Role of measurement of plasma proteins in diagnosis of weaning induced pulmonary oedema, a randomized blind study

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Abstract: Background and Purpose: to study the relationship between weaning induced pulmonary oedema and the change in plasma proteins concentration so it can be used as non-invasive diagnostic tool of weaning induced pulmonary oedema. **Aim of Work:** to confirm the relationship between the changes in plasma protein concentration during a weaning trial and the diagnosis of weaning-induced pulmonary oedema. **Methods:** patients will be admitted in intensive care department of Ain shams University, from April 2017 to May 2018 after approval of ethical committee, with diagnosis of weaning induced pulmonary oedema will be subjected to full clinical assessment with history and examination and APACHE3 score at time of admission, echocardiographic criteria were used to diagnose weaning induced pulmonary oedema, data were collected and analyzed by SPSS program, using T-test, chi square and ANOVA. **Results:** increase of plasma protein level can be used as diagnostic tool for weaning induced pulmonary oedema. **Conclusion:** Haemoconcentration occurring during weaning induced pulmonary oedema lead to increase in plasma protein level which can be considered in diagnosis of weaning induced pulmonary oedema as an alternative to other invasive methods.

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1. Introduction

Mechanical ventilation generally exerts negative hemodynamic effects in patients with normal cardiac function mainly because of the reduction in venous return induced by positive intrathoracic pressure at each insufflation. By contrast, positive pressure ventilation exerts beneficial effects in patients with cardiogenic pulmonary edema such that it is routinely used as a therapy in this category of patients. Conversely, cardiac consequences of spontaneous breathing may be responsible for weaning failure in patients with left heart disease, even though the mechanical ventilation was required for respiratory failure of non-cardiac origin (***Lamia et al., 2009)***.

Acute cardiac dysfunction and cardiogenic pulmonary edema may occur during weaning from mechanical ventilation, especially in patients with a history of left heart disease and chronic obstructive pulmonary disease. Among the complex and intricate mechanisms, myocardial ischemia, excessive increased LV afterload, and increased cardiac preload play predominant contributing roles there is no codified treatment for weaning-induced pulmonary edema. Use of diuretics and/or nitrates should be considered after careful analysis of the main contributing mechanisms ***(Papanikolaou et al., 2011).***

Measuring the elevation in pulmonary artery occlusion pressure using right heart catheterization was first proposed as a means of diagnosing weaning failure of cardiac origin ***(Gerbaud et al., 2012).***

Right heart catheterization procedure has many complication. The most frequent complications were related to venous access (e.g., hematoma, pneumothorax), followed by arrhythmias and hypotensive episodes related to vagal reactions or pulmonary vaso-reactivity testing. ***(Hoeper et al., 2006).***

Less invasive tools, such as transthoracic echocardiography or change of plasma protein concentration, have recently been proposed as valuable alternative diagnostic methods for weaning-induced pulmonary edema ***(Cabello et al., 2010)***.

Aim of Work

The aim of this work is to confirm the relationship between the changes in plasma protein concentration during a weaning trial and the diagnosis of weaning-induced pulmonary oedema.

2. Patients and Methods

Our study was conducted at Ain Shams hospital intensive care units from April 2017 to May 2018 after approval of ethical committee, on group of patients who are already on weaning trials.

Weaning criteria for performing weaning trial used in ICU unit include evidence of reversal of the underlying cause for respiratory failure, adequate

oxygenation on low PEEP, hemodynamic stability, and the ability to initiate an inspiratory effort.

Weaning failure is usually defined as an unsuccessful spontaneous breathing trial (SBT) or need for ventilator support (including noninvasive ventilation) within 48 hour after extubation.

A group of participants included in the study are patients

- BMI (18-25).
- Intubated ventilated fulfilling screening criteria for performing weaning trial.
- Low FiO_2 (< 0.5) and PEEP (< 5-8cmH2O) requirement.
- Hemodynamic stability (low dose to no inopressors).
- Able to initiate spontaneous breaths (good neuromuscular function). ***We excluded from the study those with:***

1. Patients with diagnosed neuromuscular disease.
2. Patient on tracheostomy.
3. History of congenital heart disease.
4. Obese patient (BMI >30).
5. Non sinus rhythm patients as patient with atrial flutter or fibriation rhythm.

Before performing the third weaning trial for patients who failed to be weaned in two previous trials, we will record the following (heart rate, systemic arterial pressure, oxygen saturation, respiratory rate, plasma protein and arterial hemoglobin concentrations). Left ventricular ejection fraction will be measured by Simpson method by echocardiography.

Data including heart rate, oxygen saturation, and arterial blood pressure will be recorded throughout weaning trial every 15 minutes.

The patients with failed weaning will be divided into two groups, 1st group with pulmonary oedema (PE+) and 2nd group patient without pulmonary edema (PE-) by echocardiographic criteria.

Group (I): patient with Pulmonary Edema by echocardiographic criteria.

Group (II):): patient without Pulmonary Edema by echocardiographic criteria.

Echocardiographic criteria:

We consider increase in PCWP as early mitral flow (E)/late mitral flow (A) >0.95 and early mitral flow (E)/ tissue Doppler imaging of the lateral mitral annulus on the apical four chamber view allowed peak velocity (Ea)>8.5, ***(Macintyre, 2012).***

Measurements & data collection:

Data collected will be…

1. Full demographic data including sex, age, and weight.
2. Comorbidities such as heart disease, respiratory failure, diabetes mellitus and hypertension.
3. Causes of ICU admission illness severity at admission (APACHEIII). ***(Knaus, et al., 1991)***
4. Basal vital data (HR, SAP, DAP, SPO2), plasma proteins, arterial hemoglobin concentration and Echo assessment before performing 3rd weaning trial.
5. Vital data throughout weaning trial every 15 minute.
6. At end of trial vital data, plasma protein, hemoglobin concentration and Echo assessment will be measured.

Collected data will be statistically compared.

Statistics:

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, student t- test, Paired t-test, Chi-square, Linear Correlation Coefficient by SPSS V17.

Results

1. Demographic Data:

As regard age, sex, BMI and duration of the APACHE, there were no statistically significant differences between the two groups (*p-value*> 0.05) as shown in table (R- 1).

Table (1): Comparison between the two different groups as regards age (in years), sex, weight (in Kg), BMI and APACHE.

	WIPO (n=12)	NWIPO (n=12)	p-value
Age (yr.)	45.917±5.931	47.417±5.946	50.931
Sex (M/F)	5/7	8/4	C0.673
BMI	21.417±1.782	21.500±2.111	T0.918
APACHE	210.917±68.182	254.917±80.534	T0.163

2. Other CO-morbidities

Regarding prevalence of other co-morbidities such as hypertension, diabetes, left ventricular ejection fraction there was no significant difference between the 2 groups as shown in table (R-2).

Table (2): Comparison between the 2 groups regarding other co-morbidities

Diagnosis	Group **WIPO** (n=20)	Group **NWIPO** (n=20)	Chi square test *p*-value
Hypertension (%)	3 (25%)	1 (8.3%)	0.273
DM (%)	2 (16.67%)	2 (16.67%)	1.000
Left ventricular ejection fraction, (%)	(47–59) 53.75	(44–58) 50.75	0.07

3. Hemodynamics:

Heart rate (HR), systolic blood pressure and oxygen saturation (SPO_2) and respiratory rate (RR) were monitored and recorded throughout weaning trial every 15 minutes.

A second set of measurements was performed at the end of the trial, Values were compared between the 2 groups, and an in-group analysis was done comparing each reading with its baseline reading.

a) Heart rate:

Regarding HR at different times the values are compared among the 2 groups and each were also compared with its baseline value in an in group analysis, the results are shown in table (R3) and figure (R1).

The results showed that: Regarding 2 group analysis there was significant increase in HR during weaning in WIPO group relative to NWIPO group.

Regarding in group analysis

In WIPO: the results showed significant increase in HR in the minutes 15, 30, 45, 60 regarding to baseline.

In NWIPO: the results showed no difference.

Table (4): Comparison between the 2 groups regarding HR (in b/m).

HR		**Groups**			**T-Test**	
		NWIPO	**WIPO**		**t**	**P-value**
Before	**Range**	67 - 84	68 - 90		-0.695	0.494
	Mean ±SD	77.000 ± 5.152	78.833 ± 7.542			
During weaning	**Range**	65 - 90	100 - 130		-11.053	<0.001*
	Mean ±SD	82.333 ± 7.667	118.750 ± 8.454			
Differences	**Mean ±SD**	-5.333 ± 9.820	-39.917 ± 11.301			
Paired Test	**P-value**	0.087	<0.001*			

b) Systolic blood pressure:

Regarding systolic BP at different times the values are compared among the 2 groups and each were also compared with its baseline value in an in group analysis, the results are shown in table (R4) and figure (R2).

The results showed that: Regarding 2 group analysis there was significant increase in SBP in WIPO group relative to NWIPO group.

Regarding in group analysis:

In WIPO: the results showed significant increase in systolic BP in the minutes 15, 30, 45, 60 regarding to baseline.

In NWIPO: the results showed no significant difference.

Table (5): Comparison between the 2 studied groups as regards systolic arterial blood pressure (in mmHg).

SBP		**Groups**			**T-Test**	
		NWIPO	**WIPO**		**t**	**P-value**
Before	**Range**	95 - 130	95 - 130		-0.303	0.764
	Mean ±SD	112.083 ± 10.757	113.333 ± 9.374			
During weaning	**Range**	90 - 140	120 - 170		-5.477	<0.001*
	Mean ±SD	117.917 ± 14.551	150.000 ± 14.142			
Differences	**Mean ±SD**	-5.833 ± 19.904	-36.667 ± 14.355			
Paired Test	**P-value**	0.332	<0.001*			

c) Diastolic blood pressure:

Regarding diastolic BP at different times the values are compared among the 2 groups and each were also compared with its baseline value in an in group analysis, the results are shown in table (R5) and figure (R3).

The results showed that: Regarding 2 group analysis there was significant increase in WIPO group compared to NWIPO group.

Regarding in group analysis:

In WIPO: the results showed significant increase in systolic BP in the minutes 15, 30, 45, 60 regarding to baseline.

In NWIPO: the results showed no significant difference regarding to baseline.

Table (6): Comparison between the 2 studied groups as regards diastolic arterial blood pressure (in mmHg).

DBP		Groups			T-Test	
		NWIPO	WIPO		t	P-value
Before	Range	60 - 85	60 - 90		-0.715	0.482
	Mean ±SD	71.250 ± 9.324	74.167 ± 10.624			
During weaning	Range	60 - 90	70 - 100		-2.738	0.012*
	Mean ±SD	77.583 ± 9.568	87.500 ± 8.118			
Differences	Mean ±SD	-6.333 ± 13.753	-13.333 ± 13.872			
Paired Test	P-value	0.139	0.007*			

d) Oxygen saturation:

Regarding oxygen saturation at different times the values are compared among the 2 groups and each were also compared with its baseline value in an in group analysis, the results are shown in table (R5) and figure (R3).

The results showed that: Regarding 2 group analysis there was significant decrease in WIPO group.

Regarding in group analysis: In WIPO: the results showed significant decrease in systolic BP in the minutes 15, 30, 45, 60 regarding to baseline.

In NWIPO: the results showed no significant difference.

Table (R-7): Comparison between the 2 studied groups regarding oxygen saturation.

SPO2		Groups			T-Test	
		NWIPO	WIPO		t	P-value
Before	Range	95 - 99	95 - 100		-1.527	0.141
	Mean ±SD	96.667 ± 1.231	97.583 ± 1.676			
During weaning	Range	92 - 99	50 - 66		23.952	<0.001*
	Mean ±SD	96.333 ± 2.060	59.417 ± 4.926			
Differences	Mean ±SD	0.333 ± 1.670	38.167 ± 5.654			
Paired Test	P-value	0.504	<0.001*			

e) Respiratory Rate:

Regarding systolic RR at different times the values are compared among the 2 groups and each were also compared with its baseline value in an in group analysis, the results are shown in table (R7) and figure (R5).

The results showed that: Regarding 2 group analysis there was significant increase in WIPO group.

Regarding in group analysis:

In WIPO: the results showed significant increase in RR in the minutes 15, 30, 45, 60 regarding to baseline.

In NWIPO: the results showed significant difference increase in RR in the minutes 15, 30, 45, 60 regarding to baseline.

Table (8): Comparison between the 2 groups as regards (RR).

RR		Groups			T-Test	
		NWIPO	WIPO		t	P-value
Before	Range	19 - 30	19 - 29		-1.024	0.317
	Mean ±SD	22.583 ± 2.937	23.833 ± 3.040			
During weaning	Range	19 - 28	10 - 40		1.868	0.075
	Mean ±SD	22.167 ± 2.887	16.167 ± 10.744			
Differences	Mean ±SD	0.417 ± 2.712	7.667 ± 11.316			
Paired Test	P-value	0.045*	0.039*			

4. Plasma protein concentration

Regarding plasma protein concentration the values are compared among the 2 groups and each were also compared with its baseline value in an in group analysis, the results are shown in table (R8) and figure (R7).

The results showed that: Regarding 2 group analysis there was significant increase in WIPO group.

Regarding in group analysis:

In WIPO: the results showed significant increase.

In NWIPO: the results showed no significant difference.

Table (9): Comparison between PLS-PT among the 2 groups.

PLS-PT (g/l)		Groups						T-Test	
		WIPO			NWIPO			t	P-value
Before	Range	45	-	60	44	-	64	0.157	0.877
	Mean ±SD	53.917	±	5.551	53.500	±	7.355		
During weaning	Range	48	-	62	50	-	70	--7.035	0.0162*
	Mean ±SD	55.500	±	5.283	59.417	±	7.751		
Differences	Mean ±SD	-1.583	±	1.240	-5.917	±	1.240		
Paired	P-value	<0.001**			0.058				

5. Hemoglobin concentration:

Hemoglobin concentration showed no significant difference between 2 groups (p value more than 0.05).

But regarding in group analysis WIPO group showed significant increase in heamoglobin concentration (p value less than 0.05) as shown in table (R-11) figure (R-10).

Table (10): Comparison between the 2 groups HB.

HB		Groups						T-Test	
		NWIPO			WIPO			t	P-value
Before	Range	9	-	12.5	8.5	-	12	0.610	0.548
	Mean ±SD	10.550	±	1.108	10.258	±	1.232		
During weaning	Range	9.3	-	55	11	-	15	1.657	*0.002
	Mean ±SD	21.508	±	19.032	12.375	±	1.464		
Differences	Mean ±SD	-10.958	±	19.421	-2.117	±	0.761		
Paired Test	P-value	0.077			<0.001*				

4. Discussion

Weaning-induced cardiogenic pulmonary oedema (WIPO) is a cause of weaning failure. Early diagnosis affects management as it decrease weaning trials and help disconnecting ventilator so that we can avoid many problems as ventilator associated pneumonia, complication of positive pressure ventilation such as, volutrauma, barotrauma, atelectotrauma, and shortening the time patient spend in the ICU. Early prediction of weaning induced pulmonary oedema make the cause of weaning failure preventable by using diuretics, morphine and nitrates as suggested by ***bahloul et al., in 2002***.

Several mechanisms can be involved in the development of pulmonary oedema during weaning from mechanical ventilation such as increase in afterload, increase in volume preload and myocardial ischemia resulting from increased oxygen demand due stressful state and increased work of breathing especially in patient with previous coronary artery disease. ***(Michard & Teboul, 2010)***

Classical diagnosis of WIPO can be done by measuring pulmonary capillary wedge pressure via swan gaz which is invasive method with many complications such as trauma which may lead to haematoma and pneumothorax with possibilities of hypotension or arrhythmias which are life threatening conditions. Also the interpretation of the pulmonary artery occlusion pressure trace during marked inspiratory efforts and large changes in intrathoracic pressure could be particularly difficult for non-expert practioners. In addition, physicians could be reluctant to insert a pulmonary artery catheter at the time of weaning, when invasive devices have usually been removed. Thus alternative noninvasive methods are needed for identifying weaning-induced pulmonary oedema. ***(Gerbaud et al., 2012)***

WIPO can also diagnosed by echocardiography, however it may not be applicable in some patients as

obese so using Doppler to diagnose WIPO need experienced echocardiographer and good echocardiography machine to show mitral flow transthoracic and may require even trans esophageal echocardiography which is not available in all intensive care units all the time ***(Moschietto et al., 2012).***

During cardiogenic pulmonary oedema, a hypo-oncotic fluid is filtered toward the interstitial space. Thus, we tested whether the changes in plasma protein concentration as an easy rapid noninvasive method during a weaning trial could diagnose weaning-induced pulmonary oedema.

Our study was conducted on a group of patients who are already on weaning trials. We used echocardiography to assess pulmonary edema. Patients included were divided into two groups:

Group (I) WIPO: patient with Pulmonary Edema by echocardiographic criteria.

Group (II) NWIPO:): patient without Pulmonary Edema by echocardiographic criteria.

On comparing our two study groups regarding demographic data there was no significant difference.

Regarding hemodynamics, In WIPO group: the results showed increase in HR, systolic & diastolic BP, RR and decrease in oxygen saturation in the minutes 15, 30, 45, 60 regarding to baseline. In NWIPO: the results showed no significant difference except in RR which was increased significantly in the minutes 15, 30, 45, 60 regarding to baseline. On comparing 2 groups, analysis showed that there was significant difference in the change of HR, systolic BP, diastolic BP, oxygen saturation but there was no significant difference in RR. This is different from results obtained by **Anguel et al., in 2008** in that in his study heart rate, respiratory rate, oxygen saturation, diastolic and systolic blood pressure all showed significant difference from their base line in both group WIPO and non WIPO.

Regarding pulmonary capillary wedge pressure there was significant increase in WIPO group, in group analysis showed that pulmonary capillary wedge pressure is increasing in WIPO group not in NWIPO group, this coincides with the results obtained by **Anguel et al., in 2008.**

In our study there was significant increase in plasma protein concentration with WIPO group.

In 1979 fein & colleagues analyzed alveolar fluid & plasma proteins in 24 patients with pulmonary oedema, in 21 of whom PCWP was also measured. They found significant increase in plasma proteins concentration with increase in PCWP which coincides with our results. By comparing plasma concentration of alveolar fluid & plasma they conclude that there was an increase in permeability from high hydrostatic pressure oedema and that the relative osmotic & hydrostatic forces contribute to pulmonary edema when alveolar capillary membrane is damaged, It was difficult to consider other pathophysiological hypotheses than sudden hydrostatic pulmonary oedema development to explain such abrupt changes in plasma protein concentration, neither the total amount of plasma protein nor the plasma volume in which proteins are diluted may have changed over such a short time and this support the idea of using plasma protein level as an indicator of fluid shift and pulmonary oedema diagnosis.

In 1978, Figueiras and Weil followed the onset of acute cardiogenic pulmonary edema in 21 patients, they found an increases in plasma protein concentration, and colloid osmotic pressure, which were associated with decreases in plasma volume. Accordingly, there was a loss of hypo-oncotic fluid into the extravascular spaces. Following treatment with oxygen, furosemide, and morphine sulfate and reversal of clinical and radiographic signs of pulmonary edema, decline in plasma protein concentration, and colloid osmotic pressure were associated with increases in plasma volume. Hypo-oncotic edema fluid was therefore reabsorbed into the vascular compartment. The concept that acute heart failure with pulmonary edema is associated with an increase in intravascular volume is therefore not supported. To the contrary, there is a reduction of blood volume during acute pulmonary edema. During reversal of acute pulmonary edema with diuresis, there was re-expansion rather than contraction of blood volume, by approving this concept we can say that haemoconcentration indicators as hemoglobin and plasma protein can be used for diagnosis of WIPO.

In 2008Anguel et al Performeda Prospective study in which plasma protein concentration was measured before and at the end of the spontaneous breathing trial. During the weaning trial, pulmonary oedema was observed in 24 patients. In these patients, the plasma protein concentration increased by 11% (3-25%). The plasma protein concentration did not change significantly in patients who did not experience weaning-induced pulmonary oedema and the coincides with our results.

An increase in the plasma protein concentration greater than 6% from baseline to the end of the weaning trial allowed detecting a weaning-induced pulmonary oedema, we could not define cut off value however there was positive relationship between PCWP and plasma protein concentration.

Also in agreement with our results, the study done by **Dres et al. in 2014** who studied whether the changes in extravascular lung water indexed for ideal body weight could detect weaning-induced pulmonary edema. They also studied the diagnostic value of blood volume contraction indices such as plasma

proteins and Hb concentration. In this prospective study, twenty-one patients who failed a first spontaneous breathing trial. They performed a second 60-minute T-tube spontaneous breathing trial. Before and at the end of spontaneous breathing trial, pulmonary artery occlusion pressure was recorded, as well as the extravascular lung water indexed for ideal body weight. Their results showed, extravascular lung water indexed for ideal body weight increased only in cases with weaning-induced pulmonary edema. Plasma protein concentration significantly increased only in cases with weaning-induced pulmonary edema.

Regarding change In HB concentration, in our study HB concentration showed significant increase between 2 groups which coincides with study was done by **Anguel et al. 2008** which demonstrated significant increase in hemoglobin concentration.

Recommendations

- The acute changes in plasma protein concentration during a weaning trial represent an alternative method to right heart catheterization for assessing weaning-induced pulmonary oedema.
- This would allow early detection, management, preventing complications and decreasing economic burden of health insurance.

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