procalcitonin levels in the studied groups

Groups	PCT		*t*-Test	
	Range	Mean ± SD	*t*	*P*-value
Patients	0.550–100.000	16.433 ± 26.168	3.257	0.002*
Controls	0.020–2.500	0.866 ± 0.759		

PCT, procalcitonin; *Statistically significant, $P < 0.05$.

Table 5 Relationship between culture result and serum levels of the three markers in cases of ventilator-associated pneumonia

Inflammatory marker	Culture (mean ± SD)		*t*-Test	
	No growth	Bacterial growth	*t*	*P*-value
CRP	45.900 ± 47.878	39.352 ± 58.215	0.254	0.801
PCT	55.508 ± 35.556	6.664 ± 9.523	6.176	0.000
sTREM-1	67.532 ± 49.974	337.462 ± 169.455	–3.815	0.001

CRP, C-reactive protein; PCT, procalcitonin; sTREM-1, soluble triggering receptor expressed on myeloid cells-1.

Table 6 Relationship between serum level of procalcitonin and type of causal microorganism in positive culture results in cases of ventilator-associated pneumonia

Culture	PCT		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
Pseudomonas aeruginosa	0.550–26.900	13.002 ± 13.518	1.40	0.272
MRSA	0.680–20.263	7.416 ± 9.332		
E. coli	2.690–2.990	2.827 ± 0.152		
Staphylococcus aureus	0.760–1.200	0.980 ± 0.220		
Candida	1.050–1.600	1.253 ± 0.302		

ANOVA, analysis of variance; PCT, procalcitonin.

Discussion

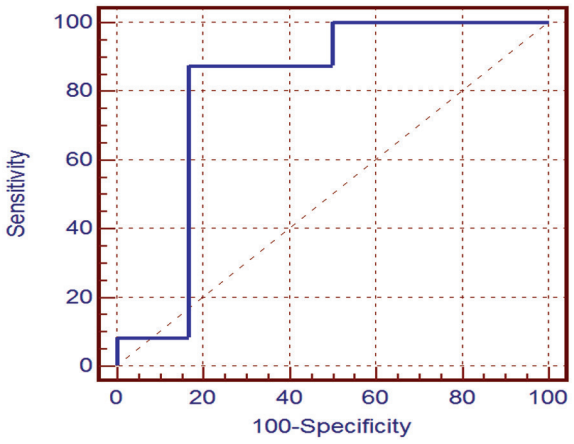
Biomarkers may facilitate clinical confirmation and aid differentiation of pulmonary from nonpulmonary sepsis. This would allow earlier, targeted antibiotic intervention, direct clinicians' decision-making for 'antibiotic use reduction' regimens, and potentially reduce selective pressure for multiresistant bacteria [6].

Some of the biomarkers that are used as an adjunct in the diagnosis of pneumonia include CRP, leukocyte count, immunoglobulins, and proinflammatory cytokines. There are other biomarkers whose importance is growing in the medical field. They are PCT and TREM-1 [10].

CRP is a protein produced in response to infection and/or inflammation and it is widely used in clinical tests to diagnose and manage patients with sepsis. Because the levels of CRP rise significantly during acute inflammation, this biomarker has been used for decades to indicate the presence of significant inflammatory or infectious disease, especially in pediatrics [11].

However, low specificity and inability to differentiate bacterial infections from noninfectious causes of inflammation makes CRP of limited diagnostic value [12].

Fig. 3



Receiver operating characteristic curve (ROC curve) of serum level of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) in positive and negative culture results.

Table 7 Relationship between serum level of soluble triggering receptor expressed on myeloid cells-1 and type of causal microorganism in positive culture results in cases of ventilator-associated pneumonia

Culture	sTREM-1		ANOVA	
	Range	Mean ± SD	*F*	*P*-value
Pseudomonas aeruginosa	456.000–728.060	549.677 ± 107.680	13.44	<0.001*
MRSA	57.120–310.000	217.551 ± 119.439		
E. coli	172.300–185.000	179.100 ± 6.398		
Staphylococcus aureus	376.130–390.000	383.710 ± 7.024		
Candida	375.000–390.000	384.880 ± 8.558		

ANOVA, analysis of variance; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; *Statistically significant, $P < 0.05$

PCT is synthesized by a large number of tissues and organs in response to invasion by pathogenic bacteria, fungi, and some parasites. At present, PCT levels have been used to guide empirical antibacterial therapy in patients with acute exacerbations of chronic bronchitis, community-acquired pneumonia, and sepsis. Moreover, PCT levels, along with standard clinical parameters, can assist in determining whether the patient's empirical antibacterial therapy is effective [11].

PCT can increase after trauma or surgery, particularly major abdominal surgery, cardiogenic shock, heat shock, immunotherapy such as granulocyte transfusion, and pancreatitis. PCT can also be elevated in renal impairment in the absence of infection. Given that PCT can be elevated in certain noninfective conditions, it is probably better used to rule out than rule in systemic bacterial infection [13].

Table 8 Receiver operating characteristic curve of serum level of soluble triggering receptor expressed on myeloid cells-1 in positive and negative culture results

ROC curve					
Accuracy	NPV	PPV	Specificity	Sensitivity	Cutoff
0.806	62.5	95.5	83.3	87.5	>110

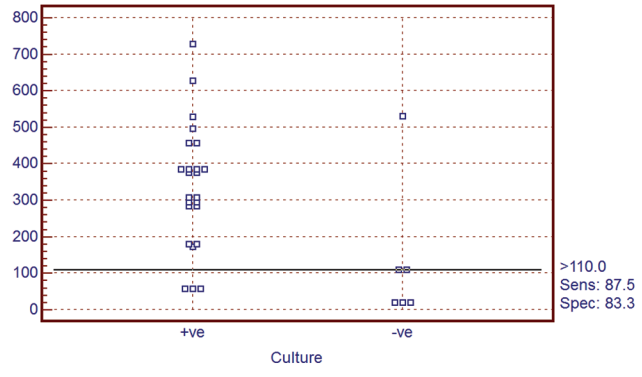
NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic.

Table 9 Comparison between the serum levels of the three markers in positive and negative culture results by receiver operating characteristic curve

ROC curve						
Inflammatory marker	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
sTREM-1	>110*	87.5	83.3	95.5	62.5	0.806
CRP	≤17.6*	75.0	50.0	85.7	33.3	0.486
PCT	≤20.26*	87.5	66.7	91.3	57.1	0.764

CRP, C-reactive value; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value; ROC, receiver operating characteristic; sTREM-1, soluble triggering receptor expressed on myeloid cells-1.

Fig. 4



Level of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) serum level, cutoff point, sensitivity, and specificity in positive and negative culture result.

The TREM-1 is a member of the immunoglobulin superfamily. Its expression on phagocytes is upregulated by exposure to bacteria and fungi. A soluble form of TREM-1 (sTREM-1) can be found in body fluids, such as plasma, pleural fluid, BALF, urine, and cerebrospinal fluid, which can be assayed by means of ELISA using commercial immunoassay kits. It has the advantage of being increased during infectious processes but not in noninfectious inflammatory conditions [11].

As regards positive culture results in VAP patients, this study showed that *MRSA* and *Pseudomonas aeruginosa* were the major isolates that were responsible for 30 and 20% of VAP cases, respectively, followed by *Escherichia coli*, *Staphylococcus aureus,* and *Candida albicans* each 10% of VAP cases.

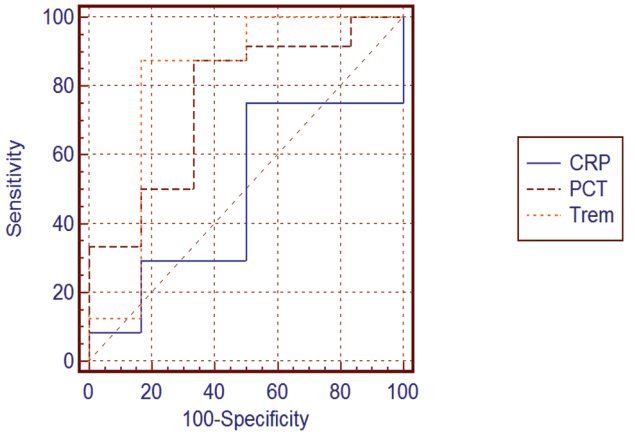
The results of Charles *et al.* [14] were compatible with our results, as they had found that *Pseudomonas aeruginosa* was the most common Gram-negative bacteria associated with VAP, followed by *Staphylococcus aureus*. In addition, Lee *et al.* [15] reported that methicillin-resistant Staphylococcus aureus (*MRSA*) was the most common gram-positive bacteria associated with VAP.

In contrast with our study, Harde *et al.* [4] reported that the most common organism was *Acinetobactor baumanni*.

This study showed that serum level of CRP has no significant difference between patients with VAP and controls ($P = 0.360$).

In agreement with our study, Oppert *et al.* [8] reported that CRP was not useful for VAP diagnosis. In addition, Linssen *et al.* [16] stated that CRP was not able to differentiate VAP patients from non-VAP patients.

Fig. 5



Comparison between the serum levels of the three markers in positive and negative culture results by receiver operating characteristic curve (ROC curve).

The findings of Povoa *et al.* [17] is in disagreement with the findings of our study; they showed that CRP has a good accuracy in the diagnosis of VAP in a population of ICU patients. However, the CRP concentrations included in the study for the nonseptic group were the values measured after 2 days of ICU stay and were compared with the leukocyte count and temperature on the day of ICU admission.

This study also showed that serum level of PCT is significantly higher in patients with VAP than in controls ($P = 0.002$).

This is in agreement with the findings of Duflo *et al.* [18], who reported that serum PCT was significantly increased in the VAP group compared with the non-VAP group. In contrast, Gilbert [19] said that there were no significant differences in the levels of PCT between patients with pulmonary infections and those without pulmonary infections. However, they could not exclude the possibility that some patients with true VAP were misclassified as not having pneumonia and recovered spontaneously.

As regards serum level of sTREM-1, this study showed that it is significantly higher in patients with VAP than in controls ($P < 0.001$).

In agreement with our study, Phua *et al.* [20] said that serum sTREM-1 levels were significantly higher in pneumonia and asthma patients than in controls. Moreover, Rivera-Chavez and Minei [21] said that measurements of sTREM-1 in plasma from patients in the surgical ICU may be a valuable tool for early distinction between infected and noninfected patients.

In contrast, Determann *et al.* [9] found that there was no relationship with development of VAP and serum sTREM-1. However, microbiological confirmation was carried out using nondirected bronchial lavage technique 'blind sampling'; thus, it is possible that some patients were misdiagnosed as having no pneumonia.

As regards the relation between culture result (bacterial growth and no growth) and serum levels of the three markers in cases of VAP, this study showed that, there was no significant relation between culture result and serum level of CRP ($P = 0.801$). There was a significant relation between culture result and serum level of PCT, with a mean of 55.508 ± 35.556 in no growth result and a mean of 6.664 ± 9.523 in bacterial growth result ($P = 0.000$). There was also a significant relation between culture result and serum level of sTREM-1, with a mean of 67.532 ± 49.974 in no growth result and a mean of 337.462 ± 169.455 in bacterial growth result ($P = 0.001$).

Delévaux *et al.* [22] reported that PCT values were more discriminative than WBC and CRP in distinguishing a bacterial infection from another inflammatory process.

Moreover, Ramirez *et al.* [23] found that, when comparing patients with VAP and nonconfirmed VAP, only PCT levels were significantly higher in patients with VAP, whereas CRP levels were not significantly different.

Porfyridis *et al.* [24] found that sTREM-1 levels were significantly higher in the pneumonia group than in the nonbacterial pulmonary disease group.

This study revealed a diagnostic cutoff value of 17.6 mg/l or less with a sensitivity of 75%, specificity of 50%, positive predictive value of 85.7%, and negative predictive value of 33.3% of CRP level to discriminate positive culture result from negative culture result.

Refaat *et al.* [25] analyzed the ability of CRP to discriminate between infection of bacterial origin and no infection. The optimal cutoff was 59 mg/l, with a sensitivity of 80%, specificity of 60%, positive predictive value of 86%, and negative predictive value of 71%.

This study also revealed a diagnostic cutoff value of 20.26 ng/ml or less with a sensitivity of 87.5%, specificity of 66.7%, positive predictive value of 91.3%, and a negative predictive value of 57.1% of PCT level to discriminate positive culture result from negative culture result.

Menéndez *et al.* [26] concluded that a cutoff value of 0.36 mg/dl for PCT to predict positive blood cultures showed a sensitivity of 85%, specificity of 42%, and negative predictive value of 98%.

Schuetz *et al.* [27] revealed that, when using the microbiological definition, at a cutoff value of 180 mg/dl, CRP had a high specificity of 86 and 100%, with a low sensitivity of 54 and 67% and concluded that high initial values of PCT and high peak levels of CRP do not *per se* point to underlying infection as the high increase in PCT and CRP rather reflects the nonspecific systemic inflammatory response due to the underlying disease and hypothermia than true bacterial infection.

The present study revealed a diagnostic cutoff value of more than 110 pg/ml with a sensitivity of 87.5%, a specificity of 83.3%, a positive predictive value of 95.5% ,and a negative predictive value of 62.5% of sTREM-1 level to discriminate positive culture result from negative culture result.

Huh *et al.* [28] obtained similar results as they studied 80 patients with suspected infectious pneumonia

whose chest radiographs revealed bilateral pulmonary infiltrations. The sTREM-1 concentration was significantly increased in patients with bacterial or fungal pneumonia compared with that in patients with viral pneumonia, atypical pneumonia, tuberculosis, or noninfectious inflammatory disease. The concentration of sTREM-1 was an independent predictor of bacterial or fungal pneumonia, and a cutoff value of more than 184 pg/ml yielded a diagnostic sensitivity of 86% and a specificity of 90%.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Sequential use of cryoextraction postelectrocautery for airway recanalization using fiberoptic bronchoscopy

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Background Airway obstruction presents with dyspnea, cough, hemoptysis, and atelectasis. Removing or decreasing the size of the obstructing lesions improves patient's symptoms and life quality.

Aim Assessing the efficacy and safety of sequential use of cryoextraction and electrocautery in achievement of airway patency using fiberoptic bronchoscopy (FOB).

Patients and methods This study was conducted at the Chest Medicine Department, Mansoura University, Egypt and included 22 patients with central airway obstruction (15 males and seven females) with a mean age of 50.5 ± 18.3 years. After etiologic diagnosis of airway obstruction, they were divided into two groups: group A (nonmalignant); eight patients and group B (malignant); 14 patients. All patients were subjected to sequential use of cryoextraction after electrocautery. Operable, unfit patients or patients with extraluminal obstruction were excluded. Clinical, radiological, functional, and bronchoscopic data were evaluated before and after FOB.

Results The improvement in performance scale was highly significant in group B ($P < 0.001$) and significant in group A ($P = 0.001$). Spirometric parameters improved in both groups but were highly significant in group B ($P < 0.001$). Radiological improvement occurred in four out of eight of group A and in three out of 14 of group B. FOB score improved in group B ($P = 0.003$) and was more significant in group A. The procedure was complicated with atrial fibrillation and hemoptysis in one case and postbronchoscopy hypoxemia in two cases with no deaths.

Conclusion Cryoextraction after electrocautery using FOB are effective, safe, easy, and cheap in achieving airway patency. *Egypt J Broncho* 2015 9:269–275

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Keywords: cryoextraction, electrocautery, lung cancer

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Introduction

Central airway obstruction from malignant or benign endobronchial tumor may lead to symptoms and respiratory failure. Therapeutic bronchoscopy offers an effective method in the palliation of lung cancer especially in alleviating dyspnea, controlling hemoptysis, and improving quality of life [1]. Endobronchial electrocautery is the application of heat produced by high-frequency electrical current to treat tumor tissue using special accessories such as coagulation probes, knives, and snares. It is considered as poor man's laser [2]. Endobronchial cryotherapy refers to the application of cold to destroy the tissue using cytotoxic effects of freezing. If the fiberoptic cryoprobe is applied to a tissue, it will stick to it and can be extracted *in toto* and may be used for tumor debulking [3].

Endoscopic treatment with fiberoptic bronchoscopy (FOB) by electrocautery and extraction provides an excellent outcome when performed by expert hands. Therefore such treatment is recommended in highly symptomatic patients or in those patients with significant bronchial obstructions [4].

Patients and methods

After approval of the local ethical committee of Faculty of Medicine, this prospective study was conducted at Chest Medicine Department, Mansoura University Hospitals, Egypt during the period from September 2012 to December 2013. Sixty-three patients with suspected central airway obstruction were enrolled in this study and 41 of them were excluded. Our study included 22 patients (15 males and seven females) with age range from 13 to 80 years and a mean age of 50.5 ± 18.3 years. Patients gave their signed written consents after detailed explanation of the protocol of the study. All the included patients were diagnosed to have tracheal, bronchial or tracheobronchial obstruction either with malignant or nonmalignant causes. They were divided into two groups according to the cause of airway obstruction: group A (nonmalignant) included eight patients with endobronchial obstruction by benign tumor, granulation tissue either post-

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tracheostomy or with foreign body and group B (malignant) included 14 patients with endobronchial obstruction by malignant tumors.

The obstructing lesions must be endoluminal in the trachea, main bronchi or lobar bronchi, and the margin between the lesion and the bronchial wall should be identified [5]. The excluded patients were 41; five were candidates for surgery, seven refused to be enrolled in the study, four with uncorrectable bleeding diathesis, five with intractable arrhythmia, two with a pacemaker, 12 with severe pulmonary dysfunction, and six with extraluminal compression on the airway were excluded from the study.

The endpoint of the procedure was a satisfactory response of airway opening or a maximum of three sessions of electrocautery and cryoextraction.

Methods

All patients were subjected to the following:

Clinical evaluation

With stress on dyspnea, cough, hemoptysis, performance status, quality of life, and lung collapsing before and 1 day after the last session of the procedure, dyspnea was evaluated according to American Thoracic Society (1999) [6]. Hemoptysis and cough were evaluated according to Walsh *et al.* [7]. Lung collapsing was evaluated according to Speiser and Spratling [8]. Performance status was done using Karnofsky performance scale (KPS) according to Muers [9] and evaluation of quality of life status was done according to Gridelli *et al.* [10].

Laboratory investigations

Complete blood count, liver function tests, kidney function tests, and coagulation profile were performed before FOB.

Radiological investigations

Chest radiography and computed tomography chest for staging and postobstruction effects as consolidation or collapse before and 1 day after the last session were performed.

Spirometry

Using smart pulmonary function test (PFT) CO with stress on FVC% and FEV_1% of the predicted and FEV_1/FVC ratio.

Fiberoptic bronchoscopy

For diagnosis and treatment: FOB (Pentax FB 19 TV; Hoya corporation, Tokyo, Japan), with porcelain tip and inner channel diameter of 3.2 mm was used after local instillation of 2% lidocaine and intravenous 5–10 mg midazolam 15 min before the procedure. Through oral route, diagnostic FOB was done for patients with suspected airway obstruction for biopsy and evaluation of the degree of airway obstruction according to Speiser [11] (Table 1). After diagnosis, the patient included in the study was subjected to therapeutic cryoextraction after electrocautery from one to a maximum of three sessions and the duration of session was a maximum of 45 min according the response to therapy and patient tolerability.

Number of sessions was individualized according to the response of the airway opening. The sessions were repeated every week for re-evaluation and application of therapy if needed.

(a) Endobronchial electrocautery was done using an electrocautery device WEM SS-100 MC, WEM equipamentos eletronicos litda: Riberao prelo (Brazil), using high-frequency electrocautery generator with blunt ended probe. It was applied in direct contact with the obstructing lesion for 3–4 s in each shot till debridement of the obstructing lesion, using energy of 70 W and utilizing the spray mode. The probe was applied to the lesion according to the site and pathology of the obstruction. If the obstruction was circumferential, the probe was applied in the four directions: at 3, 6, 9, and 12 o'clock then the rest was debrided. If the obstruction was total, the probe was applied firstly in the center of the obstructing lesion. If the obstruction was from one direction, the probe was applied to its pedicle. If the obstruction was by foreign body, debridement of the covering granulation tissue with electrocautery was followed by extraction with cryoprobe.

(b) Endobronchial cryoextraction was done by device (ERBE erbokryo ca; ERBE Elektromedizin GmbH, Tubingen, Germany). The flexible cryoprobe was used with outer diameter of 2.8 mm utilizing carbon dioxide as a cooling agent. The cryoprobe was advanced through the working channel of the bronchoscope till the site of the debrided tissue and freezing was switched on for 3–4 s and the probe within the FOB was extracted *in toto* catching the extracted tissue to its tip. In cases with foreign bodies impacted in the airways, electrocautery debridement was done first to explore the foreign body followed by cryoextraction

Table 1 Speiser score for airway obstruction (Speiser 1990) [11]

Trachea	>50% = 10	<50% = 6	<10% = 2
Main bronchus	>50% = 6	<50% = 3	<10% = 1
Lobar bronchus	>50% = 2	<50% = 1	
Atelectasis	2 per lobe		
Pneumonia	2 per lobe		

of the FB. The FOB was reintroduced more than one time after cryoextraction without the need for intubation, laryngeal mask or rigid bronchoscope.

The patients were monitored for 24 h for the possible complications as bleeding, hypoxemia, and pneumothorax.

Evaluation of response after therapy

(1) Subjective evaluation by recording the changes in patients' symptoms, performance status, and quality of life.
(2) Objective evaluation by bronchoscopic, radiologic, and functional evaluation as follows:
(a) Bronchoscopic evaluation: according to Speiser's obstruction scoring and achievement of the airway patency was evaluated according to response evaluation criteria in solid tumors (revised RECIST) (Table 2).
(b) Radiological evaluation was done with chest radiography and computed tomography scan.
(c) Functional evaluation: with spirometry measuring FEV_1, FVC, and FEV_1/FVC.

Statistical analysis

Data was analyzed using SPSS (Statistical Package for Social Sciences) version 15 (International Business Machines Corporation, New York, USA). Qualitative data was presented as number and percent. Comparison between groups was done by χ^2-test. Quantitative data was presented as mean ± SD. Student *t*-test was used to compare two groups. *P* value less than 0.05 was considered to be statistically significant.

Results

This prospective study included 22 patients with airway obstruction (15 males and seven females), with age range from 13 to 80 years and mean of 50.5 ± 18.3 years; 14 of them were of malignant etiology, 92.9% of malignant patients were non-small-cell lung cancer and eight patients of nonmalignant group were postintubation and tracheostomy tracheal stenosis in four cases, foreign body with granulation tissue was present in three (37.5%) cases, and benign tumor in one (12.5%). The trachea and main bronchus were obstructed in two (9.1%) patients, main bronchus in 10 (45.5%) patients, and lobar bronchus in 10 (45.5%) patients. Number of sessions of endobronchial therapy was from one to three. One session was applied to 14 out of 22 patients (63.6%), whereas two sessions were applied to seven (31.8%) patients and only one patient was treated with three sessions.

Figure 1 shows significant improvement in dyspnea, hemoptysis, cough, postobstructive pneumonia, and performance scale after electrocautery and cryoextraction in nonmalignant group (P = 0.015, 0.083, 0.024, 0.039, and 0.014), respectively.

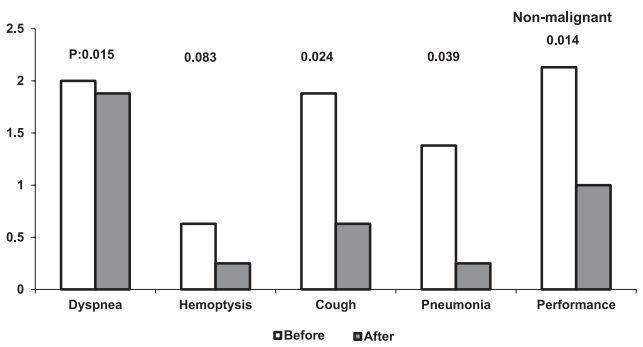
Figure 2 shows significant improvement in dyspnea, hemoptysis, cough, postobstructive pneumonia, and performance scale after electrocautery and cryoextraction in malignant group (group B) (P = 0.002, 0.02, 0.001, 0.317, and 0.001), respectively.

Figure 3 shows the effect of interventional bronchoscopy upon some spirometric parameters. All the measured variables were improved after the end of the procedure in malignant group more than

Table 2 Response evaluation criteria in solid tumors (revised RECIST) [12]

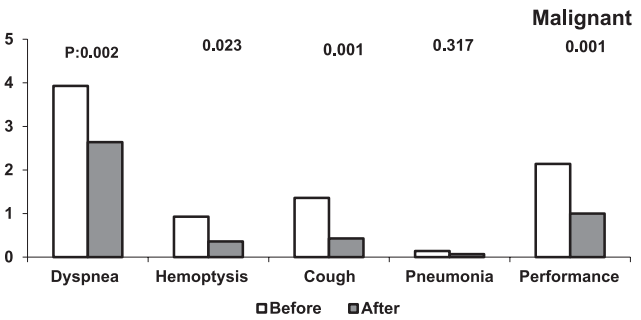
Good response	More than 50% increase in caliber of the lumen
Partial response	25–50% increase in the caliber of the lumen
No response	Less than 25% increase in the caliber of the lumen
Progressive disease	A 25% or more increase in the size of one or more measurable lesions or the appearance of new lesions

Fig. 1



Dyspnea, cough, hemoptysis, postobstructive pneumonia, and performance scores before and after treatment in nonmalignant group (group A).

Fig. 2



Dyspnea, cough, hemoptysis, postobstructive pneumonia, and performance scores before and after treatment in malignant group (group B).

nonmalignant group as the malignant patients had poor spirometric parameters before the study.

Table 3 shows that nonmalignant patients (four out of eight) showed radiological improvement as regard to chest computed tomography, meanwhile three out of 14 patients showed radiological improvement in malignant group.

Table 4 shows significant improvement (P = 0.003) in bronchoscopic score (Speiser's obstruction scoring system) after the end of procedure in malignant group with less significant improvement as compared with nonmalignant group (P = 0.012). Bronchoscopic response according to criteria for evaluation of therapeutic effects (revised RECIST) shows that all the patients in nonmalignant group showed favorable response with most of them and seven (87.5%) showed good response, whereas in malignant group 11 (78%) patients showed favorable response and five (35.7%) of them showed good response. Meanwhile only three (21.4%) patients showed no response.

Table 5 shows the incidence of complications after interventional bronchoscopy. There were no deaths, four (18.01%) patients only had complications; one had rapid atrial fibrillation, one bleeding, and two needed prolonged mechanical ventilation (Figs. 4 and 5) show the bronchoscopic view before and after the procedure.

Table 3 Collective data of chest computed tomography findings before and after the procedure in both groups separately

Lesion	Nonmalignant (group A)		Malignant (group B)	
	Before [*n* (%)]	After [*n* (%)]	Before [*n* (%)]	After [*n* (%)]
No abnormality detected (NAD)	—	4 (50)	—	1 (7.1)
Mass	—	—	6 (42.8)	8 (57.4)
Collapse	2 (25)	1 (12.5)	3 (21.4)	2 (14.2)
Mass + collapse	—	—	3 (21.4)	1 (7.1)
Pneumonia	3 (37.5)	—	—	—
Not done	3 (37.5)	3 (37.5)	2 (14.2)	2 (14.2)
Total	8 (100)	8 (100)	14 (100)	14 (100)

Table 4 Assessment of bronchoscopic score (Speiser's obstruction scoring system) and criteria for evaluation of therapeutic effects (revised RECIST) before and after the interventional procedures in both groups

Response	Group A: nonmalignant		Group B: malignant	
	Before	After	Before	After
Bronchoscopic Score Median (min–max)	5.5 (1–12)	1 (1–4)	3.5 (2–12)	1 (1–12)
P value	0.012		0.003*	
Therapeutic response [*n* (%)]				
Good	7 (87.5)		5(35.7)	
Partial	1 (12.5)		6 (42.8)	
No response	—		3 (21.4)	

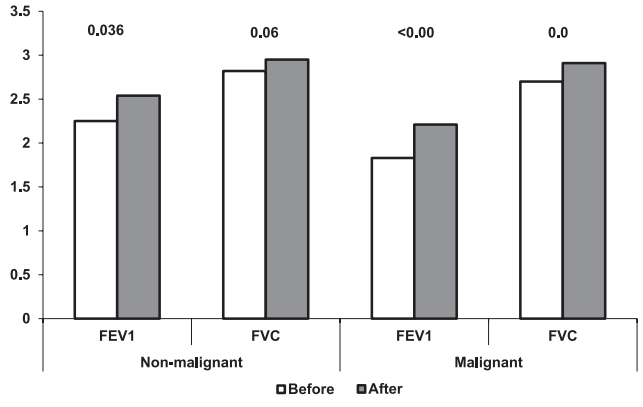
Table 5 The incidence of complications after the interventional bronchoscopic procedures among all the studied patients

Complications	*n* (%)
No complication	18 (81.8)
Hypoxemia	2 (9.1)
Arrhythmia	1 (4.5)
Bleeding	1 (4.5)
Mortality	0 (0)
Total	22 (100.0)

Discussion

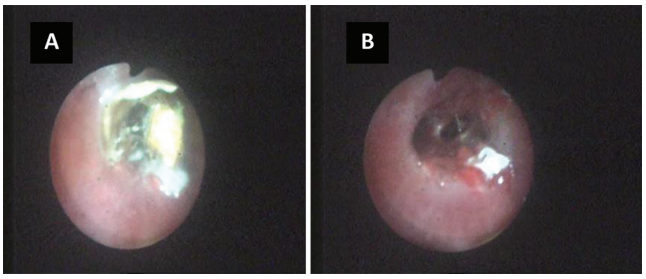
A variety of benign and malignant diseases may result in endoluminal lesions. Depending on the extent and location of an endoluminal lesion, patients may exhibit significant symptoms of dyspnea, cough, postobstructive atelectasis, and hemoptysis. Removing or decreasing the overall size of the endobronchial lesion may improve a patient's symptoms, quality of life, and life expectancy [13].

Fig. 3



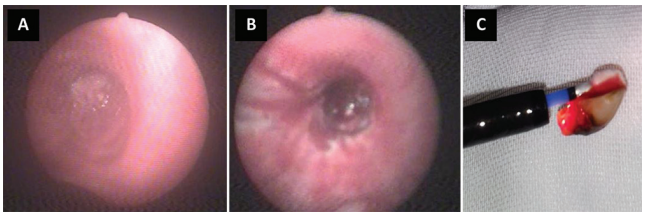
FEV_1 and FVC in both groups before and after treatment.

Fig. 4



35 year-old female presented with persistent dry cough for 1 week with history of aspiration of part of date, treated with one session of cryotherapy used: (a) fiberoptic bronchoscopy (FOB) snapshot before intervention showing the foreign body impacted at bronchus intermedius and (b) after intervention showing patent bronchus intermedius.

Fig. 5



A 63 year-old male, ex-smoker presented with progressive dyspnea and hemoptysis. Fiberoptic bronchoscopy (FOB) revealed a cauliflower mass totally obstructing left main bronchus which was diagnosed as adenocarcinoma, after two sessions of interventional bronchoscopy 1 week apart, both electrocautery and cryotherapy were used: (a) FOB snapshot before intervention showing endobronchial mass obstructing the left main bronchus, (b) after intervention showing recanalized left main bronchus, and (c) tip of FOB and the cryoprobe attached to a large piece of the extracted tumor.

Our study was planned to assess the efficacy and safety of sequential use of cryoextraction and electrocautery in achievement of airway patency which may provide answers for many questions about the impacts of interventional bronchoscopic modalities as palliative tools in patients with airway obstruction that may be caused by lung cancer and variety of nonmalignant causes.

Twenty-two patients, 15 males and seven females, whose age ranged from 13 to 80 years with a mean age of 50.5 ± 18.3 years were recruited in this study; current smokers account for 27.3% of the studied patients. The included patients were categorized according to the etiology of airway obstruction into eight patients with nonmalignant (group A) and 14 patients with malignant causes (group B).

Our study, included 14 patients with malignant airway obstruction (group B); 13 patients had bronchogenic carcinoma and one patient had lymphoma, whereas the nonmalignant group (group A) included eight patients, of which four patients were with secondary tracheal stenosis caused by prolonged endotracheal intubation or secondary to tracheostomy, one patient with endobronchial benign tumor, and three patients with foreign body with granulation tissue were included.

In our study, number of sessions ranged from 1 to 3, with most patients (14/22) required in one session. The duration of session was from 20 to 45 min with a mean of 30 min.

In our study, the percentage of improvement of dyspnea was significant as the degree of improvement in the mean grade of dyspnea was from 3.9 ± 0.9 to slight category of 2.4 ± 0.9. It was significant after intervention ($P < 0.0001$). A total of 59.1% of the patients improved from grade 4 and 5 to (50%) grade 1 and 2.

Dyspnea improved in 73% of patients in a study conducted by Sutedja and Postmus [14] who discussed various bronchoscopic techniques, in 67% of patients of a study conducted by Homasson [15] who studied endobronchial electrocautery, in 41.7% of patients in a study conducted by Mohammad [16] who studied cryotherapy, in only 37% of patients in the study of Walsh *et al.* [7] who studied cryotherapy, in 25% of patients in the study of Abdel Salam [17] who studied argon plasma coagulation for achievement of airway way patency, and in 50.5% of patients in the study of Asimakopoulos *et al.* [18] who studied cryotherapy for obstructive, symptomatic, and malignant endobronchial tumors.

In our study, there was a significant improvement in hemoptysis in 62.5% of patients with hemoptysis in nonmalignant group. In malignant group, there was an improvement in 53.3% of the patients. Compared with the result reported by Maiwand [19] there was an improvement in control of hemoptysis in 76.4% of symptomatic patients after cryotherapy, compared with Asimakopoulos *et al.* [18] who reported 61.9% of patients had reduction or cessation of hemoptysis after cryotherapy, and compared with the study by Abdel Salam [17] reported an improvement in hemoptysis in argon plasma coagulation (APC) treated cases was 83%. The cause of improvement of hemoptysis in patients with malignant or nonmalignant obstruction may be due to the coagulation of blood vessels traversing the obstructing lesions.

In our study there was a significant reduction of cough score in 95.3% of patients; these results were better than described by Maiwand and Asimakopoulos [20] who reported reduction of cough score in 69% of patients after treatment. In our study, cough intensity decreased significantly ($P < 0.0001$) in all symptomatic patients. In 11 (50%) patients cough disappeared completely. Compared with Hussein *et al.* [21] cough intensity decreased significantly ($P < 0.0001$) in all the patients.

The slight difference between the above studies and the current study may be due to the effect of usage of two modalities rather than one modality and number of the studied patients or the stage of the disease.

As regard to the KPS, there was a significant improvement from 60 to 80 in both groups A and B ($P < 0.001$ and $P = 0.001$), respectively when compared with that before treatment. These results were in agreement with Maiwand and Asimakopoulos [20] who reported improvement in Karnofsky scale treated with cryotherapy with significant improvement ($P < 0.05$) of KPS from 60 to 75 after treatment also; Asimakopoulos *et al.* [18] reported that group A included 172 patients

who underwent at least two sessions of cryotherapy showed change in KPS from 67.7 to 74.6 ($P = 0.001$). Group B included 157 patients who underwent only one session of cryosurgery showed a significant change in KPS from 67.6 to 73.6 ($P = 0.001$). These results are similar to that reported by Amer *et al.* [22] who assessed the effect of electrocautery and APC in management of endobronchial lesions which showed a significant improvement in performance scale ($P < 0.05$) and ($P < 0.01$) in both studied groups treated with electrocautery and APC, respectively. Improvement in KPS is an indication of improvement of quality of life, this may be due to reduction of tumor burden, also performance status is the one of the best factor for identifying individuals who can benefit from palliative treatment

As regard to functional response there was highly significant improvement ($P = 0.0003$) in spirometric PFTs (FEV_1%, FVC%, and FEV_1/FVC). All the measured three variables significantly improved; FEV_1% was the most markedly improved parameter ($P < 0.001$). In a study conducted by Sutedja *et al.* [23], PFTs were obtained in eight patients with two patients only having greater than a 15% improvement from baseline values. In a study conducted by Ledingham and Goldstraw [24] all the 11 patients improved symptomatically. FEV_1% improved in all 11 patients with varying degrees from 30 to 120% (mean 69%). A study conducted by Amer *et al.* [22] showed a significant improvement in FEV_1% ($P < 0.01$), in FVC% ($P = 0.05$), and in FEV_1/FVC ($P = 0.01$). A study conducted by Asimakopoulos *et al.* [18] showed an increase in the mean FEV_1% in both group A and B from 1.36 to 1.43 l ($P = 0.13$) and from 1.45 to 1.49 l ($P = 0.43$), respectively; the mean FVC% improved in both group A and B from 1.89 to 2.02 l ($P = 0.001$) and from 2.07 to 2.11 l ($P = 0.38$), respectively. The variation in results can be attributed to the type of patient illness (benign vs. malignant), the degree of airway obstruction, and the presence of concomitant diseases as chronic obstructive pulmonary disease.

A slight difference between the above studies and the current study may be due to the effect of usage of two modalities rather than one modality and number of the studied patients or the stage of the disease.

As regard to response score of bronchoscopy, response was assessed by Speiser's obstruction scoring system showing significant improvement in both A and B groups from 5.5 to 1 ($P = 0.012$) in group A and from 3.5 to 1 ($P = 0.003$) in group B. These results were similar to that reported by Safwat *et al.* [25] in which Speiser's obstruction score decreased from 5.20 before treatment to 2.47 ($P = 0.001$) after treatment. While Sindhwani *et al.* [26] studied role of endobronchial electrocautery in management of neoplastic central airway obstruction on seven cases on whom Speiser's obstruction scored 10.7 and improved to 6.7 after treatment.

Revised RECIST was used as another parameter for assessing therapeutic response after treatment; in our study most of the patients 12 (54.5%) showed good response, whereas seven (31.8%) patients showed partial response. Meanwhile only three (13.6%) patients showed no response. These results are comparable with the study conducted by Safwat *et al.* [25] that included 15 patients with endobronchial obstruction treated with intratumoral chemotherapy out of those patients, seven (46.7%) showed good response, whereas five (33.3%) patients showed partial response. Meanwhile only three (20%) patients showed no response. Hetzel *et al.* [27] studied the role of cryocanalization in achieving airway patency on 60 patients reported that complete recanalization was achieved in 37 (61%) patients. Thirteen (22%) patients' treatment was rated as partially successful and 10 (17%) patients' treatment was unsuccessful.

As regard to the radiological response in the present study, in group A there was a significant improvement in patients presented with pneumonia [3/8 (37.5%)] before treatment with 100% response. In group B [3/14 (21.4%)] patients presented with lung collapse, only one of them showed improvement. These results were in agreement with Safwat *et al.* [25] nine (60%) of the patients had pneumonia before treatment which improved after treatment to three (20%) and 14 (93.3%) of them had collapse that improved after treatment to nine (46.7%).

In our study, 4/22 (18.1%) of the patients treated were associated with complications and no mortality, one with rapid atrial fibrillation, and two patients developed marked hypoxemia that required assisted mechanical ventilation, whereas one patient complicated with bleeding and all of them were managed and the patients improved. Asimakopoulos *et al.* [18] reported bleeding in six (3.5%) patients, three (1.7%) patients had new onset of atrial fibrillation, and respiratory distress in four (2.3%), whereas bleeding was reported in 4/38 (10.5%); excessive cough occurred in 1/38 (2.6%) as reported by Coulter and Mehta [28]. The difference between the above studies and the current study in complications especially hemoptysis may be because of the effect of usage of electrocautery for hemostasis. The cost of this method was about 40 US$ and the mean duration was about 30 min. These modalities are cheap when compared with laser therapy.

Conclusion

The sequential use of cryoextraction after electrocautery for re-establishment of central airway patency is an effective, safe, cheap, and rapid method for alleviating symptoms, improving performance, quality of life, and ventilatory functions in patients with central airway obstruction.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Evaluation of cupping therapy as an adjuvant therapy in a smoking cessation program

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Background Despite the methods available to aid smoking cessation, it still remains a major problem; thus, there is a need for a new alternative approach to control smoking. This study was carried out to evaluate the effectiveness of cupping therapy as an adjuvant therapy in a smoking cessation program.

Participants and methods This pilot randomized study included 46 male smokers attending the outpatient smoking cessation clinic. Patients were divided into two matched groups: the first group included 20 male smokers subjected to a smoking cessation program, whereas the second group included 26 male smokers subjected to the same smoking cessation program as group I in addition to a monthly bloodletting cupping session for 3 consecutive months as an adjuvant. All the smokers included attended three follow-up monthly visits for assessment of outcomes and frequency of withdrawal symptoms.

Results The success rate was the highest in the first follow-up compared with the second and the third follow-up in group II. There was no significant difference between both groups in the frequency of withdrawal symptoms during the first follow-up. During the second follow-up, there was a significant decrease in the frequency of occurrence of headaches and in the frequency of anxiety in the patients in group II compared with the patients in group I. During the third follow-up, there was a significant decrease in the frequency of occurrence of headache, weight gain, and tiredness in group II compared with group I. There was no significant difference between the outcomes of groups I and II; however, the success rate in group I was higher than that in group II. No significant differences were detected between the outcome in both groups in terms of age and smoking index. There was a significant difference in the effect of the number of cupping therapy sessions in the ability to quit smoking in group II.

Conclusion Bloodletting cupping therapy, which is not harmful if performed appropriately, is a simple procedure, economic, practical, and may be effective as an adjuvant in a smoking cessation program. *Egypt J Broncho* 2015 9:276–282

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Keywords: cupping therapy, smoking cessation, smoking

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Introduction

The effects of smoking on human health are severe and in many cases, deadly. There are ~4000 chemicals in cigarettes, hundreds of which are toxic. The ingredients in cigarettes affect everything from the internal functioning of organs to the efficiency of the body's immune system. The effects of cigarette smoking are destructive and widespread and nicotine reaches the brain within 10 s after smoke is inhaled [1].

Smoking cessation is the process of discontinuing the practice of inhaling a smoked substance.

Cupping is an ancient treatment in which evacuated cups are applied to intact or scarified skin to draw blood toward or through the skin [2]. Traditionally, cupping therapy has been practiced in most cultures in one form or another. The practice of cupping has been part of Middle-Eastern cultural practice for thousands of years, with citations dating back to the time of Hippocrates (400 BC). Moreover, ancient Egyptians were the first to embrace cupping therapy and the oldest recorded medical textbook, *Ebers Papyrus*, written in ~1550 BC in Egypt mentions cupping [3].

In view of the above, this study was carried out to evaluate the effectiveness of cupping therapy as an adjuvant therapy in a smoking cessation program.

Participants and methods

This pilot randomized study included 46 male smokers selected from among those attending the outpatient smoking cessation clinic of Giza Chest Hospital. The patients were divided into two matched groups: the first group included 20 male smokers who were subjected to a smoking cessation program according to the American Cancer Association (ACA), the WHO, and the Egyptian Ministry of Health and the second group included 26 male smokers who were subjected to the same smoking cessation program as the first group in addition to bloodletting cupping therapy as an adjuvant. Each smoker in the second group received

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a monthly cupping session for 3 consecutive months as an outpatient procedure. Those sessions were conducted on the 17th, 19th, and 21st of the lunar months.

For all patients, the following were documented: detailed medical history and thorough clinical examination. All included smokers attended three follow-up monthly visits for assessment of outcome and the frequency of the withdrawal symptoms. All recruited smokers were provided with information detailing the research procedure before commencing the study and provided a written consent. The study was approved by the institutional ethical committee.

Bloodletting cupping therapy

A specific protocol for medical bloodletting cupping therapy was applied according to the modern bloodletting cupping procedure [4].

Bloodletting cupping was performed on four basic points that were selected according to traditional Arab medicine [5]:

(1) The first point is 'AI-Kahel' between the shoulders (seventh cervical spine); Ibn Al-Koff stated that cupping on the shoulders relieves dyspnea [5].
(2) The second and third points are on the region between the two shoulder blades [5].
(3) The fourth point is the 'Al-Auzon' area behind the ear; cupping on this area relieves headache and heaviness in the head.

Preparation

(1) The room was kept warm and comfortable.
(2) The procedure was explained thoroughly to the patient.
(3) The patient was made to sit on the examination bed (cupping can be performed with the patient lying down in the case of weak or frightened patients or if the patient is likely to suffer from circulatory complications. Otherwise, cupping is performed in the sitting position).
(4) The back of the patient was completely bare.

Bloodletting cupping procedure [4]

A high-quality and durable cupping set was used (Fig. 1). It had a vacuum pump (suction pump) and cups that were light weight, breakage resistant, and made of antiaging plastic. These cups are supplied in different sizes and come with a detailed user's manual.

(1) It ensured that the inside of the cup was clean and the handle was completely unfastened.
(2) The skin of the patient was dried, cleaned by an antiseptic solution, and the hair was shaved in the selected area of the skin for ideal maximum performance of the cups.
(3) An appropriate size or type of cup was selected. The cup was placed on the previous four points selected. With the rim of the cup facing downward, press tightly with one hand and screw the handle of the vacuum with the other until the cup sucks onto the skin.
(4) The handle of the cup was screwed or unscrewed to adjust the pressure inside the cup.
(5) The cups were left for a few minutes until the skin engorged, and then it was removed.
(6) The skin and under-the-skin tissues of the selected points were scarified with a very small incision (2 cm) in the longitudinal direction from upright downwards.
(7) The cup was again placed on the previous four points selected and the handle of the cup was screwed or unscrewed to adjust the pressure inside the cup (within 15 min, the bleeding stops).
(8) The cup was removed when it was one-third to two-thirds full and another cup was placed on the area.
(9) A large sterilized gauze was placed under the cup with one hand. Pressing the upper edge of the cup with the other hand, the cup was removed in an upright motion, ensuring that cup remained covered with the gauze at all times.
(10) The cupping procedure was repeated until the scarified indurations no longer bled.
(11) The cups were unscrewed after the desired time.
(12) The small wound was gently rubbed with an antibiotic ointment and then covered with a sterile bandage that had to be left for 1 day.

It is worth mentioning that if the incision is sufficient, between 30 and 60 ml of blood can be expected to be drawn into one cup. Bleeding more than once a month is acceptable, but not more than an average of 100 ml at any one time.

Fig. 1

Cupping set.

In this study, plastic, disposable vacuum and sterilized scalpels were used for the process.

Every smoker recruited had been informed that following the cupping session, his skin would show the following abnormal features [6]:

(1) Blood speckles appear on the skin, which will dissipate in a few days, and the skin would become red because of the congestion of blood flow.
(2) Blisters might appear on the skin where the cup was attached.

Statistical analysis

Numerical data were expressed as mean ± SD, minimum, maximum, and range, whereas non-numerical data were expressed as number and percentage. A χ^2-test was used to perform comparisons between two qualitative variables. The Student *t*-test was used to perform a comparison between the means of two quantitative variables. Statistical significance was set at *P* value less than 0.05. Statistical analyses were carried out utilizing the statistical package for the social sciences software (SPSS, version 10.0; SPSS Inc., Chicago, Illinois, USA) for Windows.

Results

Forty-six male smokers were included in this study. The increase in nicotine withdrawal symptoms was related to the outcome in groups I and II. The success rate was the highest in the first follow-up compared with the second and the third follow-up in group II (Tables 1 and 2).

There was no statistically significant difference between both groups in the frequency of withdrawal symptoms during the first follow-up ($P > 0.05$) (Table 3).

During the second follow-up, there was a statistically significant decrease in the frequency of occurrence of headache and in the frequency of anxiety (irritability) among smokers in group II compared with smokers in group I, whereas there was no statistically significant difference ($P > 0.05$) among smokers in both groups in terms of the rest of the withdrawal symptoms (Table 4).

During the third follow-up, there was a statistically significant decrease in the frequency of occurrence of headache, weight gain (irritability), and tiredness among smokers in group II compared with smokers in group I, whereas there was no statistically significant difference ($P > 0.05$) among smokers in both groups in terms of the rest of the withdrawal symptoms (Table 5).

There was no statistically significant difference between the outcome of groups I and II. However, the rate of success in group I was higher than that in group II (Table 6 and Fig. 2).

Table 1 Frequency of nicotine withdrawal symptoms in group I in relation to the outcome

Nicotine withdrawal symptoms in group I	Follow-up 1 [*N* (%)]		Follow-up 2 [*N* (%)]		Follow-up 3 [*N* (%)]	
	Success	Failed	Success	Failed	Success	Failed
Dizziness	2 (10)	14 (70)	0 (0)	2 (10)	0 (0)	1 (5)
Headache	4 (20)	16 (80)	2 (10)	11 (55)	2 (10)	11 (55)
Anxiety (irritability)	2 (10)	15 (75)	1 (5)	11 (55)	0 (0)	11 (55)
Boredom	1 (5)	10 (50)	0 (0)	7 (35)	0 (0)	6 (30)
Tiredness (fatigability)	1 (5)	10 (50)	0 (0)	5 (25)	0 (0)	6 (30)
Chest tightness	1 (5)	7 (35)	0 (0)	5 (25)	0 (0)	5 (25)
Weight gain	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sleep disturbance	0 (0)	2 (10)	0 (0)	2 (10)	0 (0)	1 (5)
Cough	0 (0)	4 (20)	0 (0)	2 (10)	0 (0)	2 (10)

Table 2 Frequency of nicotine withdrawal symptoms in group II in relation to the outcome

Nicotine withdrawal symptoms in group II	Follow-up 1 [*N* (%)]		Follow-up 2 [*N* (%)]		Follow-up 3 [*N* (%)]	
	Success	Failed	Success	Failed	Success	Failed
Dizziness	5 (19.23)	12 (46.15)	0 (0)	0 (0)	0 (0)	0 (0)
Headache	5 (19.23)	16 (61.54)	0 (0)	0 (0)	0 (0)	0 (0)
Anxiety (irritability)	3 (11.54)	16 (61.54)	0 (0)	2 (7.69)	0 (0)	2 (7.69)
Boredom	2 (7.69)	9 (34.62)	0 (0)	3 (11.54)	0 (0)	2 (7.69)
Tiredness (fatigability)	1 (3.85)	11 (42.31)	0 (0)	1 (3.85)	0 (0)	1 (3.85)
Chest tightness	2 (7.69)	7 (26.92)	0 (0)	0 (0)	0 (0)	0 (0)
Weight gain	0 (0)	2 (7.69)	1 (3.85)	1 (3.85)	2 (7.69)	1 (3.85)
Sleep disturbance	0 (0)	2 (7.69)	0 (0)	0 (0)	0 (0)	0 (0)
Cough	2 (7.69)	2 (7.69)	0 (0)	0 (0)	0 (0)	0 (0)

No statistically significant differences were detected between the outcomes in both groups in terms of age and smoking index (Table 7).

There was a statistically significant difference ($P<0.05$) in the effect of the number of cupping therapy sessions on the ability to quit smoking among smokers in group II (Table 8 and Fig. 3).

Discussion

Smoking cessation represents the single most important step that smokers can take to enhance the length and quality of their lives. Over time, an individual becomes physically dependent on and emotionally addicted to nicotine. Studies have shown that smokers must deal with both the physical and the mental dependency on nicotine in order to quit and not resume. Physically, the body reacts to the absence of nicotine, causing unpleasant withdrawal symptoms. Mentally, the smoker is faced with giving up a habit, which calls for a major change in behavior, making it difficult to stay away from nicotine. Both the physical and the mental factors must be addressed for the quitting process [7].

The Global Adult Tobacco Survey (GATS) estimated that overall, 19.4% (9.7 million) of adults in Egypt currently smoke tobacco: 37.7% men and 0.5% women. 95% of current smokers are daily smokers. Manufactured cigarettes are the most popular type of product smoked by men (31.7%), with an average of 19.4 cigarettes/day, followed by Shisha (6.2%); 42.2% smoke one session/day and 69.9% smoke two or fewer rocks/session. However, with respect to women smokers, 0.2% smoke manufactured cigarettes and 0.3% smoke Shisha, and the use was highest in rural Upper Egypt (0.9%) and among those with no formal education (0.7%) [8].

The value of bloodletting cupping in healing is well documented in Islamic culture, where Al-Bukhari narrated in his Sahih that the Prophet (Sallallaahu Álayhi Wasallam) said: 'Healing is in three things: drinking honey, the incision of a cupper, and cauterizing with fire, but I forbid my Ummah to use cauterizing'. In modern medical practice, Eisenberg *et al.* [9] reported that 60% of medical schools in the USA including Harvard and John Hopkins Medical Centers have

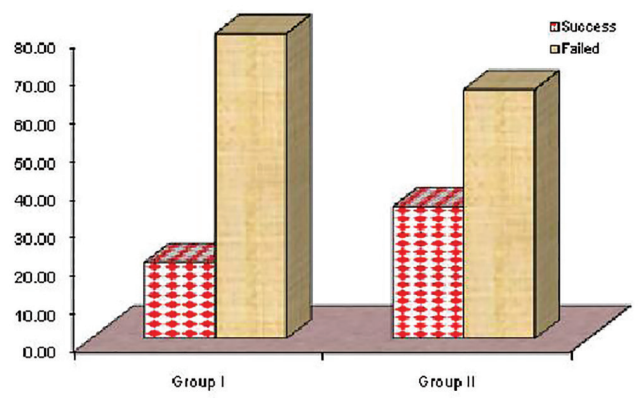
Table 3 Comparison of the frequency of nicotine withdrawal symptoms among smokers in groups I and II during the first follow-up

First follow-up	*N* (%)		χ^2	*P*
	Group I	Group II		
Dizziness	16 (80)	17 (65.38)	0.030	0.862
Headache	20 (100)	21 (80.77)	0.024	0.867
Anxiety (irritability)	17 (85)	19 (73.08)	0.111	0.739
Boredom	11 (55)	11 (42.31)	0.000	1
Tiredness (fatigability)	11 (55)	12 (46.51)	0.043	0.835
Chest tightness	8 (40)	9 (34.62)	0.059	0.808
Weight gain	0 (0)	2 (7.69)	0.182	0.176
Sleep disturbance	2 (10)	2 (7.69)	0.000	1
Cough	4 (20)	2 (7.69)	0.667	0.414

Table 4 Comparison of the frequency of nicotine withdrawal symptoms among smokers in groups I and II during the second follow-up

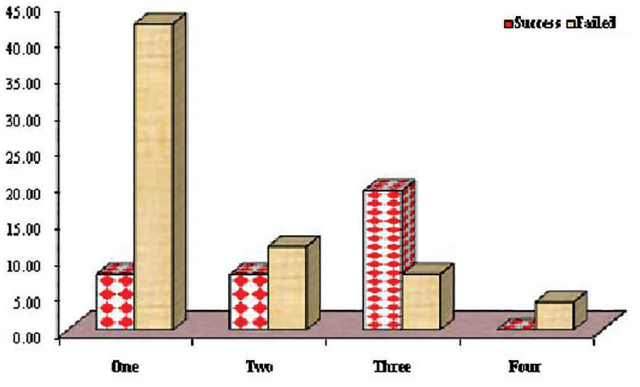
Second follow-up	*N* (%)		χ^2	*P*
	Group I	Group II		
Dizziness	2 (10)	0 (0)	0.333	0.564
Headache	13 (65)	0 (0)	10.286	0.01
Anxiety (irritability)	13 (65)	2 (7.69)	8.067	0.04
Boredom	7 (35)	3 (11.54)	1.600	0.206
Tiredness (fatigability)	5 (25)	1 (3.85)	2.667	0.102
Chest tightness	5 (25)	0 (0)	2.667	0.102
Weight gain	0 (0)	2 (7.69)	0.333	0.564
Sleep disturbance	2 (10)	0 (0)	0.333	0.564
Cough	2 (10)	0 (0)	0.333	0.564

Fig. 2



Comparison between groups I and II in the outcome.

Fig. 3



Comparison between the outcome of group II in terms of the number of cupping therapy sessions.

Table 5 Comparison of the frequency of nicotine withdrawal symptoms among smokers in groups I and II during the third follow-up

Third follow-up	*N* (%)		χ^2	*P*
	Group I	Group II		
Dizziness	1 (5)	0 (0)	0.000	1.000
Headache	13 (65)	0 (0)	10.286	0.001
Anxiety (irritability)	11 (55)	2 (7.69)	6.231	0.013
Boredom	6 (30)	2 (7.69)	2.000	0.157
Tiredness (fatigability)	6 (30)	1 (3.85)	3.571	0.049
Chest tightness	5 (25)	0 (0)	2.667	0.102
Weight gain	0 (0)	3 (11.54)	7.073	0.008
Sleep disturbance	1 (5)	0 (0)	0000	1.000
Cough	2 (10)	0 (0)	0.333	0.564

Table 6 Comparison between groups I and II in the outcome

Outcomes	*N* (%)		
	Group I	Group II	Total
Success	4 (20)	9 (34.62)	13 (28.26)
Failed	16 (80)	17 (65.38)	33 (71.74)
Total	20 (100)	26 (100)	46 (100)
χ^2		1.219	
P		0.270	

Table 7 Comparison between age (years) and smoking index (pack years) of groups I and II in the outcome

Groups	Success (mean ± SD)	Failed (mean ± SD)	*P*
Group I			
Age	36.250 ± 17.017	41.688 ± 13.705	0.505
Smoking index	58.125 ± 48.793	33.406 ± 26.002	0.171
Group II			
Age	47.778 ± 10.060	46.882 ± 13.738	0.865
Smoking index	36.722 ± 25.176	46.941 ± 38.420	0.480

Table 8 Comparison between the outcome of group II in the number of cupping therapy sessions

Number of cupping sessions in group II	Outcome [*N* (%)]			χ^2	*P*
	Success	Failed	Total		
One	2 (7.69)	11 (42.31)	13 (50)	7.273	0.044
Two	2 (7.69)	3 (11.54)	5 (19.23)		
Three	5 (19.23)	2 (7.69)	7 (26.92)		
Four	0 (0)	1 (3.85)	1 (3.85)		
Total	9 (34.62)	17 (65.38)	26 (100)		

begun teaching cupping as a part of complementary medicine. In addition, classes are now advertised in most towns in the UK. Moreover, as Abdel-Aal *et al.* [10] stated, cupping therapy is a complementary, traditional technique and, although not yet evidence based, it is nevertheless a simple procedure that can be practiced by any medical practitioner. Ullah *et al.* [11] also reported that complementary and alternative medicine is becoming more popular with the public and gaining credibility within biomedical healthcare.

The results obtained showed that there was no statistically significant increase in the success rate of quitting among smokers in group II, who were subjected to the same smoking cessation program as the first group in addition to bloodletting cupping therapy as an adjuvant, compared with those of group I. Yet, the success rate of quitting was higher among smokers in group II compared with those of group I (34 and 20%, respectively). Also, there was a significant positive statistical correlation between the number of cupping sessions received and the success rate among smokers in group II. This increase in the success rate of quitting among group II smokers might be attributed to the effect of cupping sessions that they received as an adjuvant and this effect is likely to be cumulative. This assumed effect of cupping can be attributed to the anti-inflammatory effect of cupping that was mentioned by Chirali [12], who reported that cupping eases the interruption of blood circulation and congestion and stops the inflammatory extravasation of fluids from the tissues and as smoking is known to trigger an inflammatory response, it may be concluded that cupping may ease and lessen such an inflammatory response. Also, Sack and Fye [13], Cadwell [14], and Ullah *et al.* [11] assumed that puncturing the skin increases the release of the adrenocortical hormones, known for their anti-inflammatory effects, into the circulation.

In the present study, the nicotine withdrawal symptoms were most notable in the first follow-up among smokers in both groups, but without statistically significant differences between both groups, whereas during the second follow-up, there was a statistically significant decrease in the frequency of occurrence of headache and in the frequency of anxiety among smokers in group II compared with smokers in group I. The third follow-up showed a statistically significant decrease in the frequency of occurrence of headache, weight gain, the frequency of anxiety, and tiredness among smokers in group II compared with smokers in group I. Whether or not these results might be attributed to the adjuvant cupping therapy received by smokers in group II remains an intriguing question.

Several studies in the literature have studied the effect of wet cupping mainly on headache, Duo [15], Azizkhani [16], and Ahmadi *et al.* [17], to name a few. Ahmadi *et al.* [17] concluded that it seems plausible that the mechanism of wet cupping is dominated by influences in neural, hematological, and immune system functioning, all of which contribute toward the overall well-being of an individual. In the neural system, the main effect is likely regulation of neurotransmitters and hormones such as serotonin, dopamine, endorphin, calcitonin gene-related peptide, and acetylcholine. Moreover, it seems

that wet cupping has an effect on the negative charge of neuronal cells. In the hematological system, the main effect likely occurs through two pathways:

(a) Regulate coagulation and anticoagulation systems (e.g. decrease the level of hematological elements such as fibrinogen) and
(b) Decrease the hematocrit and then increase the flow of blood and increase the end organ oxygenation.

In the immune system, the main effect likely occurs through three pathways:

(a) Irritation of the immune system by inducing an artificial local inflammation, and then activating the complementary system and increasing the level of immune products such as interferon and tumor necrosis factor;
(b) Affecting the thymus; and
(c) Increasing the flow of lymph in lymph vessels.

However, the significant decrease in some of the withdrawal symptoms only handled the physical aspect of nicotine addiction and the mental addiction to nicotine remains, which may be more powerful than physical addiction in some smokers and subsequently lead to their failure to quit. This could explain the statistically nonsignificant increase in the success rate between the two groups despite the statistically significant decrease in some of the withdrawal symptoms among smokers of group II. Also, smokers who were addicted to other substances, especially to Hashish, had a very high rate of failure because the nicotine withdrawal symptoms were markedly aggravated and could not be overcome by cupping or by other conventional therapies.

In the present study, no statistically significant correlation was found between the success rate and the occupation of smokers in both groups, although employed smokers had the highest success rate, which might be attributed to the fact that employees are better educated and may be more aware of the hazards of smoking, which could be a good motive to quit. This was in agreement with the study commissioned by the National Institute for Health and Clinical Excellence (NICE) and carried out by the UK Centre for Tobacco Control Studies (UKCTCS), which reviewed published studies between 1990 and 2007 to establish success rates for the smoking cessation services and reported that smokers are more likely to be manual workers and may experience multiple barriers that make it harder to stop smoking in the long term.

In the current study, there was no statistically significant correlation between success rate and marital status of smokers in both groups. This was not in agreement with Reitzel *et al.* [18], who suggested that social cohesion may facilitate smoking cessation among Black smokers through desirable effects on psychosocial mechanisms that can result from living in a community with strong interpersonal connections.

In this study, there was no statistically significant correlation between the age of the smokers and the success rate of cessation, which is not in agreement with the findings of GATS [8], which showed that quitting in the past 5 years decreased with age, from 89.2% for ages 15–24 years to 22.7% for ages 65 years and older. However, the study by Messer *et al.* [19] suggested that young adults were more likely than older adults to quit smoking successfully and explained that young adults have more widespread interest in quitting, higher prevalence of smoke-free homes, lower levels of dependence, and different social norms.

Also, the present study found no statistically significant correlation between smoking index and smoking cessation among smokers in both groups and this is in agreement with Dennis and Scott [20] in the national health survey that was conducted in Canada, and showed that measures of nicotine dependence such as the Heaviness of Smoking Index (HSI) have yielded mixed success in predicting cessation. The HSI score, on its own, does not adequately identify smokers who are not able to quit. The HSI may be less effective for explaining quitting behavior for a general population.

Finally, it would not be accurate to discuss the possible mechanisms of cupping without mentioning the possibility of a placebo effect. The effect of placebos remains controversial in the literature, but there is consensus at least that placebos may help patients improve. Unlike most placebos, which have biological effects (e.g. a 'sugar pill'), cupping influences the neurological, hematological, circulatory, and immunological systems. Therefore, cupping is also an important tradition in Islamic culture; thus, it would be fair to surmise whether or not religious beliefs may play a role.

In fact, researches in understudied fields such as this one often inspire more questions than they answer. There is a need for a case–control design to test the efficacy of cupping in comparison with other, more empirically supported techniques and in comparison with placebo or nontreatment groups.

It remains unclear as to how cupping works. Hypotheses on its effects on various body symptoms have been proposed, but further research on this topic is needed.

Finally, cupping should be tested in other cultures and, in particular, among individuals who are not familiar with the technique and therefore perhaps not biased by any long-held cultural or spiritual placebo influences.

Despite these remaining questions, wet cupping remains an appealing treatment option because it is easy to administer, requires only basic low-cost technology, and offers an inexpensive remedy with no significant side effects.

In conclusion, bloodletting cupping therapy, which may not be harmful if performed appropriately under complete aseptic conditions, is a simple procedure, economic, practical, easy to apply, and may be effective as an adjuvant in a smoking cessation program. It plays an important role in decreasing the physical withdrawal symptoms resulting from nicotine craving and actually leads to failure of cessation. Moreover, it may enable tissues to eliminate toxins and can be considered as a filter to retain the beneficial elements in the body. The procedure of bloodletting cupping does not seem to be harmful if performed appropriately.

Finally, the frequency of cupping sessions can be varied from one smoker to another depending on the decrease in the smoking dose until permanently quitting. Still more researches are required to establish the beneficial role of bloodletting cupping therapy in a smoking cessation program and probably other diseases, and to study the usefulness of its application and exact mechanisms of action.

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Conflicts of interest
There are no conflicts of interest.

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A study of CA-125 in patients with pleural effusion

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Background A significant concern of physicians treating patients with pleural effusion is to rule out a malignant etiology, which, in the majority of series, is the first cause of pleural exudates. Determination of tumor markers in serum and pleural fluid has been proposed as a nonaggressive means of establishing a diagnosis of pleural malignancy. Cancer antigen 125 (CA-125) is not a specific tumor marker and it is synthesized by normal and malignant cells of different origins. Recently, it has been shown that various diseases are associated with increased CA-125 levels, especially in the presence of serosal fluid.

Aim The aim of this study was to determine the level of serum and pleural fluid CA-125 to evaluate its value as a marker for differentiation between different types of pleural effusion.

Patients and methods The study was carried out on 30 patients with pleural effusion of different etiologies. They were further subdivided into two groups: exudates and transudates; the levels of both serum and pleural fluid CA-125 were evaluated.

Results In terms of pleural CA-125, there was a statistically significant increase in the exudative subgroup compared with transudative subgroup. Furthermore, it was found that malignant effusion was observed more frequently compared with benign effusion and tuberculosis was observed more frequently in comparison with other infections.

Conclusion The highest level of pleural fluid CA-125 was found in malignancy, followed by tuberculosis, and so pleural fluid CA-125 can be used as a marker for the diagnosis of pleural effusion. *Egypt J Broncho* 2015 9:283–286

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Keywords: CA-125, malignancy, pleural effusion, tuberculosis

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Introduction

Undiagnosed pleural effusions are a major clinical problem; thus, scientists spend considerable effort and time seeking a new parameter to aid the diagnosis of etiology of different types of pleural effusions [1]. In some pleural effusions, the cause might be obvious, such as pleural effusions associated with congestive heart failure or liver cell failure. In other cases, the cause of pleural effusions might not be obvious, necessitating extensive diagnostic procedures in an attempt to identify the cause of effusion [2].

CA-125 (cancer antigen 125 or carbohydrate antigen 125), also known as mucin 16 or MUC16, is a protein that is encoded by the *MUC16* gene in humans [3]. CA-125 is a 200 kDa glycoprotein that exists on the surface of ovarian and some inflammatory and noninflammatory cells. Proliferation of these cells causes this antigen to be released in the serum. CA-125 was first known to a specific tumor marker of the ovary, but gradually, it was found that inflammation even without polymorphism (the early stage of pregnancy, menstrual cycle, and endometriosis) causes this tumor marker to increase. Later, it was found that tuberculosis in various sites of body also causes an increase in serum antigen level [4].

The aim of the present study is to determine the level of serum and pleural fluid CA-125 to evaluate its value as a marker for differentiation between different types of pleural effusion.

Patients and methods

The present study was carried out on 30 patients admitted to Chest Department, Kasr El-Aini Hospital, during the period between August 2011 and October 2012 with pleural effusion of different etiologies. Written informed consent was obtained from all the participants before the study.

All patients were subjected basically to a full assessment of history, thorough clinical examination, routine laboratory investigations, plain chest radiography (posteroanterior and lateral views), and thoracentesis. Medical thoracoscopy was carried out for cases with undiagnosed exudative pleural effusion. The pleural fluid obtained was examined for the following: gross appearance and nature of the fluid, total protein (g/dl) was measured on a Synchron CX5 Autoanalyzer (Chemical analyzer, manufacturer: Beckman coulter), lactate dehydrogenase enzyme was measured in IU/l, adenosine deaminase enzyme was measured in IU/l, total and differential cell count of the pleural fluid, bacteriological examination by culture, sensitivity, and Ziehl–Neelsen stain for acid-fast bacilli, and cytological examination for malignant cells. Levels of CA-125 were measured in U/ml using the

commercially available ELISA kit (catalog number: EK-310-13; Phoenix Pharmaceuticals, Chemical analyzer, manufacturer: Beckman coulter) in pleural fluid. Venous blood samples were obtained simultaneously to measure protein, glucose, lactate dehydrogenase enzyme, adenosine deaminase enzyme, and CA-125. The CA-125 ELISA test is based on the principle of a solid-phase enzyme-linked immunosorbent assay. The assay system utilizes a monoclonal antibody directed against a distinct antigenic determinant on the intact CA-125 molecule that is used for solid-phase immobilization (on the microtiter wells).

Results

Table 1 shows that more than 63% of the studied cases were men, average age 51 years (Table 2).

Table 3 shows no statistically significant difference between the subgroups studied in serum CA-125 using the Kruskal–Wallis test.

Table 1 Distribution of the studied group in terms of general data

Variables	*N* (%)
Age	
<30	4 (13.3)
31–50	10 (33.3)
>51	16 (53.3)
Mean ± SD	51 ± 11 (25–67)
Sex	
Male	19 (63.3)
Female	11 (36.7)

Table 2 Distribution of the studied group in etiology

Variables	*N* (%)
Exudates	
Mesothelioma	6 (20)
Adenocarcinoma	1 (3.3)
Para pneumonic	5 (16.7)
Pleural metastasis	1 (3.3)
Empyema	3 (10)
TB	5 (16.7)
Transudate	
Chronic liver disease	7 (23.3)
Heart failure	2 (6.7)

TB, tuberculosis.

Table 3 Comparison between etiology in serum CA-125 among the group studied

Variables	Serum CA-125		*P*
	Mean	SD	
Exudates			
Malignancy	159	29	>0.0 (NS)
Parapneumonic and empyema	63	40	
TB	51.6	20	
Transudate			
Chronic liver disease	45.7	21	
HF	48.6	20	

HF, heart failure; TB, tuberculosis.

Table 4 shows that the malignancy group had higher pleural fluid CA-125 compared with the other subgroups, with a statistically significant difference between the subgroups studied using the Kruskal–Wallis test.

Table 5 shows no statistically significant difference between the subgroups studied using the Mann–Whitney test.

Table 6 shows that CA-125 is considered more sensitive than specific in detection of exudates due to malignant lesions.

Table 7 shows that pleural CA-125 is considered better positive than negative in detection of exudates due to TB, while serum better negative than positive.

Figure 1 shows that CA-125 is considered more sensitive than specific in the detection of exudates because of malignant lesions.

Figure 2 shows that pleural CA-125 is considered better positive than negative (more specific) in the detection

Table 4 Comparison between etiology in pleural fluid CA-125 among the studied group

Variables	Pleural fluid CA-125		*P*
	Mean	SD	
Exudates			
Malignancy	1482	540	<0.001 (HS)
Parapneumonic and empyema	59.5	30	
TB	597	320	
Transudate			
Chronic liver disease	70	39	
HF	73	20	

HF, heart failure; HS, highly significant; TB, tuberculosis.

Table 5 Comparison between transudate and exudate in serum CA-125

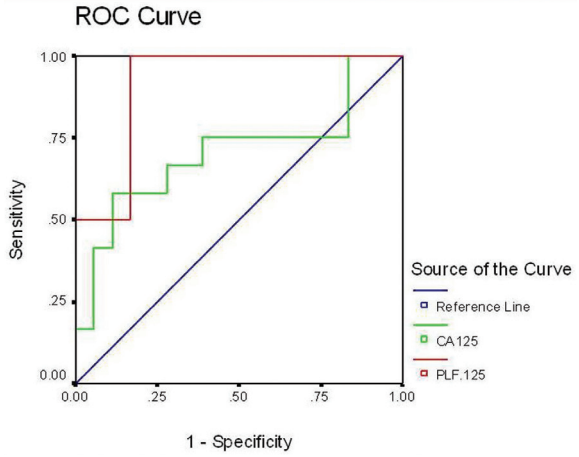
Variables	Serum CA-125		*Z*	*P*
	Mean	SD		
Exudate	111	60	1	<0.05 (NS)
Transudate	44.4	20		

Table 6 Validity of CA-125 in the prediction of pathology of pleural fluid (benign or malignant)

Variables	Serum CA-125	Pleural CA-125
Best cut-off	150	700
AUC (%)	75	90
Sensitivity (%)	79	94
Specificity (%)	68	87
PPV (%)	73	95
NPV (%)	77	93

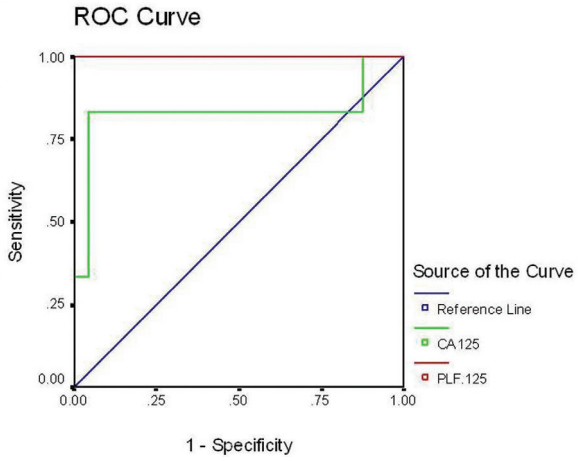
AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

Fig. 1



ROC curve of CA-125 in exudates due to malignant lesions.

Fig. 2



ROC curve of CA-125 (pleural and serum) in exudates due to tuberculosis.

Table 7 Validity of CA-125 in the prediction of pathology of pleural fluid tuberculosis versus other

Variables	Serum CA-125	Pleural CA-125
Best cut-off	100	600
AUC (%)	0.83	0.99
Sensitivity (%)	84	99
Specificity (%)	96	78
PPV (%)	78	99
NPV (%)	97	89

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

of exudates because of tuberculosis, whereas serum CA-125 is better negative than positive (more sensitive).

Discussion

In practice, the cause of pleural effusions might not be obvious, necessitating extensive diagnostic procedures in an attempt to identify the cause of effusion [2]. Pleural fluid cytology and blind pleural biopsy are the methods used most commonly, but are inadequate procedures for the diagnosis. In some studies, blind pleural biopsy has been reported to be inadequate in up to 40% of the patients [5].

This situation indicates the need for a different method with a focus on pleural fluid. Certain molecular markers, if proven to be sensitive and specific enough, can help the physician decide whether the patient should undergo further investigation or not to diagnose a suspected malignancy; that is, open pleural biopsy (VATS, minithoracotomy) or not. Among these biomarkers, insulin growth factor, hepatocyte growth factor, and Simian virus-40 have been proven to play an important role in the development and progression of malignant mesothelioma [6].

The present study was carried out on 30 patients with pleural effusion of different etiologies, admitted to Chest Department, Kasr El-Aini Hospital, during the period from August 2011 to October 2012. There were 19 men and 11 women ranging in age from 29 to 67 years.

The etiology of pleural effusion was established. The effusions were classified as transudates and exudates considering the underlying etiology. The patients were classified into two groups according to the type of effusion, whether transudate (30%) or exudates (70%).

For pleural CA-125, there was a statistically significant difference between the subgroups studied (transudates and exudates) in its value. Also, it was found that in malignant effusion, the value was higher than that in benign effusion; in addition, it was also higher in tuberculosis in comparison with other infections.

In our study, patients with transudative effusions had a mean serum CA-125 level of 44.4 U/dl as shown in Table 5, whereas in the study carried out by How *et al.* [7], 76.9% of patients with transudative effusions had elevated serum CA-125 reaching 291 U/dl, suggesting that the insult to the pleural mesothelial cells is probably not related to inflammation.

Tables 3 and 4 shows that the level of pleural CA-125 in different etiologies is higher than the serum level, except in pneumonia and parapneumonic effusion, and this is also the same as the result of the study carried out by How *et al.* [7] and Kalantri *et al.* [8]; this means that there is some sort of CA-125 reabsorption from the pleural fluid into the serum.

Shokouhi *et al.* [4] showed that the amount of CA-125 in the pleural fluid of patients affected by pleural

effusion secondary to malignancy was higher than the number of tumor markers in the pleural fluid of those affected with tuberculosis; that is, in malignancy, the mean ± SD CA-125 was 2149 ± 4513.6 U/ml, whereas in tuberculosis, the mean ± SD CA-125 was 159.1 ± 214, and this was the same in our study as shown in Table 4 as the mean ± SD CA-125 in malignancy was 1482 ± 540 compared with a mean ± SD of CA-125 of 597 ± 320 in tuberculosis.

Aoki *et al*. [9] compared the amounts of CA-125 in the serum of 11 cases of tuberculous pleurisy and 28 nontuberculosis cases and reported that the average in tuberculous pleuritis cases was higher than that of other infections. In contrast, our study showed that serum CA-125 was lower in tuberculosis than that in other nontuberculous infections as shown in Table 3.

Also, Tomita [10] clinically studied the histological distribution of CA-125 in patients affected by pleural effusion. In examining 51 patients affected by pleural effusion secondary to malignancy and 38 patients affected by benign effusion, they determined that the amount of CA-125 in malignant effusion is markedly higher than benign cases; this means that CA-125 in pleural effusion is produced by both malignant cells and active mesothelial cells. Our study also showed that both serum and pleural fluid CA-125 are higher in patients with malignant effusion than those with benign effusion as shown in Tables 3 and 4.

Ferrer *et al*. [11] showed in their study that in the group proved to have malignant effusion, pleural fluid CA-125 was higher than serum CA-125, and the same result was fund in our study as shown in Tables 3 and 4, suggesting pleural production of the tumor marker than passive diffusion from serum. This is in agreement with previous studies that mesothelial cells express CA-125.

Table 6 shows that serum and pleural CA-125 were more sensitive than specific in the detection of malignant pleural effusion. Also, in Table 7, pleural CA-125 was more sensitive than specific in the detection of tuberculous pleural effusion. To our knowledge, there have been no comparable studies in terms of these results.

The exact origin of CA-125 in patients with ascites and pleural effusion has not been defined as yet, but there are three theories: Kabawat *et al*. [12] detected CA-125 in all kinds of celomic epithelium derived from the same origin as pericardium, pleura, and mesothelial cells lining the peritoneum. Mezger *et al*. [13] defined CA-125 as a strong immunohistochemical marker in mesothelial cell proliferation. Mezger *et al*. [14] and Molina *et al*. [15] suggested that CA-125 may be synthesized from peritoneal epithelial cells as a response to mechanic distress because of ascites and then diffuse to serum.

In conclusion, the highest level of pleural fluid CA-125 was found in malignancy, followed by tuberculosis. The differential diagnosis of effusions might be further improved by including CA-125 concentrations in the diagnostic armamentarium available to the clinician.

Acknowledgements

Conflicts of interest

None declared.

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Role of pulmonary function tests in screening pulmonary arterial hypertension in scleroderma

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Introduction Pulmonary arterial hypertension (PAH) is a life-threatening complication of scleroderma. Its prevalence is estimated to be between 12 and 29%. The symptoms are usually nonspecific and overlooked in those patients already limited by other complications of their condition. It is recommended to perform noninvasive screening for scleroderma patients for early detection of PAH, which has a significant impact on treatment strategy and clinical outcomes.

Aim of the study The aim of this study was to assess the role of certain pulmonary function parameters [forced vital capacity (FVC), diffusion capacity of the lung for carbon monoxide (DLCO), FVC/DLCO] in the early prediction of PAH in scleroderma patients.

Patients and methods This prospective study was conducted on 30 scleroderma-diagnosed patients; all patients were subjected to routine laboratory investigations, plain chest radiographic posteroanterior view, computed tomography of the chest, transthoracic echocardiography, spirometry, and DLCO.

Results The echocardiographic results showed pulmonary artery systolic pressure greater than 35 mmHg in eight patients, which led to suspect a possibility of pulmonary hypertension (PH) in those patients. On comparing patients with suspected PH and others, we found significant differences in the values of FVC% and DLCO%, which was significantly lower in patients with suspected PH ($P < 0.05$), and FVC%/DLCO% was significantly higher in those patients ($P < 0.05$). The best cutoff value of FVC/DLCO for predicting suspected PH among the studied cases was a value greater than 1.91, with a sensitivity of 87.5% and a specificity of 100%.

Conclusion Assessment of pulmonary functions is an easy and helpful tool in screening pulmonary vasculopathy in scleroderma patients. It helps to suspect patients with early PH, which can be subsequently confirmed with further appropriate tests. *Egypt J Broncho* 2015 9:287–292

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Keywords: diffusion capacity of the lung for carbon monoxide, pulmonary arterial hypertension, pulmonary function tests, scleroderma

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Introduction

Scleroderma, also known as systemic sclerosis, is a multisystem autoimmune connective tissue disorder characterized by microvascular damage and fibrosis in multiple organs, which leads to significant morbidity and mortality [1]. Pulmonary involvement in systemic sclerosis is common; it most often comprises fibrosis or interstitial lung disease, and pulmonary vascular disease leading to pulmonary arterial hypertension (PAH) [2]. Pulmonary complications are usually associated with unfavorable prognosis and considered the leading cause of disease-related morbidity and mortality in scleroderma patients [2]. PAH is a progressive vasculopathy that is advanced by the time symptoms develop. As symptoms are nonspecific, continued progression toward end-stage disease occurs for an average of 2 years between symptom onset and diagnosis, and usually this is associated with high mortality despite therapy [3]. Therefore, there is an urgent need for earlier diagnosis, which may have a significant impact on the treatment strategy and clinical outcome [4]. Quality of life and prognosis are substantially improved with early diagnosis and treatment, and the outcomes are clearly better [5].

It is recommended to screen patients with systemic sclerosis without clinical signs and symptoms of pulmonary hypertension (PH) with a two-step approach using clinical assessment for the presence of telangiectasia and anticentromere antibodies, pulmonary function tests and single-breath diffusion capacity of the lung for carbon monoxide assessment (DLCO-SB) measurements, ECG in the initial stage, followed by echocardiography and consideration of right heart catheterization in patients with abnormal findings [5].

Aim of the study

The aim of this study was to assess the role of certain pulmonary function parameters in the early prediction

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of PAH in scleroderma patients, which are as follows: forced vital capacity (FVC) % of the predicted value, DLCO-SB% of the predicted value, and FVC/DLCO%.

Patients and methods

This prospective study was conducted on 30 patients diagnosed with scleroderma, recruited from the Rheumatology Department of Ain Shams University Hospital. For all patients, the following were performed and documented: detailed medical history, thorough clinical examination, full laboratory investigations, chest radiographic posteroanterior view, computed tomography of the chest with high resolution and without contrast, transthoracic echocardiography, spirometric study, and DLCO. Exclusion criteria were as follows: patients with concurrent lung diseases, patients with occupational history predisposing to lung disorders, smokers, patients who cannot undergo spirometry and DLCO, patients complaining of moderate or severe dyspnea, patients with clinical or laboratory evidence of other collagen vascular diseases or evidence of parenchymal abnormality on high resolution computed tomography chest, and cardiac patients. All patients provided consent to participate and the study was approved by the institutional ethical committee.

Spirometry

FVC, forced expiratory volume in 1 s (FEV_1), FEV_1/FVC, and maximum midexpiratory flow (MMEF) were measured using the spirometry system (Masterscreen 2001, version 4.5; Erich Jaeger GmbH, Friedberg, Germany). Readings were recorded in triplicate, with the highest values recorded and expressed as a percentage of the predicted value according to the guidelines of the American Thoracic Society (ATS) [6].

Single-breath diffusion capacity of the lung for carbon monoxide

Carbon monoxide diffusing capacity single-breath method (DLCO-SB) was measured using the system (Masterscreen 2001, version 4.5; Erich Jaeger GmbH) according to the ATS guidelines [7]. The following activities were avoided before the test: vigorous exercise within 30 min of the test, consumption of a large meal within 2 h of testing, and inhalation of supplemental oxygen within 10 min before the test.

The procedure of DLCO-SB was performed as follows:

The equipment was calibrated with a 3-l syringe.

The tests were well explained to the patients.

The weight and height were recorded.

The patient was in a sitting position with the head slightly elevated.

The mouthpiece was placed, and the patient was instructed to close his lips around the mouthpiece.

Tidal breathing was carried out for a sufficient time to ensure that the patient was comfortable with the mouthpiece.

Deep inspirations had to be avoided during this period, as they could increase subsequent CO uptake.

The DLCO maneuver began with unforced exhalation to residual volume.

At residual volume, the patient's mouthpiece was connected to a source of test gas and the patient inhaled rapidly to total lung capacity.

The patient was asked to hold his/her breath by maintaining full inspiration using only the minimal effort necessary. The breath-hold time was for about 10 s, after which the patient exhaled maximally.

Standard criteria checked for DLCO testing are as follows:

Use of a proper quality-controlled equipment.

Inspired volume of 85% of largest vital capacity in 4 s.

A stable calculated breath-hold for 10 s, with no evidence of leaks, or Valsalva or Mueller maneuvers.

Expiration in 4 s with appropriate clearance of dead space (VD) and proper sampling/analysis of alveolar gas.

Statistical analysis

Data were collected, tabled, and statistically analyzed using SPSS, (Chicago, IL, USA) version 15.

(1) Parametric data were expressed as minimum, maximum, and mean ± SD.
(2) Nonparametric data were expressed as number and percentage.
(3) Comparison between parametric data of the two groups was made using the unpaired *t*-test.
(4) Comparison between nonparametric data of two groups was made using the χ^2-test.
(5) Pearson's correlation was used to study the correlation between two parameters: direct (+) correlations for two variables that move in the same direction and indirect (–) or inverse correlation for two variables that move in the opposite directions.

Receiver operating characteristic (ROC) curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. The area under the ROC curve is a measure of how well a parameter can distinguish between two diagnostic groups (diseased/normal). ROC curve was determined using Medcalc software, version 15.2.2.

Two-tailed *P* value greater than 0.05 was considered nonsignificant, *P* value of 0.05 or less was considered significant, and *P* value of 0.01 or less was considered highly significant.

Results

The study included 30 patients with scleroderma, four were male (13.3%) and 26 were female (86.7%). The age of the studied patients ranged from 28 to 60 years with a mean age of 42.06 ± 8.88 years (Table 1). As regards the anthropometric measures, the mean weight of the studied cases was 73.33 ± 11.89, the mean height was 162.9 ± 6.01, and the mean BMI was 27.58 ± 3.89 (Table 2).

As regards the results of pulmonary function tests, the mean FVC% was 81.27 ± 13.47, the mean FEV_1% was 77.88 ± 13.06, the mean FEV_1/FVC% was 83.44 ± 8.46, the mean maximum midexpiratory flow was 66.86 ± 23.05, the mean DLCO% was 59.41 ± 19.82, the mean carbon monoxide transfer coefficient (KCO) was 76.77 ± 22.92, and the mean FVC%/DLCO% was 1.49 ± 0.47 (Table 3).

As regards the transthoracic echocardiographic findings of the studied patients, the mean pulmonary artery systolic pressure (PASP) was 27.56 ± 8.87, the mean right ventricular systolic pressure (RVSP) was 29.83 ± 9.42, and the mean ejection fraction % was 59.05 ± 5.5 (Table 4). According to the value of PASP (≥35 mmHg) as a cutoff for suspecting a potential or early-developing pulmonary vasculopathy (PH) [8], the prevalence of patients with suspected PH among the studied cases was 8/30 (26.7%).

Studying the difference between patients with suspected PH and those with no suspected PH showed no significant association between PH and the sociodemographic distribution of the patients ($P > 0.05$) (Table 5).

Studying the difference between patients with no suspected PH and those with suspected PH as regards anthropometric measures showed no significant association between PH and the anthropometric measures of the patients ($P > 0.05$) (Table 6).

A comparison of the results of patients with no suspected PH and those with suspected PH as regards pulmonary function tests showed significant differences with respect to FVC%, FEV_1%, DLCO%, and carbon monoxide transfer coefficient (KCO),

Table 1 Sociodemographic data of the studied cases

Sex [*N* (%)]	
Male	4 (13.3)
Female	26 (86.7)
Age	
Range	28–60
Mean ± SD	42.06 ± 8.88

Table 2 Anthropometric measures of the studied cases

Weight (kg)	
Range	55–108
Mean ± SD	73.33 ± 11.89
Height (cm)	
Range	155–175
Mean ± SD	162.9 ± 6.01
BMI	
Range	21–36.1
Mean ± SD	27.58 ± 3.89

Table 3 Pulmonary function test results

Pulmonary function test	Range (mean ± SD)
FVC%	45–103.9 (81.27 ± 13.47)
FEV_1%	41–99 (77.88 ± 13.06)
FEV_1/FVC%	64.3–99.53 (83.44 ± 8.46)
MEEF	23.2–120 (66.86 ± 23.05)
DLCO%	20–85.3 (59.41 ± 19.82)
KCO	19.9–112 (76.77 ± 22.92)
FVC%/DLCO%	1.1–2.63 (1.49 ± 0.47)

DLCO, diffusion capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 4 Echocardiographic findings in the studied cases

Echocardiography finding	Range (mean ± SD)
PASP (mmHg)	16–45 (27.56 ± 8.87)
RVSP (mmHg)	18–48 (29.83 ± 9.42)
EF%	50.2–70.2 (59.05 ± 5.5)

EF, ejection fraction; PASP, pulmonary artery systolic pressure; RVSP, right ventricular systolic pressure.

Table 5 Differences between patients with no suspected pulmonary hypertension and patients with suspected pulmonary hypertension as regards sociodemographic data

Sociodemograhic data	Patients with no suspected PH (*n* = 22)	Patients with suspected PH (*n* = 8)	*P*
Sex			
Male	4	0	0.1
Age			
Range	28–60	35–50	0.6
Mean ± SD	42.5 ± 9.88	40.9 ± 5.6	

PH, pulmonary hypertension.

with values significantly lower among patients with suspected PH. However, FVC%/DLCO% was significantly higher among patients with suspected PH ($P < 0.05$). There were no significant differences between the two groups as regards FEV_1/FVC% and maximal expiratory flow (MEEF) ($P > 0.05$) (Table 7).

As regards the echocardiographic findings of the studied patients, there was a highly significant difference between patients with suspected PH and the others as regards the mean RVSP, which was higher among patients with suspected PH. However, the mean ejection fraction was lower among patients with suspected PH ($P < 0.01$) (Table 8).

Table 6 Differences between patients with no suspected pulmonary hypertension and patients with suspected pulmonary hypertension as regards anthropometric measures

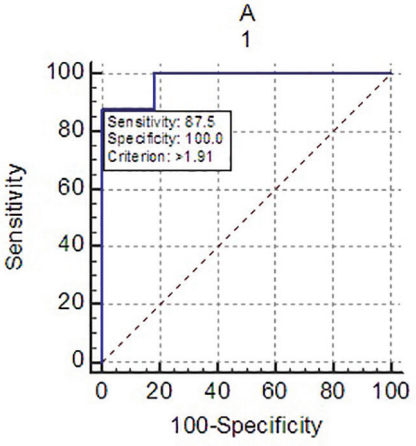
Anthropometric measures	Patients with no suspected PH (n = 22)	Patients with suspected PH (n = 8)	t	P
Weight (kg)				
Range	55–108	56–82	1.27	0.2
Mean ± SD	75 ± 12.5	68.8 ± 9.3		
Height (cm)				
Range	155–175	155–170	1.67	0.1
Mean ± SD	164 ± 5.9	159.9 ± 6		
BMI				
Range	21–63.1	23.3–32	0.55	0.5
Mean ± SD	27.8 ± 4.1	26.9 ± 3.2		

PH, pulmonary hypertension.

The best cutoff value of FVC%/DLCO% for detecting a suspicion for PH among the studied cases was a value greater than 1.91 and area under the curve of 0.977, with a P value of 0.0001, a sensitivity of 87.5%, and a specificity of 100% (Table 9 and Fig. 1).

Among the studied patients there were highly significant direct correlations between FVC/DLCO and each of PASP and RVSP (Table 10 and Figs 2 and 3).

Fig. 1



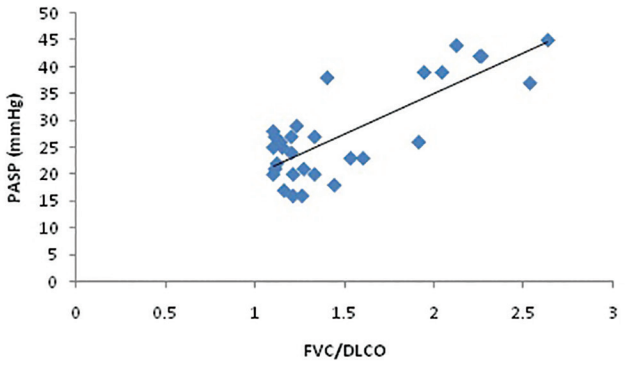
ROC curve of FVC%/DLCO% in detecting a risk for pulmonary hypertension. DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; ROC, receiver operating characteristic.

Table 7 Differences between patients with no suspected pulmonary hypertension and patients with suspected pulmonary hypertension as regards pulmonary function test results

Pulmonary function test	Patients with no suspected PH (n = 22)	Patients with suspected PH (n = 8)	t	P
FVC%				
Range	70.2–103.9	45–87.2	4.05	0.0004**
Mean ± SD	86.1 ± 9.1	67.9 ± 15		
FEV_1%				
Range	59.9–99	41–85.6	3.21	0.003**
Mean ± SD	81.9 ± 9.8	66.8 ± 15.1		
FEV_1/FVC%				
Range	64.3–99.53	78.2–91.3	0.4	0.6
Mean ± SD	83.05 ± 9.5	84.5 ± 5.1		
MEEF				
Range	34.2–120	23.2–96.6	1.45	0.15
Mean ± SD	70.5 ± 22.5	56.9 ± 22.8		
DLCO%				
Range	45.1–85.3	20–50.1	7.57	0.0001**
Mean ± SD	69 ± 11.6	32.9 ± 11.4		
KCO				
Range	70.5–112	19.9–87.4	6.14	0.0001**
Mean ± SD	87.1 ± 11	48.5 ± 23.7		
FVC%/DLCO%				
Range	1.1–1.91	1.4–2.63	7.3	0.0001**
Mean ± SD	1.3 ± 0.2	2.1 ± 0.4		

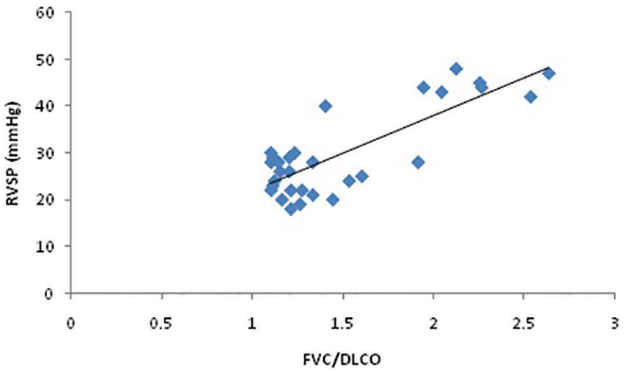
DLCO, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PH, pulmonary hypertension; **$P \leq 0.01$, highly significant.

Fig. 2



Direct correlation between FVC%/DLCO% and PASP. DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; PASP, pulmonary artery systolic pressure.

Fig. 3



Direct correlation between FVC%/DLCO% and RVSP. DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; RVSP, right ventricular systolic pressure.

Table 8 Echocardiographic findings in the studied cases

Echocardiography finding	Patients with no suspected PH (n = 22)	Patients with suspected PH (n = 8)	t	P
RVSP (mmHg)				
Range	18–30	40–48	13.3	0.0001**
Mean ± SD	24.6 ± 3.8	44.1 ± 2.6		
EF (%)				
Range	51.6–70.2	50.2–59.6	3.93	0.0005**
Mean ± SD	61 ± 4.7	53.7 ± 3.8		

EF, ejection fraction; PH, pulmonary hypertension; RVSP, right ventricular systolic pressure; $^{**}P \leq 0.01$, highly significant.

Table 9 Reliability for prediction of a suspected pulmonary hypertension using forced vital capacity/diffusion capacity of the lung for carbon monoxide

Best cutoff point for FVC/DLCO	
Area under the curve	0.977
SE	0.025
Significance (P)	<0.0001**
Confidence interval (95%)	
Lower bound	0.845
Upper bound	1

DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; $^{**}P \leq 0.01$, highly significant.

Table 10 Correlations of forced vital capacity/diffusion capacity of the lung for carbon monoxide among all cases

Echocardiography finding	r	P
PASP (mmHg)	0.799	0.0001**
RVSP (mmHg)	0.812	0.0001**

PASP, pulmonary artery systolic pressure; RVSP, right ventricular systolic pressure; $^{**}P \leq 0.01$, highly significant.

Discussion

PAH is a serious complication of scleroderma and the most frequent cause of death in this disease [9]. The recent advances in PH therapies have led to a remarkable improvement in patient survival, but survival benefits are greatest for those diagnosed at earlier stages [10]. Several studies have indicated that early treatment of PAH can improve hemodynamics, exercise capacity, and survival [11,12].

The assessment of PASP with transthoracic echocardiography is currently regarded as the most useful noninvasive method of screening of PAH [13]. The results of our study showed that eight out of 30 studied patients had a PASP of 35 mmHg or greater, and it has been demonstrated that patients presenting these values should be suspected as developing early PH [8].

On comparing the results of patients with no suspected PH and those with suspected PH as regards pulmonary function tests, we found significant differences in terms of FVC%, FEV_1%, and DLCO%, with values significantly lower among patients with suspected PH, and FVC%/DLCO% was significantly higher among patients with suspected PH ($P < 0.05$). These results are in accordance with the results of Thakkar *et al.* [13], who demonstrated that patients who had DLCO less than 70.3% and higher FVC/DLCO ratio were regarded as having a 'positive' screen for PAH. The best cutoff value of FVC%/DLCO% in our study for detecting a suspected PH was a value greater than 1.91, with a sensitivity of 87.5% and a specificity of 100%, whereas Thakkar and colleagues reported FVC%/DLCO% of 1.82 or greater, with a sensitivity of 50.0% and a specificity of 100%.

The retrospective study by Steen and Medsger [14] found that a decreasing DLCO is an excellent predictor of the subsequent development of isolated PH in limited scleroderma. They demonstrated that DLCO may decrease for many years before the diagnosis of PH. Our results also showed a significant difference in DLCO values between patients with suspected PH and the others.

In contrast, other authors [15] did not report DLCO to be a useful method for identifying patients with early pulmonary vasculopathy associated with systemic sclerosis. Our results demonstrated the reliability of DLCO and DLCO/FVC in suspecting PH, correlating these results with echocardiographic findings.

Among the studied patients there were highly significant direct correlations between FVC/DLCO and each of PASP and RVSP. This is in disagreement with the results of Nathan *et al.* [16], who found no significant correlation between FVC%, DLCO%, and the ratio of the two with mean pulmonary artery pressure, but this study differs from ours in being a retrospective study that examined the ability of pulmonary function tests to predict PH in idiopathic pulmonary fibrosis patients.

Right heart catheterization remains the gold standard for determining the presence of PH, although the latest (5th) World Symposium guidelines have abandoned the need for vasoreactivity testing, as 'responders' are exceedingly rare in patients with scleroderma associated PAH [17]. From the results of our study, we conclude that pulmonary function tests and FVC/DLCO ratio can be very useful for screening and early suspicion of PH in patients with scleroderma; it is an easy, cost-effective, and noninvasive approach, and suspected patients are recommended to undergo further appropriate diagnostic testing for confirmation of PH.

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Conflicts of interest
There are no conflicts of interest.

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Pulmonary plasmacytoma in multiple myeloma: a rare case of extramedullary spread

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Multiple myeloma (MM) is a systemic disease primarily involving the bone marrow, constituting about 1% of all malignancies and 10% of hematological malignancies [1]. It is a neoplastic proliferation of monoclonal plasma cells that can result in renal impairment, osteolytic lesions, hypercalcemia, bone marrow failure, and the production of serum monoclonal proteins. Although usually restricted to the bone marrow, extraskeletal spread in the form of plasmacytoma, which represent localized extramedullary collections of malignant plasma cells, can occur in a significant number of patients. However, symptomatic pulmonary involvement during the course of MM has rarely been reported [2].

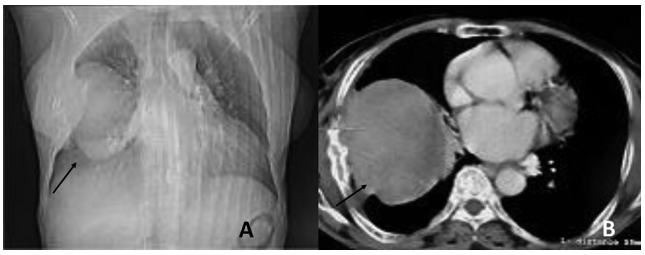
A 55-year-old, nonsmoker, woman presented with complaints of cough, chest pain, breathlessness, hoarseness of voice, and significant weight loss. Cough with breathlessness, which was present for 3 months, aggravated in the last 10 days before presentation, hampering her routine activities. Dull aching pain on the right side of the chest was noted, which increased on inspiration. She had been diagnosed with MM 5 years back and had received five cycles of chemotherapy, with no subsequent follow-up. On general physical examination, she was diagnosed to be hypertensive, with bilateral axillary lymphadenopathy with two to three mobile, nonmatted lymph nodes in the bilateral axilla. Spine tenderness was also noted. Dullness with reduced breath sounds and vocal resonance over the right mammary and infra-axillary areas during the respiratory system examination were noted. Hemogram was essentially normal (hemoglobin 10.3 g/dl, white blood cells 7100 cells/mm^3, creatinine 1.2 mg/dl), except for erythrocyte sedimentation rate, which was elevated (140 mm/h), and unexplained thrombocytosis (332 000 cells/mm^3).

Indirect laryngoscopy showed nonspecific vocal cord keratosis that was incidental and not associated with the primary disease. Ultrasonogram indicated bilateral small axillary lymph nodes that were 5–8 mm in size, likely to be reactive and insignificant.

Radiography showed a collapse fracture in T12 vertebrae with osteolytic lesions in the skull. Chest radiograph and computed tomography topogram showed a homogeneous opacity in the right lung (Fig. 1a). Contrast-enhanced computed tomography chest showed a large enhancing homogenous soft tissue density lesion (Fig. 1b) in the right lung (8.6 × 10 × 1 cm). Lytic lesions were also noted in the posterior aspect of bilateral two to four ribs and expansile lytic lesions involving the right fifth and sixth ribs.

Serum protein electrophoresis showed a symmetrical spike in the β region suggestive of paraprotein (Fig. 2a). Bone marrow aspiration and biopsy showed marrow plasmacytosis of 30% with focal and diffuse interstitial infiltration of plasma cells (Fig. 2a–d), suggesting

Fig. 1



Computed tomography topogram chest (a) showed a homogeneous opacity in the right lung (black arrow). Contrast enhanced computed tomography chest (b) showed a large enhancing homogenous soft tissue density lesion (Figure 1 B black arrow) in the right lung (8.6 × 10 × 11 cms). Lytic lesions were also noted in the posterior aspect of bilateral 2–4 ribs and expansile lytic lesions involving the right 5th and 6th ribs.

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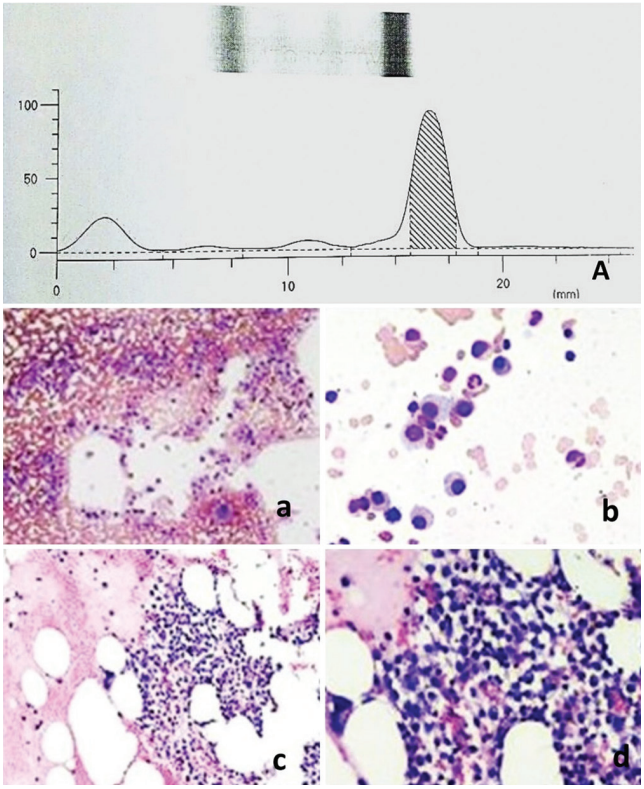
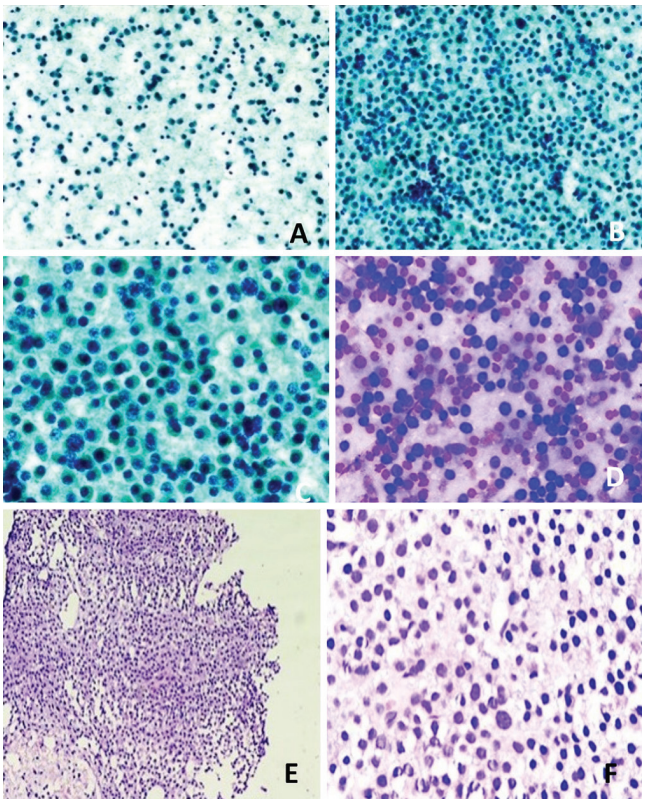
Fig. 2



Serum electrophoresis (A) shows a symmetrical spike in the β region suggestive of paraprotein. Bone marrow aspiration and biopsy (a–d) show a plasmacytosis of 30% with focal and diffuse interstitial infiltration of plasma cells — myeloma relapse.

Fig. 3



(a–d) Fine needle aspiration cytology of the lung mass. (a) Cellular smears showing plasma cells (Pap stain; ×100). (b) Sheets of plasma cells (Pap stain; ×200). (c) Plasma cells with eccentrically placed nuclei and some showing prominent nucleoli (Pap stain; ×400). (d) Numerous plasmablasts (May grunwald giemsa (MGG) stain; ×400). (e, f) Lung biopsy. (e) Fragment of tumor tissue showing monoclonal neoplastic plasma cells (H&E stain; ×40). (f) Plasmablasts showing pleomorphism and prominent nucleoli (H&E stain; ×400).

myeloma relapse. In this case, the lesion was peripheral and there was no role for fiber optic bronchoscopy-guided transbroncial lung biopsy.

Computed tomography-guided fine needle aspiration and biopsy of the lesion in the lung was performed. Fine needle aspiration cytology showed plasma cells with eccentrically placed nuclei and some with prominent nucleoli (Fig. 3a–d). Histopathology indicated monoclonal neoplastic plasma cells and plasmablasts with pleomorphism and prominent nucleoli (Fig. 3e and f). The lung lesion was concluded to be pulmonary plasmacytoma as a manifestation of extramedullary spread of myeloma. The differential diagnosis to be ruled out by immunohistochemistry was mucosa associated lymphoid tissue (MALT) lymphoma with plasma cell differentiation, which could be CD20+ and negative for CD138 and CD79a [3]. CD138 and CD79a will be positive in pulmonary plasmacytoma. Pulmonary plasmacytoma can be distinguished from plasma cell granulomas in which there will be an admixture of inflammatory cells such as lymphocytes and macrophages within a fibrous stroma. Immunohistochemistry can be required rarely to differentiate between both the conditions.

Extramedullary plasmacytoma is a monoclonal proliferation of plasma cells in soft tissues or an organ [4]. The sites of extramedullary dissemination reported in the literature are the spleen, liver, lymph node, kidneys, thyroid gland, adrenal gland, ovary, testis, lung, pleura, pericardium, intestinal tract, and skin [5]. They account for about 3% of plasma cell malignancies, ~80% of which occur in the upper respiratory tract, namely, oropharynx and paranasal sinuses. In the lower airway, plasmacytoma settles in the tracheobronchial tree, structures of the hilum, or rarely in the lung parenchyma. The association of MM with lung plasmacytoma is extremely rare – only 5% of patients with extramedullary plasmacytomas have coexistent MM [3]. Second, plasmacytoma presenting as a mass lesion in the lung mimics commonly occurring lung malignancies. The differential diagnoses are metastatic carcinoma and lymphoma [1]. Such a clinicradiological presentation is rare.

Other case reports of pulmonary manifestations of pulmonary myeloma include homogenous

opacification, multiple pulmonary nodules and mediastinal lymphadenopathy, reticulonodular infiltrates, and intrapulmonary calcification.

Extramedullary plasmacytoma in patients with MM carries a poor prognosis and treatment that includes chemotherapy and autologous stem cell transplantation [6].

Despite advances in the diagnosis of MM, it remains an incurable disease because the disease follows a relapsing course in the majority of patients, irrespective of the treatment regimen or initial response to treatment.

Although pulmonary plasmacytomas are rare, they must be considered in the differential diagnosis of patients presenting with pulmonary manifestations in MM as the management is different for both types of plasma cell dyscrasias, with primary pulmonary plasmacytomas having a better prognosis than pulmonary MM.

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Conflicts of interest
There are no conflicts of interest.

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Postpartum pulmonary edema in twin parturient: beyond the fluids

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Pulmonary edema (PE) after postpartum hemorrhage (PPH) resuscitation is mainly due to fluid overload or transfusion-related acute lung injury. Here we present the case of a 30-year-old primigravida having uncomplicated twin pregnancy. She developed PPH and PE simultaneously during the early postpartum period. Chest radiography was inconclusive to exclude fluid overload. Echocardiography and lung ultrasound ruled out volume overload. PE could be due to adverse effects of drugs, or negative pressure from laryngospasm originating from incisional pain during uterine manipulation. Caution should be exercised while administering methylergometrine or carboprost for atonic PPH, with continued vigilance for detection of signs of PE, especially in high-risk pregnancy. Moreover, the risk versus benefit ratio should be considered for performing abdominal uterine massage as it may be more harmful than beneficial in such subset of patients. *Egypt J Broncho* 2015 9:296–298

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Keywords: carboprost, laryngospasm, methylergometrine, postpartum pulmonary edema, ultrasound

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Introduction

Postpartum pulmonary edema (PE) is a rare entity in healthy women, but it carries significant morbidity and mortality. Early detection and identification of the etiologies can lead to treatment in right direction and save the life. Cardiogenic PE is usually due to a chronic condition but can be acute in presentation. The onset of acute PE in a young, previously healthy postpartum patient, mainly directs towards a noncardiogenic origin. Here, we report a rare case of noncardiogenic PE during the postpartum hemorrhage (PPH) management. Written informed consent was taken from the patient before reporting the case.

Case presentation

A 30-year-old primigravida having a supervised and otherwise uneventful pregnancy was referred to us at term for management of twin pregnancy. She had no comorbidities. Her investigations were unremarkable, except for a platelet count of 49 300/mm^3 (no bleeding) since the last 2 days without any significant cause. The patient then exhibited nonreassuring fetal heart rate and an emergency cesarean section was planned. Her airway examination revealed adequate mouth opening with modified Mallampati grade II. She was premedicated with intravenous metoclopramide 10 mg and ranitidine 50 mg before shifting to the operating theater. General anesthesia was chosen in view of thrombocytopenia. Rapid sequence induction with cricoid pressure was conducted using intravenous thiopental 250 mg and succinylcholine 100 mg. The chest was clear on auscultation. Anesthesia was maintained with atracurium and isoflurane in 40% nitrous oxide with oxygen. Perioperatively, the patient was monitored with ECG, pulse oximetry, noninvasive blood pressure, end-tidal carbon dioxide, temperature, and airway pressure. The twins were delivered and weighed 1.9 and 2.4 kg with favorable Apgar scores. Fentanyl 75 mcg was administered intravenously after delivery of the second fetus. Oxytocin 40 U in the form of intravenous infusion was started as titration dosage. The 1.5 h surgery was uneventful with an expected blood loss of 1 l. A total volume of only 1.5 l of 0.9% saline was administered intraoperatively, without transfusion of blood products. Perioperatively, monitoring parameters, including urine output, were within normal limits. Neuromuscular paralysis was fully reversed with neostigmine–glycopyrrolate and the patient was uneventfully extubated with full consciousness without any residual anesthetic effect and 100% oxygen saturation in pulse oximetry. The patient had normal breathing pattern with regular chest movements during the immediate postoperative period on facemask oxygen. On performing vaginal toileting, fresh bleeding was observed and atonic PPH was suspected. The uterus felt flabby and per abdominal uterine massage was instituted. Fluids and blood products were again started. Intramuscular methylergometrine and intramuscular carboprost were

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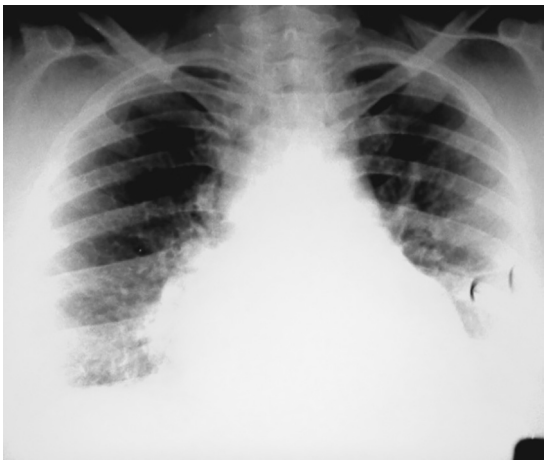
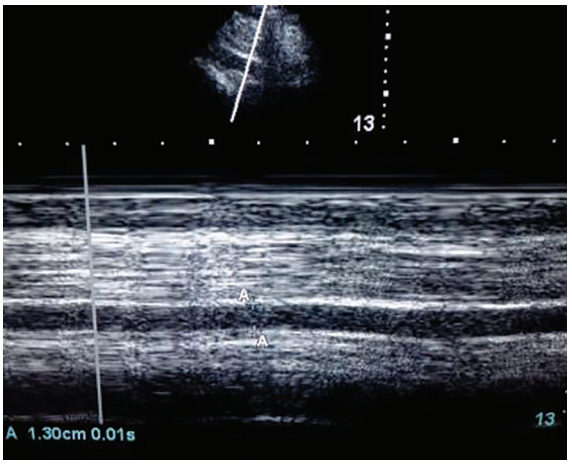
injected. A repeat dose of carboprost was injected and oxytocin infusion rate was increased. The uterus became harder. The patient then acutely developed a respiratory distress with hypotension (86/44 mmHg). On auscultation, air entry was reduced bilaterally with basal crepitations. Arterial blood gas analysis showed the following results: pH 7.36, $PaCO_2$ 42 mmHg, PaO_2 55 mmHg, and HCO_3 26 mmol/l on 100% oxygen mask. Radiograph of the chest revealed bilateral alveolar infiltrates suggestive of PE (Fig. 1). Fluids were then restricted, with a total infusion volume of 1 l colloids only (postoperatively). The patient was reintubated with the help of succinylcholine and midazolam. Immediately after intubation, endotracheal suctioning revealed pink frothy secretions. The secretions were so copious that they repeatedly filled up the endotracheal tube and were hard to clear by tracheal suctioning. Intravenous frusemide 20 mg was injected and the patient was shifted to ICU. She was put on mechanical ventilation. Central venous cannulation showed a central venous pressure of 10 mmHg. Echocardiography was performed and revealed the left ventricular end-diastolic diameter to be less than 5 cm and that of the inferior vena cava to be 1.3–1.8 cm (five readings) with normal hepatic veins (Fig. 2). Ejection fraction was 45–50%, with no organic lesions, or significant right ventricular dysfunction. Ultrasound of the chest revealed multiple interstitial B lines (Fig. 3). After 4 h of ventilation, the tracheal secretions remarkably reduced and the chest was clear on auscultation. A repeated chest radiography and ultrasound of the chest showed markedly cleared lung fields (Fig. 4). Arterial blood gas parameters improved. Postpartum urine output was adequate. The patient was extubated 2 h later and discharged from ICU after 24 h of observation. On follow-up consultations with cardiologist and pulmonologist, no organic cause was found.

Fig. 1



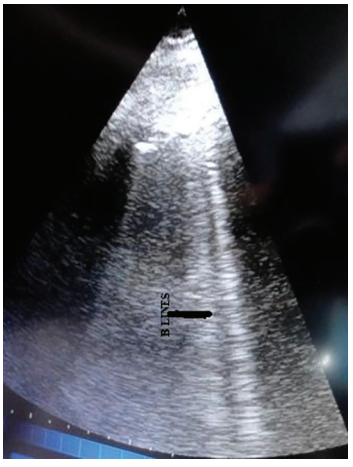
Chest radiograph suggestive of pulmonary edema.

Fig. 2



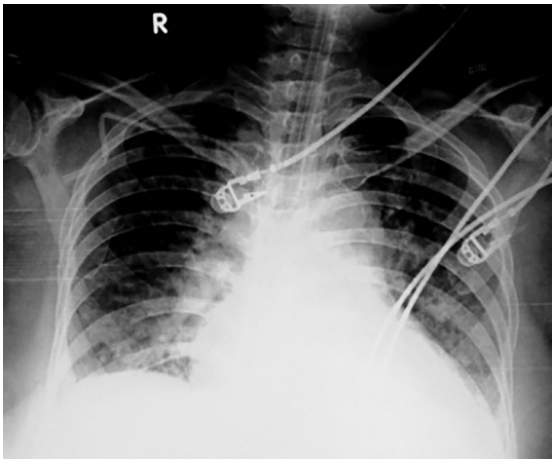
Inferior vena cava diameter in ultrasonography.

Fig. 3



Chest ultrasound demonstrating comet tail or B-line artifacts.

Fig. 4



Clearing of lung fields in radiology.

Discussion

The incidence of acute PE in a parturient is 0.08% [1]. There is a long list for differential diagnosis of post partum PE [2]. Negative pressure PE is known to occur in patients who generate enough inspiratory pressures against a closed glottis. Most cases are seen secondary to laryngospasm, which is common in pediatrics [3]. In our case, the etiology for PE could be due to laryngospasm provoked by pain [4]. Uterine massage and vigorous compression of freshly sutured anterior abdominal wall incites pain, which may lead to laryngospasm through vagus nerve stimulation (abdominolaryngeal reflex). This coupled with exaggerated inspiratory efforts might end up precipitating frank PE. Other possibilities may have been caused by the use of carboprost or methylergometrine (uterotonic) [5,6]. Administration of prostaglandin $F_2\alpha$ ($PGF_2\alpha$) is known to increase pulmonary arterial pressure, which predisposes to fluid transudation across the pulmonary capillaries. Tocolytic drugs are more common offender for PE compared with uterotonic [7]. There are many drugs that cause PE, but drugs we used in this patient did not produce PE, except uterolytic agents. Twin pregnancy imposes greater physiological challenges to the mother when compared with single pregnancy. There is a greater expansion of plasma volume leading to reduced plasma oncotic pressure predisposing to edema. Interestingly, both etiologies of edema formation dramatically subside within 4–6 h of elective ventilation as was the case in our patient. Negative pressure PE due to painful stimulation in twin parturient has never been described in the literature. The authors hence suggest that caution be exercised while administering methylergometrine and carboprost for atonic PPH with continued vigilance for detection of signs of PE, especially in multiple gestation females. In addition, the risk versus benefit ratio should be considered before applying abdominal uterine massage as it may cause more harm than good in such subset of patients. Perioperative as well as postoperative ultrasound monitoring is a good idea for detection of PE with its underlying etiologies [8].

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Conflicts of interest

There are no conflicts of interest.

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