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ORIGINAL ARTICLE

Impact of nitroglycerin infusion on weaning off hypertensive mechanically ventilated chronic obstructive pulmonary disease patients

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KEYWORDS

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Abstract *Introduction:* Mechanical ventilation (MV) weaning trial can be compared to a cardiac stress test where spontaneous ventilation is a form of an exercise and therefore hemodynamic compromise can occur during the weaning process in critically ill patients. The combined increase in arterial pressure and heart rate during unsuccessful weaning is quite suggestive of weaning failure of cardiac origin. Assessment and prediction of weaning failure from cardiac origin remain complicated in patients with chronic obstructive pulmonary disease (COPD). Recent data showed that COPD itself is a powerful independent risk factor for cardiovascular morbidity and mortality, suggesting that occult cardiac dysfunction could be frequent in patients with COPD. The immediate transition from positive pressure mechanical ventilation to spontaneous ventilation may generate significant cardiopulmonary alterations that are complex and mainly include the inspiratory fall in intrathoracic pressure, the increase in work of breathing, and the catecholamine discharge that occur during abrupt transfer from mechanical ventilation to spontaneous breathing. Therefore, it could be suggested that a treatment targeting the cardiovascular system decreasing the preload might help the heart to tolerate the critical period of weaning more effectively.

Methods: This study was carried on 60 adult male and female patients admitted to the Critical Care Medicine Departments in the Alexandria Main University Hospital and who fulfilled the diagnosis of acute exacerbation of COPD according to the Global initiative for chronic obstructive lung disease (GOLD) [1], and considered eligible for weaning after at least 24 h of invasive mechanical ventilation exhibiting systemic arterial hypertension during the start of spontaneous breathing trial. 30 of them were adult patients and served as the study group (Group I), and the other 30 were age-matched adults who served as the control group (Group II). Each group was subjected to spontaneous breathing trial (SBT) using a T-piece receiving FiO_2 the same as during mechanical ventilation. Control group underwent SBT alone while the nitroglycerin group underwent continuous nitroglycerin infusion started at the beginning of the SBT and titrated to maintain normal arterial

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systolic blood pressure that is; 120–139 mmHg). Hemodynamic, oxygenation and respiratory measurements were performed on the start of SBT, and after a 2-h T-piece SBT.

Results: Compared to the start of SBT, systolic arterial blood pressure and mean arterial blood pressure decreased [from (Mean ± SD) 150.33 ± 14.26, 112.56 ± 9.37 mmHg to 134.33 ± 11.04, 92.78 ± 5.81 mmHg, respectively] in the nitroglycerin group, while the opposite occurred in the control group as systolic arterial blood pressure and mean arterial blood pressure increased [from (Mean ± SD) 144.67 ± 13.58, 109.78 ± 10.09 mmHg to 158.0 ± 19.43, 114.73 ± 10.82 mmHg, respectively]. Mixed central venous saturation ($S_{cv}O_2$) decreased significantly in the control group at the end of SBT [from (Mean ± SD) 71.90 ± 1.84 to 69.25 ± 2.20%], while in the nitroglycerin group, $S_{cv}O_2$ did not change at the end in comparison to the start of SBT [from (Mean ± SD) 71.63 ± 1.75 to 71.12 ± 1.65%]. Nitroglycerin infusion at the start of SBT enabled a successful weaning from mechanical ventilation in 90% of patients in comparison to a successful weaning from mechanical ventilation of only 63.3% in the control group.

Conclusions: Nitroglycerin infusion might facilitate the weaning off hypertensive COPD patients by alleviating the cardiovascular compromise occurring during liberation from MV.

Introduction

The worldwide chronic obstructive pulmonary disease (COPD) epidemic affects nearly 600 million people and accounts for more than 2.2 million deaths each year [1]. COPD is the fourth leading cause of death in the United States and is the only common chronic illness for which mortality rates continue to increase [2].

The Global Initiative for chronic obstructive lung disease (GOLD) defines COPD [3] as follows: ''Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases''.

Airflow obstruction makes COPD an even greater health burden because it independently contributes to the morbidity and mortality of coexisting chronic conditions, such as ischemic heart disease and heart failure [4]. Airflow obstruction and emphysema have been associated with impaired left ventricular filling [5].

Periods of acute worsening of this disease are termed as exacerbations. An exacerbation of COPD is defined as ''an event in the nature course of the disease characterized by a change in the patient's baseline dyspnea, cough and/or sputum that's beyond normal day-to-day variation, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD'' [3]. The principal identified causes of COPD exacerbations include bacterial [6], and viral infections [7], pollution events [8,9], cold weather [10], and interruption of regular treatment [11].

Chronic obstructive pulmonary disease (COPD) is a common co-morbidity in patients with heart failure, and vice versa ''strengthens the hypothesis that pulmonary obstruction itself is a major risk factor for heart failure'' [12]. The long-term risk of developing heart failure increased with reduced lung function as measured by forced expiratory volume (FEV1) by spirometry, findings which were not altered by age, prior heart disease, or cardiovascular risk factors (including smoking) [13].

Considerable negative intra-thoracic pressures developed at inspiration during airway obstruction or pulmonary dynamic hyperinflation or both increase venous return (that is, preload) and also effectively increase left ventricular after load [14,15]. Such increases may not be tolerated by spontaneously breathing patients with compromised heart function [14].

COPD is a powerful independent risk factor for cardiovascular morbidity and mortality, suggesting that occult cardiac dysfunction could be frequent in patients with COPD [16]. Weaning-induced acute cardiac dysfunction resulting in acute pulmonary congestion is a known cause or cofactor of weaning failure in predisposed COPD patients, particularly in those with pre-existing cardiac disease [17–20].

In COPD patients without obvious cardiac disease, a spontaneous breathing trial induced a significant left ventricular ejection fraction reduction not explained by a myocardial contractility decrease due to ischemia, thus implying a weaning-induced increase in the after load [21]. This increase in left ventricular after load should be higher in patients demonstrating systemic arterial hypertension, which is quite frequent in COPD patients during weaning failure [19,22].

Vasodilators decrease the pressure gradients for venous return and right and left ventricular ejection and can affect left ventricular performance in a manner similar to that of the increased intra-thoracic pressure [21]. Venous dilation reduces venous pressure and decreases ventricular preload. This reduces ventricular stress wall and oxygen demand by the heart, thereby enhancing the oxygen supply/demand ratio. A reduction in preload (reduced diastolic wall stress) also helps to improve subendocardial blood flow [23].

The efficacy of nitrates primarily arises from a decrease in left ventricular preload, manifested by a fall in pulmonary capillary wedge pressure, and from decreases in pulmonary artery, right ventricular, and right atrial pressures. In addition, the arterial-arteriolar dilating effects of nitroglycerin in congestive heart failure may result in a decrease in left ventricular after load or impedance to ejection, with a subsequent increase in stroke volume and cardiac output [24].

Therefore, it could be suggested that a treatment targeting the cardiovascular system decreasing the preload might help the heart to tolerate the critical period of weaning more effectively.

Aim of the work

The aim of the present study was directed to study the impact of using nitroglycerin infusion on weaning off mechanically ventilated COPD patients.

Patients and methods

Patient selection

Chronic obstructive pulmonary disease (COPD) patients who were admitted to The Critical Care Department in the Alexandria Main University Hospital (AMUH) and had met the inclusion criteria, intubated and mechanically ventilated because of acute decompensation. COPD was diagnosed on the basis of clinical history, arterial blood gases, chest radiographic findings and hospital admissions. Informed written consent was obtained from each patient's close relative. Approval for the study was obtained from the ethics committee of the faculty.

Inclusion criteria for study entry were the following: (a) The underlying cause of acute decompensation of COPD had been resolved and the patients were ready to wean by performing spontaneous breathing trials. Criteria used for not attempting such spontaneous breathing trials are those of evidence-based guidelines for weaning and discontinuing ventilatory support: facilitated by ACCP/AARC/ACCM [25]: (1) Tachypnea (frequency of greater than 35 breaths per minute). (2) Arterial hemoglobin oxygen saturation (S_aO_2) of less than 85–90% on pulse oximetry. (3) Tachycardia (heart rate of greater than 120–140 beats per minute) or a sustained change in heart rate of more than 20%. (4) Systolic arterial blood pressure of greater than 180–200 mmHg or less than 90 mmHg. (5) Arrhythmias. (6) Increased accessory muscle use, diaphoresis, and onset or worsening of discomfort. (b) Patients exhibiting systemic arterial hypertension, defined as systolic arterial blood pressure of at least 140 mmHg during mechanical ventilation and just before the start of spontaneous breathing trial. Exclusion criteria were: (1) Pregnant female. (2) Occurrence of unstable coronary episode (Acute myocardial infarction or unstable angina. (3) Arterial systolic blood pressure <120 mmHg. (4) Prior Sildenafil use in the last 48 h [26].

Protocol

The study was carried on 60 patients of both sexes who were intubated and mechanically ventilated because of acute decompensation and were considered eligible for weaning, 30 of them were adult patients and served as the study group (Group I), and the other 30 were age-matched adults serving as the control group (Group II). Each group was subjected to SBT using a T-piece receiving FiO_2 the same as during mechanical ventilation. The control group underwent SBT alone while the nitroglycerin group underwent continuous nitroglycerin infusion started at the beginning of the SBT and titrated to maintain normal arterial systolic blood pressure that is; 120–139 mmHg). Whenever SBT failed, administration of nitroglycerin was stopped at the time of resumption of mechanical ventilation. In case of trial success, nitroglycerin was gradually decreased and ceased during the subsequent hours.

Measurements

Once the selected 60 patients were considered eligible for the study, they were evaluated as regards: (a) Hemodynamic variables including heart rate, respiratory rate, systolic and mean arterial blood pressure. (b) Oxygenation including Partial pressure of oxygen (P_aO_2), Fraction of inspired oxygen (F_iO_2), Hypoxemic index (HI), Arterial oxygen saturation (S_aO_2) and Central mixed venous pressure of oxygen ($S_{cv}O_2$). (c) Partial pressure of carbon dioxide (P_aCO_2). (d) Arterial blood acidity (pH_a).

Weaning policy

Patients were placed in semi recumbent position while ventilated in the synchronized intermittent mechanical ventilation (SIMV) mode with the ventilator settings prescribed by the primary physician. Patients underwent a spontaneous breathing trial via a T-piece circuit while receiving the same F_iO_2 as during mechanical ventilation and gas humidification. Trials lasted for 2 h unless patients had met the criteria used to define spontaneous breathing trial failure as mentioned before. The ability of the patient to remain free of these criteria at the end of the trial was defined as successful spontaneous breathing trial, and the patient was extubated. Extubation was defined as successful when spontaneous breathing was sustained for more than 48 consecutive hours after the T-piece trial, without development of any of the criteria of weaning failure. Patients who had met these criteria during the 2-h trial or within 48 h after extubation, were put back on the synchronized intermittent mechanical ventilation (SIMV) mode, and weaning was defined as spontaneous breathing trial failure or extubation failure, respectively. Weaning failure or success was judged by the primary physicians, who were not the study investigators. After resumption of mechanical ventilation, small-bolus infusions of propofol (0.5–1 mg/kg) were given if required in weaning failure patients to achieve synchronization with the ventilator, and patients were not disconnected from the ventilator for the subsequent 24 h.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 [27,28]. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected a count less than 5, correction for chi-square was conducted using Fisher's Exact test or Monte Carlo correction. The distributions of quantitative variables were tested for normality using Kolmogorov–Smirnov test, Shapiro–Wilk test and D'Agostino test, also Histogram and QQ plot were used for vision test. If it reveals normal data distribution, parametric tests were applied. If the data were abnormally distributed, non-parametric tests were used. For normally distributed data, comparison between the two studied groups was done using independent *t*-test. Significance test results are quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

Results

Group I and Group II were homogeneous in terms of size, and demographic characteristics of the patients as shown in Table 1 and Figs. 1 and 2 with no statistically significant difference between them.

The effects of nitroglycerin on hemodynamics are shown in Table 2 and Figs. 3 and 4. No significant difference was detected between Group I and Group II at the start of SBT. From the start to the end of SBT, systolic arterial blood pressure (SABP), and mean arterial blood pressure (MABP) decreased in Group I [from (Mean ± SD) 150.33 ± 14.76, 112.56 ± 9.37mmHg to 134.33 ± 11.04, 92.78 ± 5.81 mmHg, respectively] compared with Group II whereas, both of them increased [from (Mean ± SD) 144.67 ± 13.58, 109.78 ± 10.09 mmHg to 158.0 ± 19.43, 114.73 ± 10.82 mmHg, respectively] with statistically significant difference between both groups at the end of SBT ($p < 0.001^{*}$).

The effects of nitroglycerin on oxygenation variables are shown in Table 3 and Fig. 5. Oxygenation variables were similar in Group I and Group II at the start of SBT. During the spontaneous breathing trial, central mixed venous saturation decreased [from (Mean ± SD) 71.90 ± 1.84 to 69.25 ± 2.20%] in Group II, but did not change in Group I.

Table 1 Comparison between Group I and Group II according to demographic characteristics.

	Group I ($n = 40$)		Group II ($n = 40$)		p
	No.	%	No.	%	
Gender					
Male	27	90.0	25	83.3	0.706
Female	3	10.0	5	16.7	
Age					
Min.–Max.	45.0–84.0		47.0–84.0		
Mean ± SD	66.13 ± 9.0		67.23 ± 9.0		0.638
Median	66.0		67.0		

p, value for comparing between the two groups; SD, standard deviation.

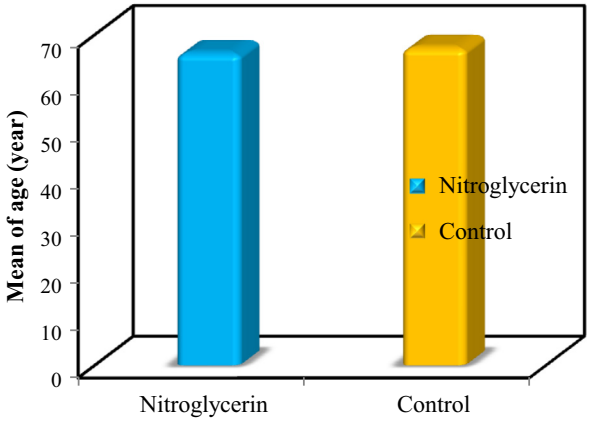

Figure 1 Comparison between the studied groups according to age.

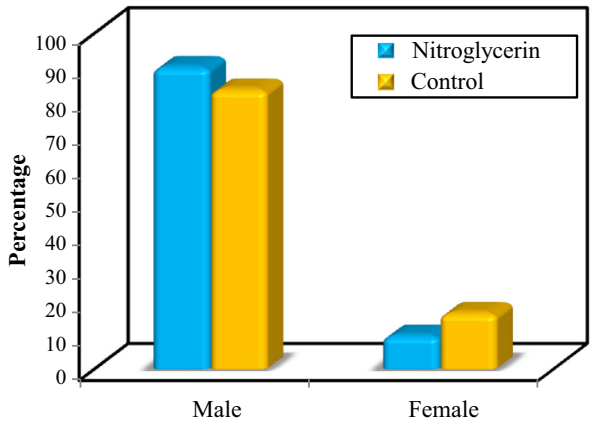

Figure 2 Comparison between the studied groups according to sex.

Tidal volume decreased throughout the spontaneous breathing trial in both groups [from (Mean ± SD) 6.97 ± 0.70 ml/kg in Group I and 6.76 ± 0.47 ml/kg in Group II at the start of spontaneous breathing trial to 5.47 ± 0.70 and 5.23 ± 0.49 ml/kg in Group I and Group II at the end of spontaneous breathing trial, respectively], with no statistically significant difference between Group I and Group II at the end of the study ($p = 0.117$) Table 4.

In both groups, partial pressure of carbon dioxide ($PaCO_2$) and arterial blood acidity (pH_a) increased slightly throughout the spontaneous breathing trial [from (Mean ± SD) 59.77 ± 12.40 mmHg, and 7.40 ± 0.03 to 61.97 ± 19.17 mmHg, and 7.41 ± 0.0, in Group I, respectively], and [from (Mean ± SD) 65.63 ± 11.62 mmHg, and 7.40 ± 0.03 to 67.40 ± 17.92 mmHg, and 7.39 ± 0.10, in Group II, respectively], with no statistically difference of significance between both groups at end of the study Table 5.

Nitroglycerin administration enabled a successful spontaneous breathing trial in 90% of patients in Group I, compared with a successful breathing trial of only 63.3% in Group II without nitroglycerin administration, with statistically significant difference between both groups at end of the study ($p = 0.015^{*}$) Table 6 and Fig. 6.

Discussion

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. COPD is the fourth leading cause of death in the world [1], further increases in its prevalence and mortality can be predicted in the coming decades [29].

AECOPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD [30,31].

The aim of the study is to evaluate the impact of using nitroglycerin infusion on weaning off mechanically ventilated COPD patients.

We conducted a prospective observational study on 60 adult male and female patients admitted to the Critical Care

Table 2 Comparison between Group I and Group II according to hemodynamics during spontaneous breathing trial.

Hemodynamics	Group I (n = 30)		Group II (n = 30)		P
	Start	End	Start	End	
HR (beats/minutes)					
Minimum	63.0	69.0	62.0	71.0	0.140[a]
Maximum	105.0	125.0	99.0	118.0	
Mean	84.40	95.40	80.27	93.07	
SD	11.54	15.06	9.97	13.23	0.526[b]
Median	87.0	96.50	79.0	91.50	
RR (cycles/minutes)					
Minimum	17.0	23.0	16.0	24.0	0.741[a]
Maximum	26.0	35.0	25.0	33.0	
Mean	21.33	28.60	21.13	29.47	
SD	2.26	2.62	2.40	2.65	0.208[b]
Median	21.50	29.0	21.0	30.0	
SABP(mmHg)					
Minimum	120.0	120.0	120.0	130.0	0.120[a]
Maximum	180.0	160.0	170.0	210.0	
Mean	150.3	134.3	144.7	158.0	
SD	14.26	11.04	13.58	19.43	< 0.001[*,b]
Median	150.0	130.0	145.0	155.0	
MABP(mmHg)					
Minimum	86.70	86.70	86.70	95.0	0.273[a]
Maximum	126.7	106.7	123.3	135.0	
Mean	112.6	92.8	109.8	114.7	
SD	9.37	5.81	10.09	10.82	< 0.001[*,b]
Median	113.3	91.65	110.0	115.0	

HR, heart rate; RR, respiratory rate; SABP, systolic arterial blood pressure; MABP, mean arterial blood pressure; p, value for comparing between the two groups.

[a] p-value of comparison between both groups at the start of spontaneous breathing trial.

[b] p-value of comparison between both groups at the end of spontaneous breathing trial.

[*] Statistically significant at $p \leqslant 0.05$.

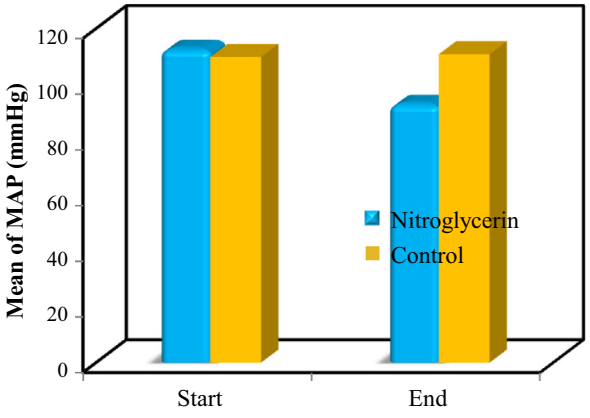

Figure 3 Comparison between the studied groups according to MABP during SBT.

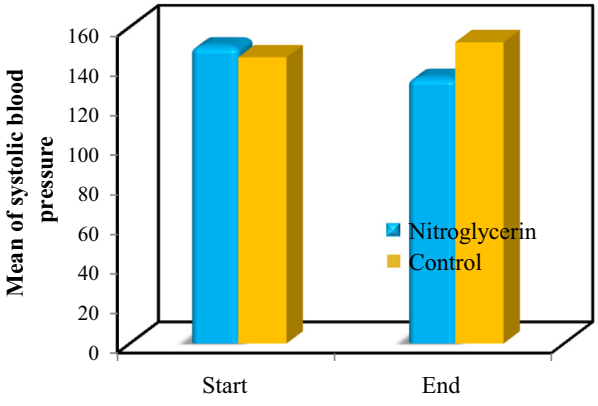

Figure 4 Comparison between the studied groups according to SABP during SBT.

Medicine Departments in the Alexandria Main University Hospital and who fulfilled the diagnosis of acute exacerbation of COPD according to the Global initiative for chronic obstructive lung disease (GOLD), and considered eligible for weaning after at least 24 h of invasive mechanical ventilation according to evidence-based guidelines for weaning and discontinuing ventilatory support: facilitated by ACCP/AARC/ACCM [25], exhibiting systemic arterial hypertension during the start of spontaneous breathing trial.

Weaning critically ill patients from mechanical ventilation (MV) is a gradual and challenging process. Discontinuation of MV should be considered when patient is able to follow commands and maintain appropriate minute ventilation. In addition, protective airway reflexes should be intact and patient clinical status must have improved. In general,

Table 3 Comparison between Group I and Group II according to oxygenation variables during spontaneous breathing trial.

Oxygenation variables	Group I (n = 30)		Group II (n = 30)		P
	Start	End	Start	End	
P_aO_2 (mmHg)					
Minimum	65.0	65.0	68.0	70.0	0.375[a]
Maximum	152.0	136.0	214.0	176.0	
Mean	99.43	95.0	105.9	98.53	
SD	22.31	19.27	32.52	23.25	0.524[b]
Median	95.10	95.0	95.50	93.50	
F_iO_2					
Minimum	0.28	0.28	0.28	0.28	0.939[a]
Maximum	0.40	0.40	0.40	0.40	
Mean	0.32	0.32	0.32	0.32	
SD	0.05	0.05	0.05	0.05	0.960[b]
Median	0.30	0.29	0.30	0.29	
HI					
Minimum	215.0	211.0	243.0	245.0	0.585[a]
Maximum	478.0	410.0	535.0	440.0	
Mean	318.6	302.2	328.7	310.0	
SD	80.27	54.05	61.73	47.79	0.556[b]
Median	298.5	283.0	312.0	311.5	
S_aO_2 (%)					
Minimum	92.0	90.0	92.0	88.0	0.506[a]
Maximum	99.0	97.0	99.70	92.0	
Mean	96.70	93.73	97.07	89.90	
SD	2.23	2.05	2.01	1.03	< 0.001[*,b]
Median	97.0	94.0	98.0	90.0	
$S_{cv}O_2$ (%)					
Minimum	68.0	67.0	69.0	64.0	0.568[a]
Maximum	74.0	73.50	75.0	72.50	
Mean	71.63	71.12	71.90	69.25	
SD	1.75	1.65	1.84	2.20	< 0.001[*,b]
Median	72.50	71.50	72.25	69.25	

P_aO_2, partial pressure of oxygen; F_iO_2, fraction of inspired oxygen; HI, hypoxemic index; S_aO_2, arterial oxygen saturation; $S_{cv}O_2$, central mixed oxygen saturation; p, p value for comparing between the two groups.

[a] p-value of comparison between both groups at the start of spontaneous breathing trial.

[b] p-value of comparison between both groups at the end of spontaneous breathing trial.

[*] Statistically significant at $p \leqslant 0.05$.

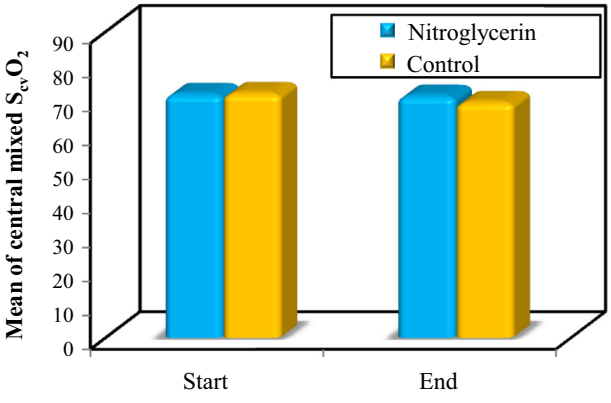

Figure 5 Comparison between Group I and Group II according to $S_{cv}O_2$ during spontaneous breathing trial.

mechanical weaning parameters are poor at predicting weaning success because they do not take into account cardiac reserves [32]. Both experimental and clinical data give convincing evidence of acute cardiac dysfunction as the origin or a cofactor of weaning failure.

Nitroglycerin is vasodilator agent that decreases the pressure gradients for venous return and right and left ventricular ejection and can affect left ventricular performance in a manner similar to that of the increased intra-thoracic pressure. Venous dilation reduces venous pressure and decreases ventricular preload. This reduces ventricular stress wall and oxygen demand by the heart, thereby enhancing the oxygen supply/demand ratio. A reduction in preload (reduced diastolic wall stress) also helps to improve subendocardial blood flow [23].

MV weaning trial can be compared to a cardiac stress test where spontaneous ventilation is a form of an exercise [32]. The immediate transition from positive pressure mechanical ventilation to spontaneous ventilation may generate significant cardiopulmonary alterations that may not be tolerated by spontaneously breathing patients with compromised heart [33]. Furthermore, in COPD patients without obvious cardiac disease, a SBT induced a significant left ventricular ejection fraction reduction implying a weaning-induced increase in afterload [34]. This increase in left ventricular afterload should

Table 4 Comparison between Group I and Group II according to tidal volume (ml/kg) during spontaneous weaning trial.

Tidal Volume(ml/kg)	Group I (n = 30)		Group II (n = 30)		P
	Start	End	Start	End	
Minimum	5.50	4.0	6.30	4.60	0.177[a]
Maximum	8.50	7.0	8.20	6.70	
Mean	6.97	5.47	6.76	5.23	
SD	0.70	0.70	0.47	0.49	0.117[b]
Median	6.90	5.40	6.50	5.0	

p, value for comparing between the two groups.
[a] p-value of comparison between both groups at the start of spontaneous breathing trial.
[b] p-value of comparison between both groups at the end of spontaneous breathing trial.

Table 5 Comparison between Group I and Group II according to tidal volume (ml/kg) during spontaneous weaning trial.

	Group I (n = 30)		Group II (n = 30)		P
	Start	End	Start	End	
$PaCO_2$ (mmHg)					
Minimum	41.0	31.0	41.0	69.5	0.064[a]
Maximum	81.0	123.0	82.0	108.0	
Mean	59.77	61.97	65.63	70.67	
SD	12.40	19.17	11.62	15.65	0.061[b]
Median	57.50	58.0	66.0	69.50	
pH_a					
Minimum	7.35	7.23	7.35	7.20	0.899[a]
Maximum	7.47	7.54	7.45	7.57	
Mean	7.40	7.41	7.40	7.39	
SD	0.03	0.08	0.03	0.10	0.478[b]
Median	7.40	7.43	7.40	7.41	

p, value for comparing between the two groups.
[a] p-value of comparison between both groups at the start of spontaneous breathing trial.
[b] p-value of comparison between both groups at the end of spontaneous breathing trial.

Table 6 Comparison between Group I and Group II according to tidal volume (ml/kg) during spontaneous weaning trial.

	Group I (n = 30)		Group II (n = 30)		P
	No.	%	No.	%	
Results					
Successes	27	90.0	19	63.3	0.015*
Failed	3	10.0	11	36.7	

p, value for comparing between the two groups.
* Statistically significant at $p \leqslant 0.05$.

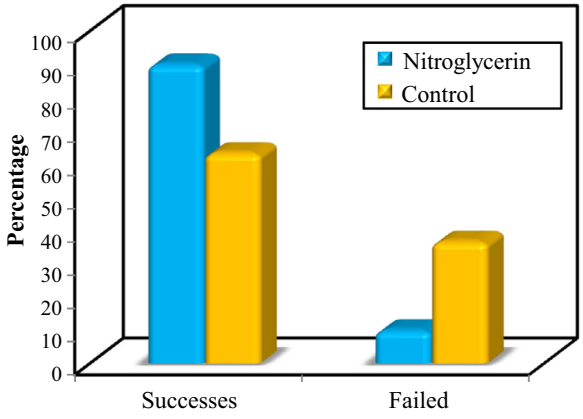

Figure 6 Comparison between the studied groups according to results.

be higher in patients demonstrating systemic arterial hypertension [36,36].

In our study there was no significant difference between the two groups as regards demographic characteristic data, including age, sex and smoking, among both groups.

In current study as regards hemodynamic variables, heart rate increased throughout the study in both groups but without significant difference between both groups at end of the study. Also, respiratory rate increased throughout the study in both groups but without significant difference between both groups at end of the study. In the nitroglycerin group, systemic and mean arterial blood pressure decreased at the end of the study. While in the control group, systemic and mean arterial blood pressure did not change significantly throughout the study until the end.

In agreement with our study, Routsi et al. [37] conducted a prospective interventional non-randomized study on twelve difficult-to-wean COPD patients who presented with systemic arterial hypertension during weaning failure. Patients were studied in two consecutive days, i.e., first day without nitroglycerin infusion (control day) and the second day with nitroglycerin infusion started at the beginning of the SBT, and titrated to maintain normal systolic blood pressure (study day). Routsi et al. [37] demonstrated a slight increase in heart rate and respiratory rate throughout the SBT until the end of the study compared with mechanical ventilation on both control and nitroglycerin days with (P = 0.26). Also, Routsi et al. [37] demonstrated that from the start to the end of SBT, mean and systemic arterial blood pressure increased compared with mechanical ventilation on control day but did not change on nitroglycerin day (P = 0.002 & $<$0.001), respectively.

In current study as regards oxygenation, in the nitroglycerin group, P_aO_2 decreased at the end of the study compared to the beginning, however, there was no significant difference between the nitroglycerin and control groups at the end of the study, however, it was not significant (P = 0.872). There

was also no significant difference between the two groups as regards hypoxemic index.

In both groups, S_aO_2 decreased throughout the study but with a significant decrease in the control group. This decrease can be attributed to multiple causes. First, a SBT induced a significant left ventricular ejection fraction reduction implying a weaning-induced increase in after load [34] and this increase in left ventricular after load should be higher in patients demonstrating systemic arterial hypertension [35,36] thus leading to left ventricular dysfunction and decreasing S_aO_2, however, nitroglycerin infusion restored these changes leading to a decrease in the after load of the heart and better toleration of the critical period of weaning on the heart. Second, the significant decrease in S_aO_2 in the control group can be attributed to a significant decrease in $S_{cv}O_2$ among control group and nitroglycerin infusion restored these changes by alleviating acute cardiac dysfunction induced by weaning.

As regards central mixed venous saturation ($S_{cv}O_2$), $S_{cv}O_2$ decreased significantly in the control group at the end of SBT, while in the nitroglycerin group, $S_{cv}O_2$ did not change at the end in comparison to the start of SBT resulting in a significant difference between both groups at the end of the study. This decrease in $S_{cv}O_2$ in the control group and absence of any change in the nitroglycerin group at end of the study can be explained by weaning-induced acute cardiac dysfunction resulting in acute pulmonary congestion that is a known cause or cofactor of weaning failure in COPD patients [38].

Moreover, if oxygen consumption increased in healthy individuals cardiac output will increase to maintain the balance between oxygen delivery and demand/consumption. But, in the critically ill patients with inadequate cardiac reserve, the response to an increase in oxygen consumption is restricted to the patient's ability to extract more of the available oxygen, thus decreasing S_vO_2 [39]. Although the absolute values of $S_{cv}O_2$ and S_vO_2 differ, previous studies have shown close tracking of the two measurements across a wide range of hemodynamic conditions [40]. So decrease in S_vO_2 correlates with the decrease in S_vO_2 and nitroglycerin infusion restored these changes by alleviating acute cardiac dysfunction induced by weaning.

In agreement with our study as regards oxygenation, Routsi et al. [37] found the effects of nitroglycerin on oxygenation variable were similar to control and study day. P_aO_2 decreased from 132 ± 35 mmHg to 89 ± 23 mmHg in nitroglycerin day and also P_aO_2 decreased from 130 ± 35 mmHg to 66 ± 17 mmHg at end of the study but there was not significant difference between both groups with ($P = 0.23$). Routsi et al. [37] also found that during SBT, mixed venous saturation decreased from 75.7 ± 3.5% with mechanical ventilation to 69.3 ± 7.5% on control day but did not change on the study day with intravenous nitroglycerin infusion ($P = 0.04$).

In a similar study, Chick et al. [41], who studied the effect of nitroglycerin on gas exchange, hemodynamic and oxygen transport in patients with COPD, found that arterial PO_2 slightly decreased about 2 mmHg following administration of nitroglycerin however, this finding did not reach significance.

In consistence with Chick et al., Kochukoshy et al. [42], who also studied the effect of nitroglycerin in gas exchange on patients with COPD, noted that there was slight decrease in arterial oxygen tension for the duration of the study; the maximal changes were from a mean pre-nitroglycerin value of 53.5 mmHg to 50.3 mmHg at 30 min and also this value failed to reach a significance. These findings were consistent with previous study of Brent et al. who studied contrasting acute effects of vasodilator (nitroglycerin, nitroprusside, and hydralazine) on right ventricular performance in patients with COPD and pulmonary hypertension.

In current study, tidal volume (VT/kg) decreased at end of the study in both but without significant difference between both groups at the end of the study.

In agreement with our study, Routsi et al. [37] found that tidal volume decreased throughout the SBT compared with mechanical ventilation on both control day and nitroglycerin day ($P = 0.18$).

In current study, Partial pressure of carbon dioxide (P_aCO_2) was not significantly changed in both groups at the end of the study.

In agreement with our study, Routsi et al. [37] found that P_aCO_2 slightly increased throughout the SBT compared with mechanical ventilation on both control day and nitroglycerin day but without significant difference between both control and nitroglycerin infusion ($P = 0.18$).

In current study, the arterial blood acidity (pH_a) was not significantly changed in both groups at the end of the study.

In agreement with our study, Routsi et al. [37] found that there was not significantly change as regards the arterial blood acidity (pH_a) in comparison with mechanical ventilation on both control day and nitroglycerin day with $P = 0.20$.

In the current study, as regards weaning success, there was a significant difference between both groups at the end of the study with more success rate in the nitroglycerin group. At the end of the study, all patients met the criteria of weaning failure in both groups, had been put back on mechanical ventilation, receiving small-bolus infusion of propofol (0.5–1 mg/kg) to achieve synchronization with the ventilator and were not disconnected from the ventilator for the preceding 24 h and were excluded from the study.

In agreement with our study as regards weaning success, Routsi et al. [37] noticed that on control day, all patients met the criteria of weaning failure after 49 ± 33 min and were returned to mechanical ventilation. In contrast, with nitroglycerin infusion on the study day, 11 out of 12 patients (92%) tolerated the spontaneous breathing trial ($P > 0.001$); one patient failed this trial because of severe bronchospasm.

Similarly, Morley et al. [43] conducted a study to determine if there was any short term hemodynamic improvement in patients with stable severe COPD and cor pulmonale. They found that the heart rate was increased by an infusion of nitroglycerin from a mean of 104 ± 16 before nitroglycerin to 113 ± 17 beats/min after nitroglycerin. Also P_aO_2 was not significantly changed by nitroglycerin administration from 49 ± 9 mmHg before nitroglycerin to 48 ± 10 mmHg after nitroglycerin. The P_aCO_2 decreased slightly following nitroglycerin administration from 54 ± 9 mmHg before nitroglycerin to 51 ± 10 mmHg after nitroglycerin. The mixed venous oxygen tension decreased significantly about 11% after nitroglycerin infusion and was not accounted for by an increase in oxygen delivery. Morley et al. suggested a reduction in the cardiac output or worsening of ventilation–perfusion relationships as a possible outcome. However, Morley et al. failed to document strong correlation coefficients between the change in mixed venous oxygen tension and the change in cardiac index. Morley et al. concluded that hemodynamic testing would be required in individual patient to document

improved hemodynamic effects. Also, suggested that it may be argued that the condition of patients without cor pulmonale may be more responsive to vasodilator therapy.

Limitations of the study

The results of this study clearly showed that nitroglycerin infusion can facilitate the weaning of hypertensive COPD patients, yet the study had some limitations. First, the study was a single-center study and the sample size was small and heterogeneous. Second the target of normal systolic arterial blood pressure in the nitroglycerin group was achieved only partly in some patients and their systolic blood pressure intermittently remained higher than normal. Third, Swan Ganz catheter was not inserted to get the right atrial (RAP), pulmonary artery (PAP), pulmonary artery occlusion (PAOP) pressures, and cardiac index (CI) changes during nitroglycerin infusion. Fourth, we could not assess the ventilation perfusion effects of nitroglycerin infusion. Finally, this study was conducted only on hypertensive COPD, and did not evaluate the effects of nitroglycerin infusion in normotensive COPD patients.

Conclusion

Nitroglycerin infusion can facilitate the weaning off hypertensive COPD patients by alleviating the cardiovascular compromise occurring during liberation from MV.

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