Effects of airway pressure release ventilation on extra vascular lung water in acute lung injury and acute respiratory distress syndrome

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Abstract

***Background*: Extra Vascular Lung Water plays an important role in the pathophysiology of Acute Lung Injury and Adult Respiratory Distress Syndrome, and correlates with oxygenation and survival. Our trial is testing the hypothesis that Airway Pressure Release Ventilation reduces the EVLW (primary endpoint) in ALI/ARDS patients through the increase in the mean airway pressure paralleling the improvement in oxygenation (secondary endpoint).**

***Methods*: A pilot study to test the effect of APRV on the EVLW in patients with ALI/ARDS compared to conventional mechanical ventilation. EVLW was measured by the thermodilution method using the PiCCO2 system. Measurements were done on conventional ventilation, after 1 and 6 hours from switching to APRV. Six patients with the diagnosis of ALI/ARDS < 72 hours were enrolled during a 3 months period.**

***Results*: Results are reported in mean ± SD, and statistical analysis is done with one way multi-measurement ANOVA. P value of 0.05 was considered significant. Regression analysis was used to test the correlation between variables. EVLWI was significantly reduced by 24 % (19.6 ± 7.5 to 15 ± 4.1) in 1 hour and 11 % (17.5 ± 6) in 6 hours, P value: 0.017. The mPaw was significantly increased by 68 % (15.8 ± 5.5 to 26.5 ± 4.7) in 1 hour and by 55 % (24.5 ± 3.8) in 6 hours, P value: 0.004. PaO_2/FiO_2 was increased by 47 % (163.6 ± 67.6 to 239.8 ± 132.4) in 1 hour and 68% (275.8 ± 165.3) in 6 hours, P value: 0.064. The mPaw/EVLWI index was significantly increased by 114 % (0.87 to 1.86) in 1 hour and by 76% (1.53) in 6 hours, P value: 0.015. Strong relations were found between mPaw and EVLWI (R = 0.85), mPaw and PaO_2/FiO_2 (R = 0.88), EVLWI and PaO_2/FiO_2 (R = 0.99), mPaw/EVLWI Index and $PaO2/FiO_2$ (R = 0.79).**

***Conclusion*: APRV reduced EVLW, and improved PaO2/FiO2. Mean airway pressure may play an important role in the reduction of EVLW and improvement in oxygenation during APRV. Reduction of EVLW improves oxygenation in ALI/ARDS.**

Key words: Airway pressure release ventilation, extra vascular lung water, mean airway pressure, acute lung injury, acute respiratory distress syndrome, positive end expiratory pressure.

Introduction

Extra vascular lung water (EVLW) is a sum measure of alveolar and interstitial fluid in the lungs, and is indexed to the body weight as EVLWI (ml/kg). It is usually measured by the double indicator dilution technique (thermo-dye) (1) and the ex-vivo gravimetric method. (2) Recently, the single-indicator (cold saline) dilution method (3) has emerged as an alternative practical way to make the calculation at the bedside and showed close correlation and agreement with the previous two methods. (4)

The role EVLW plays in acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) had been

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recognized over the last decade on the severity of sepsis induced lung injury. (3) Moreover it has been correlated to the survival of patients with sepsis, (5) and elevated values have been recognized as a poor prognostic value in the critically ill patients. (6) Medical interventions usually through fluid restriction and diuretics, aiming at reducing the EVLW in ALI/ARDS had shown improvements in oxygenation and duration of mechanical ventilation. (7-9) Those interventions may be difficult to be subscribed to patients with lung injury especially for those who are hemodynamically unstable secondary to shock or those who are suffering kidney injury. (10)

Multiple studies have evaluated the effects of positive end expiratory pressure (PEEP) on EVLW but with conflicting results. Some studies have shown no effect, (11,12) while others (7,13,14) have documented positive effect on reducing the EVLW with the application of, or increasing the PEEP. The recognized beneficial effects of PEEP on oxygenation are mostly the prevention of lung derecruitment during exhalation, and improvement in the respiratory system compliance through restoration of the lung functional residual capacity (FRC). (15)

Airway pressure release ventilation (APRV) is a form of non-conventional pressure targeted intermittent mandatory ventilation that was introduced to clinical practice more than two decades ago. (16) The benefits of APRV on oxygenation in ALI/ARDS have been documented, and can be summarized as: the effects of spontaneous breathing, prolonged mandatory inspiratory time, increased mean airway pressure (mPaw), lung recruitment, and prevention of lung derecruitment during a short release time. (17)

To our knowledge no studies have been done to investigate the effect of APRV on EVLW.

Our current study aimed to test the effect of applying APRV on the EVLW in patients with ALI/ARDS without any other medical interventions, and to test the correlation between the change in the mean airway pressure, EVLW and oxygenation.

Materials and Methods

Patients and demographics

During a 3 months period, patients admitted to the medical ICU at our organization were screened for inclusion (inclusion and exclusion criteria below). Patients' demographics are summarized in **Table 1**.

Inclusion criteria: Adult patients ≥18 years with ALI/ARDS defined by the American-European consensus conference on ARDS (18) ($PaO_2/FiO_2 \leq 300$ in ALI and ≤ 200 in ARDS regardless of PEEP level, bilateral infiltrates on chest radiograph, no evidence of left atrial hypertension or pulmonary artery wedge pressure ≤18 mmHg), and onset of ALI/ARDS ≤72 hours.

Exclusion criteria: onset of ALI/ARDS ≥96 hours, cardiogenic etiology of the pulmonary edema, severe obstructive airway disease, absence of spontaneous breathing, contraindication for spontaneous breathing or the need for paralytic agents usage, suspected or confirmed increase of the intracranial pressure, contraindication for the insertion of a femoral arterial line, and if the primary treating team thought that switching to APRV is not in the patient's best interest. Twenty patients were screened upon admission to our ICU. Fourteen patients met the exclusion criteria and six were included in the study.

Study protocol

The study was approved by our Institute Review Board (IRB).

After the signed consent by the patient's next of kin was obtained, a femoral arterial line catheter was placed by one of the study investigators. Baseline measurements of data were obtained on conventional ventilation (0 hour) either volume or pressure targeted ventilation, then the ventilator mode was changed to APRV according to the protocol below. The same measurements were repeated after 1 and 6 hours. The primary treating team was not blinded to the data about oxygenation/ventilation or other hemodynamics from the PiCCO2 except for the EVLWI.

Ventilator protocol settings when switching from conventional ventilation to APRV: The number of releases were set between 6 to 10 per minute according to the patients arterial partial pressure of carbon dioxide (PaCO2) (6 releases if PaCO2 less than 40 mmHg, 8 if the value between 40 to 60 mmHg and 10 if the value above 60 mm Hg). P High (high pressure or mandatory inspiratory pressure) was set equal to the plateau pressure (P plat) in volume controlled continuous mandatory ventilation (VC-CMV), or the peak inspiratory pressure (PIP) in pressure controlled continuous mandatory ventilation (PC-CMV) but P High more than 35 cmH2O was avoided. P Low (low pressure or mandatory expiratory pressure) was always set at zero cmH2O. T Low (release time) was adjusted to be about 50% to 75% of the peak expiratory flow (PEF) not to exceed 0.8 seconds. T High (the mandatory inspiratory time i.e. the duration of the P High) was adjusted according to the number of releases and the T Low to achieve 85-95% of the duty cycle (T High/T High+T Low).

Automatic Tube Compensation (ATC) was set between 50% and 75% according to the endo-tracheal tube size (50% for sizes 7.5-8 mm, and 75% for sizes 7 mm and less). Arterial blood gas was obtained on conventional ventilation before the switch to APRV and after 1 hour, and after 6 hours from the switch. The P High and number of releases were changed if needed according to the PaCO2 levels and the release volumes. Patients were allowed to breathe spontaneously, sedation was given according to our ICU protocol, but no muscle paralytic agents were allowed. Conventional ventilator settings before the switch to APRV are summarized in **Table 2**.

Measurements

Our ICU nurses were trained on using the PICCO2 system prior to the trial. The EVLWI and other hemodynamics were measured using the single indicator thermodilution method (3) using 10 cc of cold saline according to the PICCO2 system's manual. The cold saline was injected through a central line (internal jugular vein or subclavian vein). Three measurements were done each time and the average recorded on the PICCO2 unit was recorded.

Statistics

The mean values after 1 and 6 hours were compared to 0 hours as percentage differences. One way multi-measurement ANOVA was used to test the difference between each variable, using p value of 0.05 as a significant value to reject the null hpothesis. Regression analysis was used to test the correlation between variables with a confidence interval of 95%. Correlations tested were: mPaw to PaO2/FiO2, mPaw to EVLWI, EVLWI to PaO2/FiO2, and mPaw/EVLWI Index to PaO2/FiO2.

Results

The results are summarized in **Table 3**. Results are reported in mean values ± SD, percentage differences, and p values between the variables on conventional ventilation (hour 0), the 1st hour (hour 1), and the 6th hour (hour 6) after switching to APRV. The reported results are: EVLWI (ml/kg), mPaw (cmH2O), PaO2/FiO2, mPaw/EVLWI index (cmH2O/ml/kg), cardiac index (CI) (L/min/m2), and MAP (mmHg).

EVLWI was significantly reduced by 24% (19.6±7.5 to 15±4.1) in 1 hour, by 11% (17.5±6) in 6 hours, p value: 0.017 (**Figure 1**). The mPaw was significantly increased by 68% (15.8±5.5 to 26.5±4.7) in 1 hour and by 55% (24.5±3.8) in 6 hours, p value: 0.004 (**Figure 2**). PaO2/FiO2 was increased by 47% (163.6±67.6 to 239.8±132.4) in 1 hour, 68% (275.8±165.3) in 6 hours, almost reached statistical significance, p value: 0.064 (**Figure 3**). The mPaw/EVLWI index was significantly increased by 114% (0.87 to 1.86) in 1 hour and by 76% (1.53) in 6 hours, p value: 0.015 (**Figure 4**). CI was significantly increased by 10% (3.07±0.72 to 3.375±0.83) in 1 hour, 7% (3.275±1.07) in 6 hours, p value: 0.003 (**Figure 5**). MAP was significantly increased by 8% (67.2±8.23 to 73±2.28) in 1 hour and by 13% (75.7) in 6 hours, p value: 0.001 (**Figure 6**).

Regression analysis was used to test the correlation coefficient between variables. The results are represented in **Figures 6-11**. Strong positive relation was found between mPaw and EVLWI (R=0.85), strong positive relation was found between mPaw and PaO2/FiO2 (R=0.88), strong

positive relation was found between mPaw/EVLWI Index PaO2/FiO2 (R=0.79), strong negative relation was found between EVLWI and PaO2/FiO2 (R=0.99).

Discussion

This is the first study to test the effect of APRV on the measured EVLWI, and attempts to find the relations between the mean airway pressure, extra vascular lung water and oxygenation. This pilot prospective trial sheds light on some important issues.

Our findings support the hypothesis that APRV safely reduces EVLW without requiring other interventions like fluid restriction or diuretics. It illustrates another path by which APRV may play on improving oxygenation through the reduction of the EVLW. The improved oxygenation after applying APRV has been described previously in multiple studies. (19-21) This has been attributed to multiple factors including the role spontaneous breathing plays in lung recruitment, the higher mandatory inspiratory time and the resulting increase in mean airway pressure on lung recruitment, the prevention of lung derecruitment during the short release time, and finally the improved hemodynamics and perfusion. (17,22) This study adds yet another possible mechanism through which APRV improves oxygenation.

In agreement with two previous studies, (7,23) our results confirm their findings that reducing the EVLW may improve oxygenation. Szakmany and colleagues (7) found a negative correlation between EVLW and PaO2/FiO2, and a positive one between PEEP levels and EVLW in thirty-two patients with sepsis induced ARDS. Similarly Davey-Quinn and colleagues (23) in a small study of eleven patients found that EVLW as well as serum albumin were the only independently predictive factors affecting the PaO2/FiO2 ratio. They also found that the four survivors had greater initial EVLW than non-survivors, and showed a greater reduction in lung water over time. On the other hand, a small study of fourteen patients by Brigham and colleagues (24) found that EVLW did not correlate with intravascular pressures or with alveolar-arterial oxygen pressure difference, also EVLW levels were not different between survivors versus non survivors.

The most common ways to achieve the goal of reducing the EVLW are the restrictive fluid strategy and diuretics. To date the largest trial, which studied that issue, was designed by the ARDS network (FACTT study) published in 2006 (25) and included one thousand patients. This trial compared liberal versus restricted fluid strategy and diuretics based on the central venous pressures (CVP), and the pulmonary artery occlusion pressure (PAOP). Though there were no mortality differences between both strategies, the restrictive strategy group had better oxygenation and fewer ventilator days. One of the drawbacks of this study is that the management protocol depended on the cardiac filling pressure markers for volume status i.e. CVP and PAOP. Both of those parameters have shown to be poor predictors of volume status, (26) and poor predictors of lung water. (27) Another drawback of that study is that the lung water was not measured to document that the restrictive strategy group indeed had “drier lungs”. Another smaller trial by Mitchell and colleagues (8) included eighty-nine patients with pulmonary edema and used a fluid management protocol guided by measuring the EVLW versus conventional management guided by PAOP. Their results were similar to the FACTT study, where the restrictive fluid group had fewer ventilator and ICU days with a trend towards improved oxygenation.

The fear of the restrictive strategy arises specifically in patients who are in shock with reduced organ perfusion risking further deterioration of their hemodynamics. Matter of fact, the protocol used in the FACTT study allowed suspending the diuretics and allowed fluid resuscitation if the patients went into shock or oliguria. (25) There was no increase in the incidence of non-pulmonary organ failure in both studies. (8,25) The issue of diuretics in critically ill patients with acute kidney injury is still controversial. Some studies showed worsen mortality and reduced renal recovery, (10) while others have shown no worsening mortality related to this therapy. (28)

APRV on the other hand have shown preservation of hemodynamics and organ perfusion in multiple studies. (19,22,29,30) Thus APRV may be a better and safer option for such clinical conundrum. Our results support those

claims, showing slight yet significant improvement in hemodynamics (mean arterial pressure and cardiac index).

Normally the EVLW is resorbed back to the pulmonary and bronchial circulation through alveolar re-absorption back to the capillary endothelium, lung lymphatics, pleural spaces, and mediastinum. (31) The exact mechanism of the reduction in the EVLW using APRV is unknown, and our study was not designed for that purpose. Speculated theories include: the increased surface area of recruited alveoli may cause increase the EVLW re-absorption. The increased cardiac output reported in some studies (30) may reduce the hydrostatic vascular pressure and transmural pressures with decreased fluid leakage from lung capillaries. Other possible mechanism is that the spontaneous breathing can cause pleural pressure swings, which may facilitate fluid movements along in the peri bronchial lymphatics. (31)

Mean airway pressure reflects mean alveolar pressure and correlates with alveolar ventilation, arterial oxygenation, hemodynamic performance, and barotrauma. (32,33) Our results have shown strong correlation between increasing the mean airway pressure and reducing EVLW by switching from conventional mechanical ventilation to APRV.

PEEP is a significant contributor to the mean airway pressure, which in turn plays an important role in oxygenation. (32,33)

Multiple studies (7,14,15,34,35) have studied the effects of applying or increasing the PEEP on EVLW, and have shown good correlation between PEEP levels and EVLW. In summary, they attributed those benefits to several factors including: enhanced alveolar fluid clearance, (35) improved lymphatic drainage, (36) decreasing atelectasis, (7) and reduction of transmural pressure diminishing the filtration pressure. (37) Logically talking, applying or increasing PEEP would increase the mean airway pressure (32,33) but interestingly, none of the authors of those studies had commented on the role mean airway pressure may play through increasing PEEP. Ruiz-Bailen and colleagues (14) compared the effects of applying PEEP either immediately, or after 2 hours, to no PEEP on EVLW in an animal model of ALI. In their study, they have reported only the peak inspiratory airway pressures (PIP), which was higher in the group with the immediate PEEP and the highest reduction of the EVLW. Similarly, García-Delgado and his colleagues (35) in their study comparing the effect of 10 cmH2O of PEEP to 0 cmH2O of PEEP on alveolar fluid clearance, they reported that the plateau pressures (Pplat) were higher in the groups were PEEP was applied. The information from those studies are not enough to calculate the mean airway pressure (missing the respiratory rate, inspiratory time, and PIP, Pplat if any inspiratory pauses were applied). (32) Though speculative, the mean airway pressure was probably higher in those studies using PEEP compared to none.

Care has to be taken when adjusting the ventilator settings on conventional mechanical ventilation to achieve a higher mean airway pressure. Increasing the PEEP too high may result in barotrauma, increase dead space, reduction of cerebral perfusion and hemodynamic compromise through reduction of the right ventricular preload, and ejection. (37) Increasing the inspiratory pressures may subject the alveoli to strain and ventilator induced lung injury (VILI). (38,39) Increasing the respiratory rate can come with the risk of VILI secondary to cyclical alveolar opening and collapsing. (38) Prolonging the inspiratory time as in inverse ratio ventilation, usually requires high levels of sedation along with the risk of hemodynamic compromise and auto-PEEP. (40) APRV on the other hand as previously mentioned, has shown to preserve and improve hemodynamics, oxygen delivery and organ perfusion, (17,30) while reserving spontaneous breathing and possibly patient comfort and synchrony with the ventilator. (20,22) Additionally, studies in patients with ALI/ARDS have shown that APRV allowed a reduction in the inspiratory pressures while having higher mean airway pressures compared to conventional positive pressure ventilation adjusted to deliver a comparable ventilatory support. (29,41) Conceptually those effects of lowering airway pressures may lead to reduced incidence of VILI. (17,21) A recent animal study showed that APRV decreases bronchoalveolar lavage fluid high-mobility group box-1 levels and lung water compared to low tidal volume ventilation signifying a decreased risk for VILI. (42) However the relationship between APRV and VILI is more theoretical and has not been well studied or

documented. (43) Our study has some drawbacks and the results have to be interpreted carefully. The small number of patients enrolled is an obvious one. We recognize that obtaining statistically significant values is very difficult with such a small number of patients, but surprisingly we found significant values between the variables using the multi-measurement ANOVA. The study was intended to be a feasibility trial before a larger one to be planned. As a tertiary referral center, a big portion of our admitted patients gets transferred to us from other hospitals after several days of having respiratory failure. We tried to include patients with early stages of their diseases i.e. ≤72 hours, and that made our patient pool much smaller.

Another drawback is the short time i.e. 6 hours that we included for analysis according to our protocol. After the 6 hour study, the primary team caring for the patient was free to continue APRV or switch back to conventional ventilation, 4 of the 6 patients were kept on APRV for more than 48 hours, but the EVLW measurements and ventilator protocols were not followed. We did not include those measurements in our analysis. A larger trial with prolonged stay on APRV might be required to confirm our results to determine if such reduction in EVLW is sustainable.

Our study was not randomized or blinded. We used the same patients as their own controls while on conventional ventilation. The treating physicians were blinded to the values of the EVLWI, but they were not blinded to the other hemodynamics or the ventilatory parameters. Blinding all those values is a very difficult task as per our unit protocol, those numbers have to be entered into the patients electronic medical numbers.

Conclusion

APRV is capable of improving oxygenation through the positive effect of increasing the mean airway pressure on the extra vascular lung water. APRV significantly reduced EVLW, improved PaO2/FiO2 and hemodynamics. Reduction of EVLW improves oxygenation in ALI/ARDS. Larger randomized study may need to be performed to confirm our results.

Table 1. Patients demographics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Mean Values
Age	59	75	62	22	48	64	55
Gender	Female	Male	Male	Male	Female	Female	NA
Cause of respiratory failure	Sepsis	Mycoplasma pneumonia	CMV pneumonia	Non found	Streptococcus pneumonia	Sepsis	NA
APACHE II	24	17	18	19	18	31	21
LIS	13	14	12	8	10	8	11
OI	8.1	7.9	3.9	26.7	13.7	7.1	16.9
Duration of ARDS at inclusion	48 hours	48 hours	≤24 hours	≤24 hours	≤24 hours	24-48 hours	NA
Duration of mechanical ventilation before APRV	38 hours	48 hours	18 hours	13 hours	20 hours	42 hours	NA
Duration of mechanical ventilation	5 days	12 days	4 days	25 days	5 days	6 days	NA
Outcome at 28 days	Liberated Survived	Liberated Survived	Liberated Survived	Liberated Survived	Liberated Survived	Liberated Survived	Liberated Survived

Legend: APACHE II=Acute Physiology and Chronic Health Evaluation II; LIS=lung injury score; OI=oxygenation index; Liberated=off mechanical ventilatory support for at least 48 hours; NA=not applicable.

Table 2. Conventional ventilator settings before switching to APRV

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Mean Values
Ventilator mode	VCV	PCV	PCV	PCV	PCV	PCV	NA
Approximate inspiratory pressure above PEEP (cmH2O)	12	26	20	24	15	20	19.5
Approximate PEEP (cmH2O)	8	8	7	14	12	8	9.5
Approximate inspiratory time (seconds)	0.9	0.8	0.8	1	0.8	0.7	0.83
Approximate set frequency (per minute)	16	24	14	25	15	14	18
Approximate mean airway pressure (cmH2O)	12	14	11	26	18	14	15.8
Approximate tidal volume (ml/kg IBW)	6.2	7.4	7.1	6.8	7.3	6.9	6.95
Approximate FiO2 (%)	100	90	50	100	100	70	85

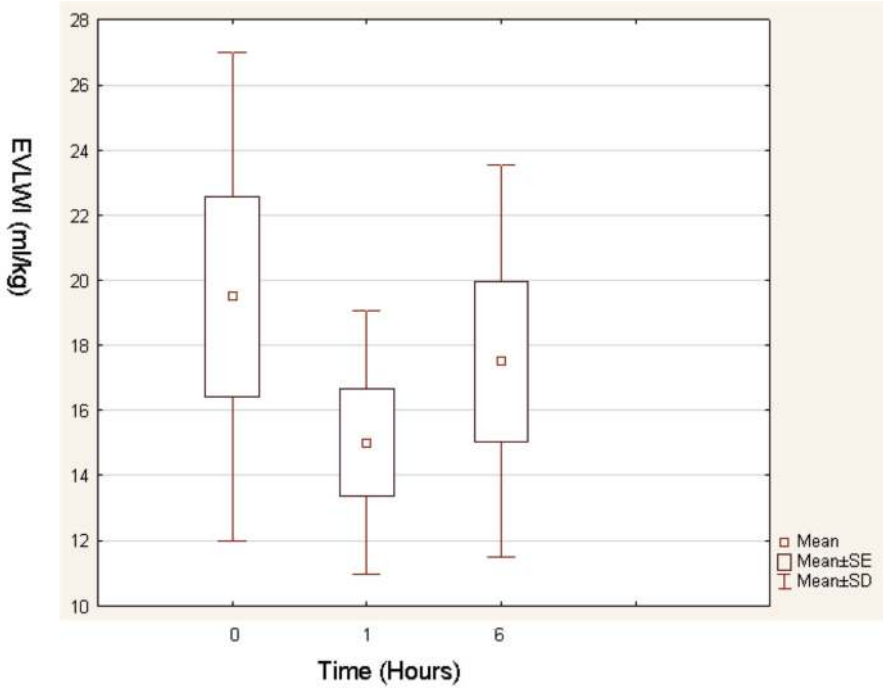
Legend: PCV=pressure controlled continuous mandatory ventilation; VCV=volume controlled continuous mandatory ventilation; PEEP=positive end expiratory pressure; IBW=ideal body weight; FiO2=fraction inspired oxygen; NA=not applicable.

Table 3. Mean values and standard deviation of parameters measured during the 6 hours trial, the percentage change of the values, and statistical significance before and after switching to APRV

	Hour 0	Hour 1	Hour 6	P value
EVLWI (ml/kg)	19.6±7.5	15±4.1	17.5±6	0.017*
mPaw (cmH2O)	15.8±5.5	26.5±4.7	24.5±3.8	0.004*
PaO2/FiO2	163.6±67.6	239.8±132.4	275.8±165.3	0.064
mPaw/EVLWI (cmH2O/ml/kg)	0.87	1.86	1.53	0.015*
CI (L/min/m2)	3.07±0.68	3.37±0.82	3.25±1.04	0.003*
MAP (mmHg)	67.2±8.23	73±2.28	75.7±8.1	0.001*

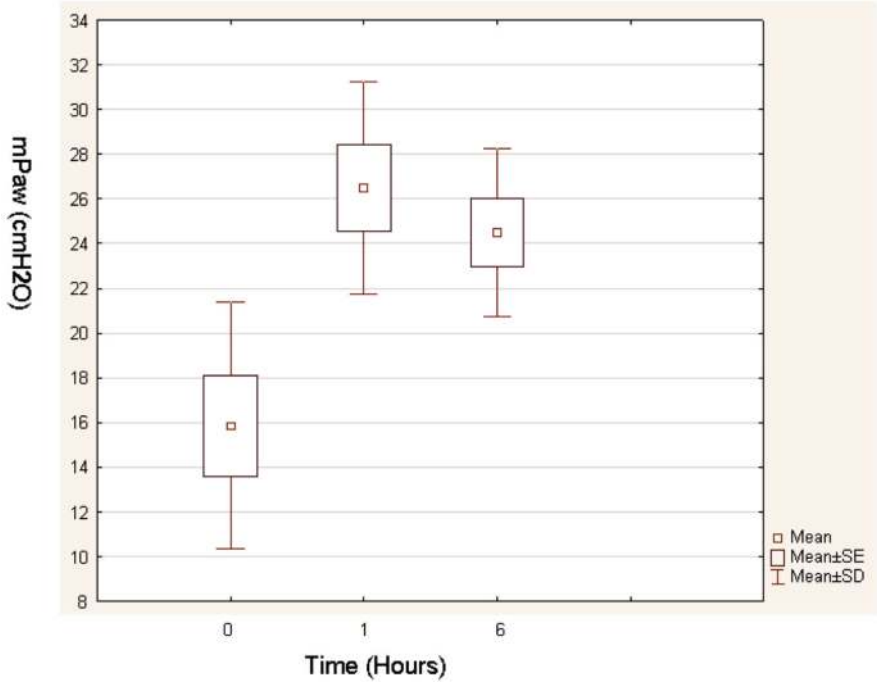
Legend: Hour 0=conventional ventilation; hour 1=1 hour after switching to APRV; hour 6=6 hours after switching to APRV; EVLWI=extra vascular lung water index; mPaw=mean airway pressure; PaO2/FiO2=partial pressure of oxygen to fraction of inspired oxygen ratio; mPaw/EVLWI=mean airway pressure to extra vascular lung water index; CI=cardiac index; MAP=mean arterial pressure; *=statistical significance according to multi measurement ANOVA.

Figure 1. Bar histogram of EVLWI in ml/kg against time in hours



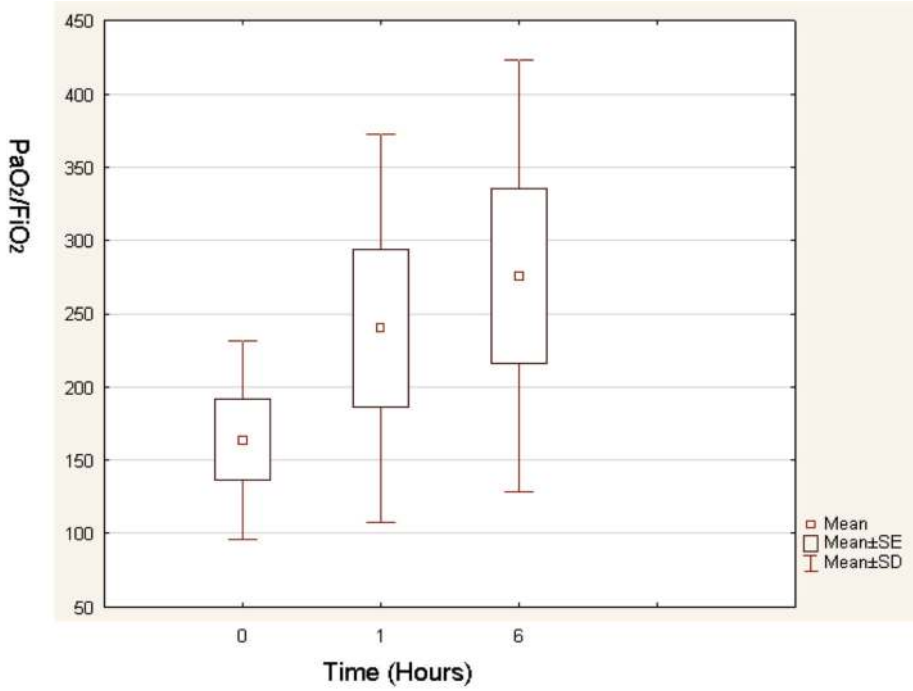
Legend: EVLWI=extra vascular lung water index. Small squares represent means; large squares represent means and standard error (SE); whiskers represent means and standard deviation (SD).

Figure 2. Bar histogram of mPaw in cmH2O against time in hours



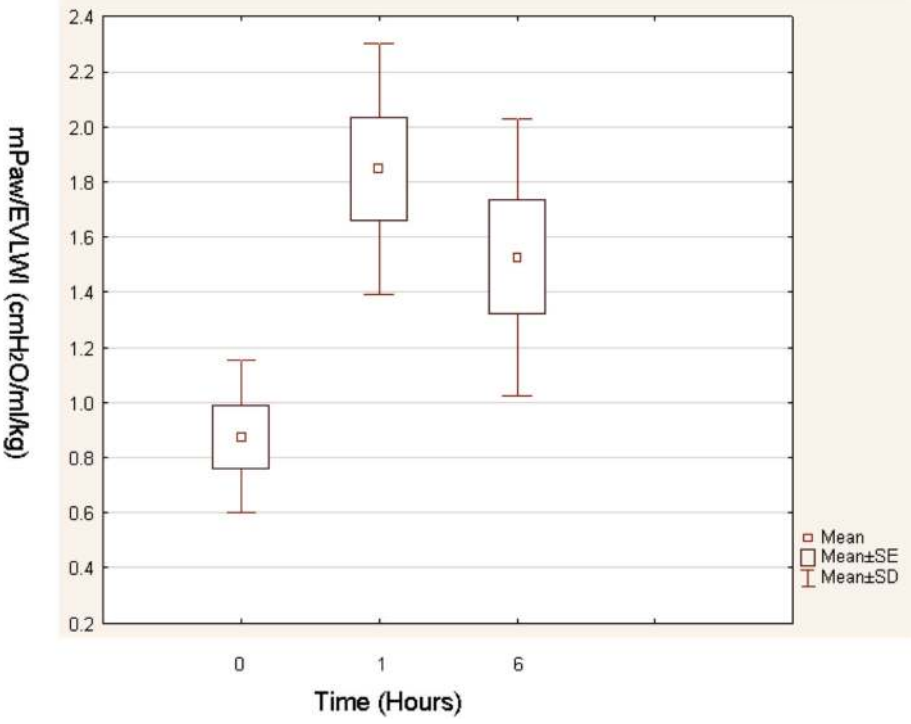
Legend: mPaw=mean airway pressures. Small squares represent means; large squares represent means and standard error (SE); whiskers represent means and standard deviation (SD).

Figure 3. Bar histogram of PaO2/FiO2 ratio against time in hours



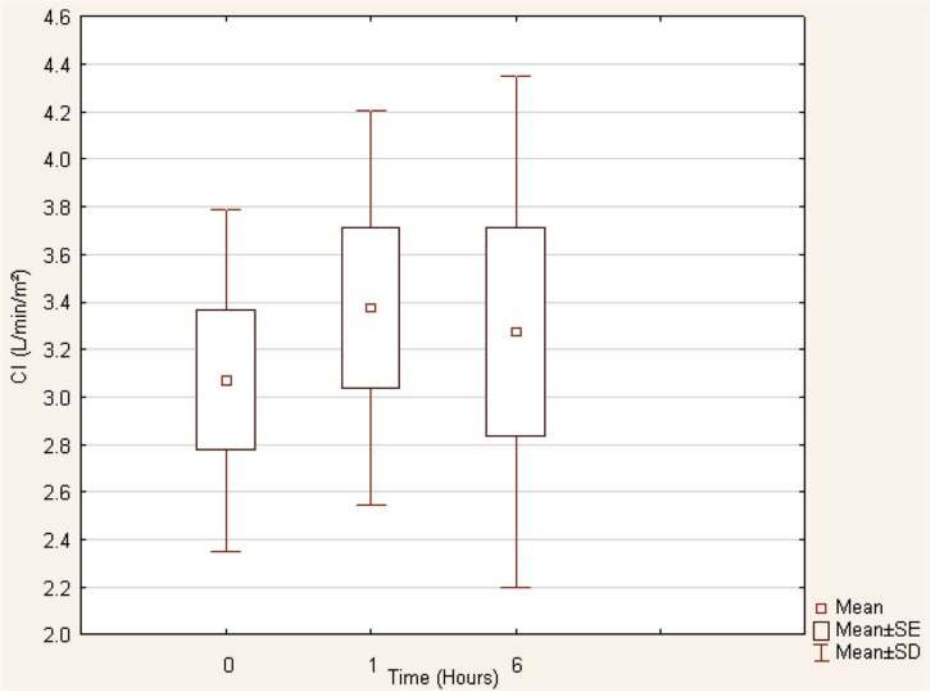
Legend: PaO2/FiO2=ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen. Small squares represent means; large squares represent means and standard error (SE); whiskers represent means and standard deviation (SD).

Figure 4. Bar histogram of mPaw/EVLWI in cmH2O/ml/kg against time in hours



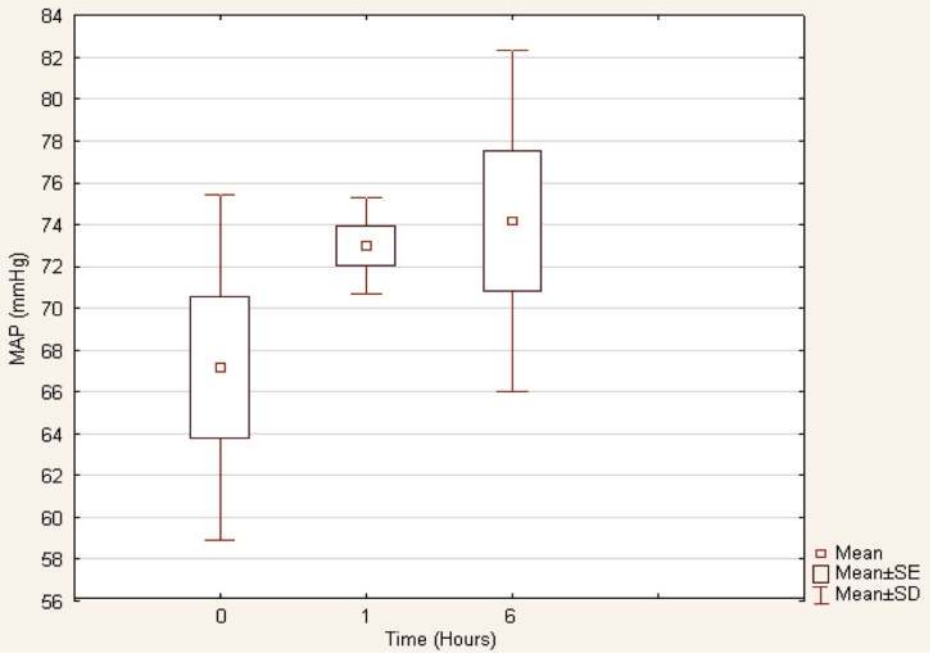
Legend: mPaw/EVLWI=ratio of mean airway pressure to the extra vascular lung water index. Small squares represent means; large squares represent means and standard error (SE); whiskers represent means and standard deviation (SD).

Figure 5. Bar histogram of CI in L/min/m2 against time in hours



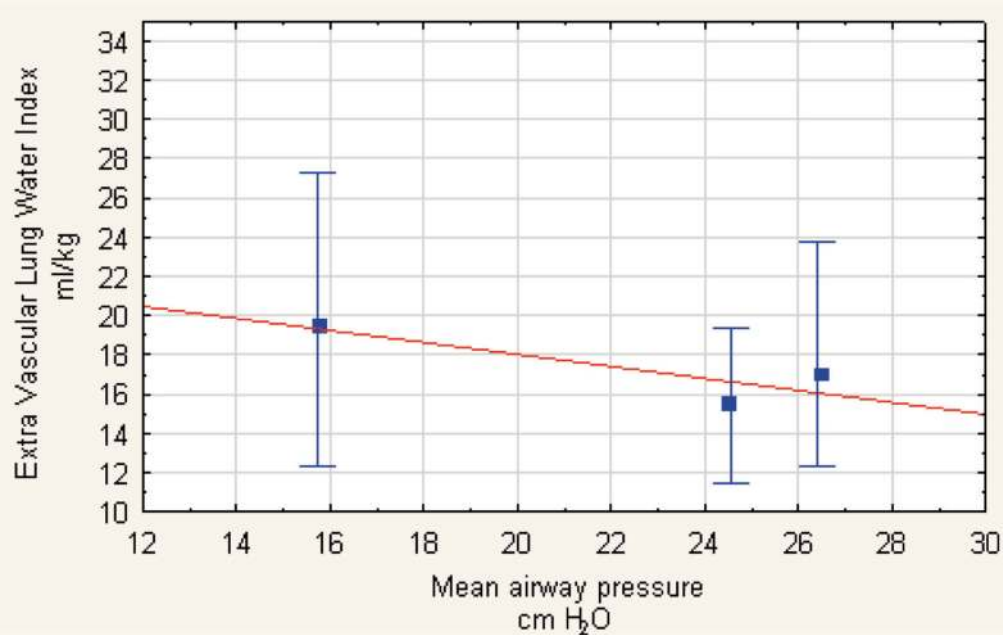
Legend: CI=cardiac index. Small squares represent means; large squares represent means and standard error (SE); whiskers represent means and standard deviation (SD).

Figure 6. Bar histogram of MAP in mmHg against time in hours



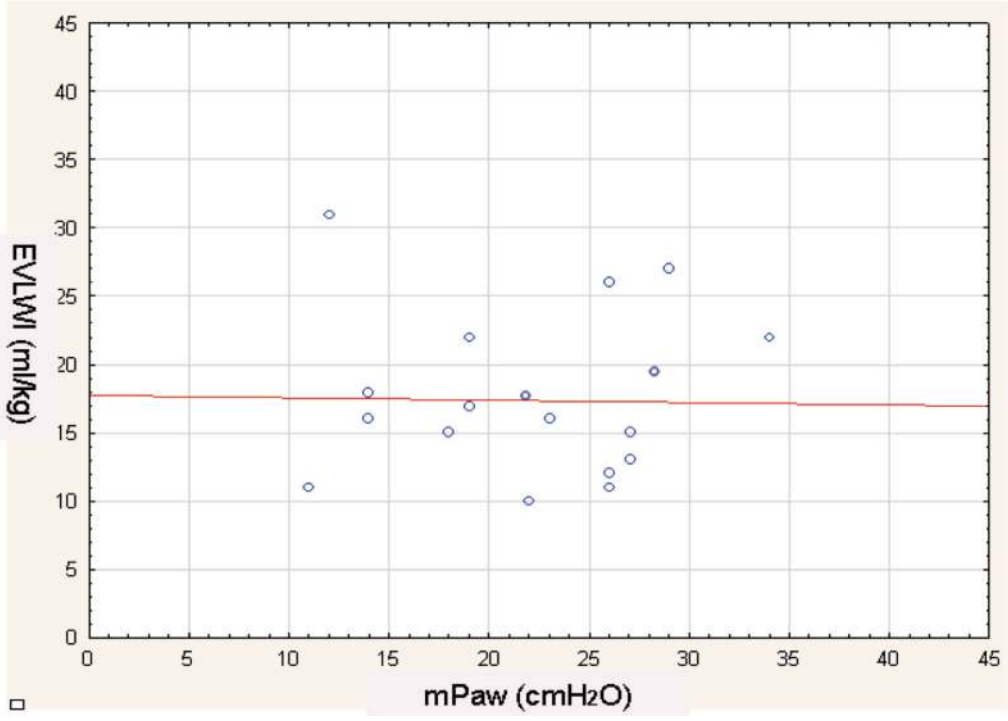
Legend: MAP=mean arterial pressure. Small squares represent means; large squares represent means and standard error (SE); whiskers represent means and standard deviation (SD).

Figure 7A. Negative correlation between the mPaw in cmH20 and the EVLWI in ml/kg



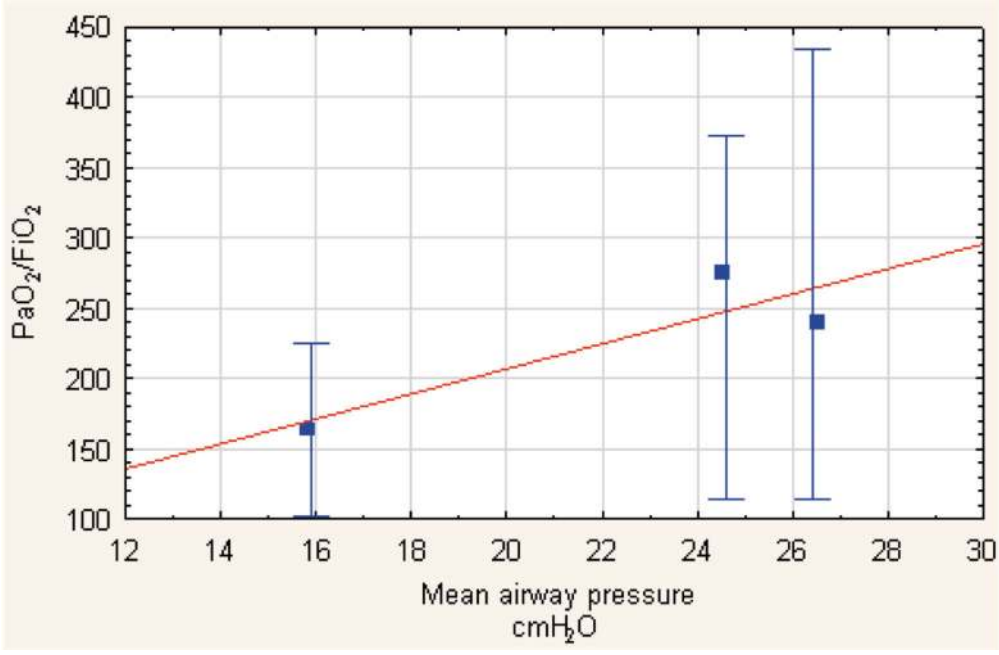
Legend: Squares express means; whiskers express standard deviation.

Figure 7B. Scatter plot diagram showing the relation between the mPaw in cmH2O and EVLWI in ml/kg



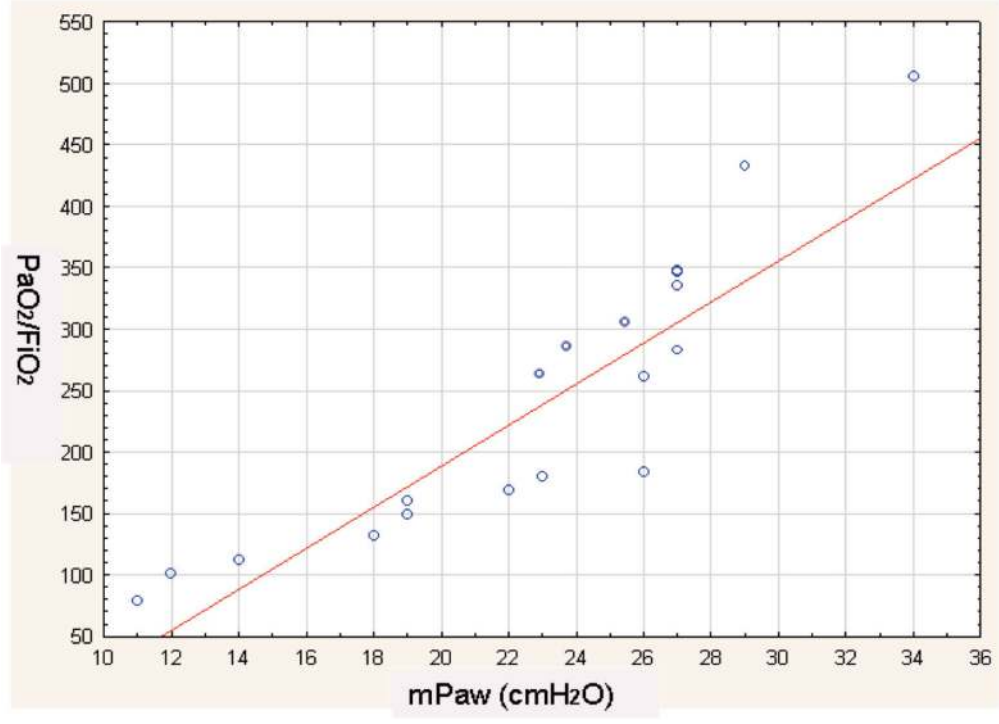
Legend: EVLWI=extra vascular lung water index; mPaw=mean airway pressure.

Figure 8A. Positive correlation between the mPaw in cmH2O and the PaO2/FiO2



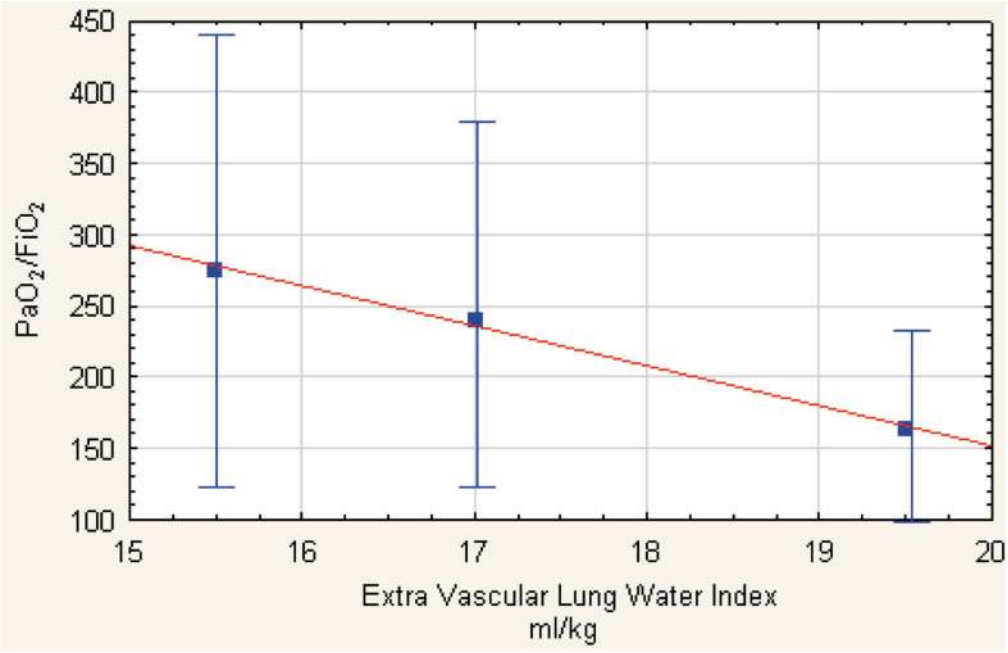
Legend: Squares express means; whiskers express standard deviation.

Figure 8B. Scatter plot diagram showing the relation between the mPaw in cmH2O and PaO2/FiO2



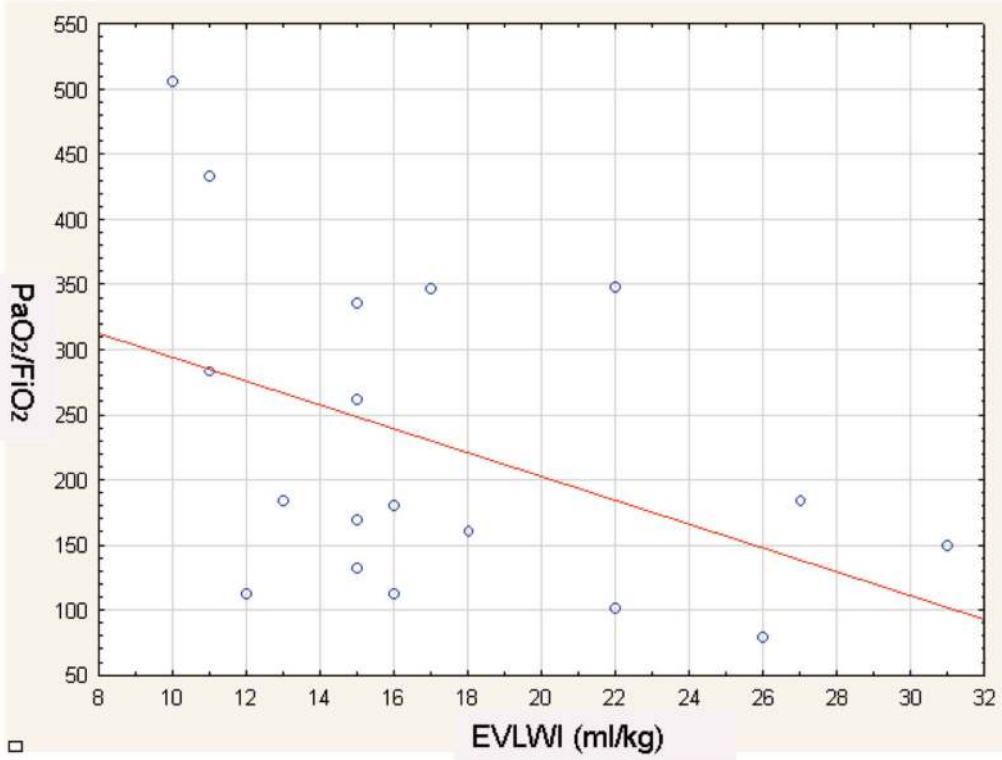
Legend: mPaw=mean airway pressure; PaO2/FiO2=ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen.

Figure 9A. Negative correlation between the EVLWI in ml/kg and the PaO2/FiO2



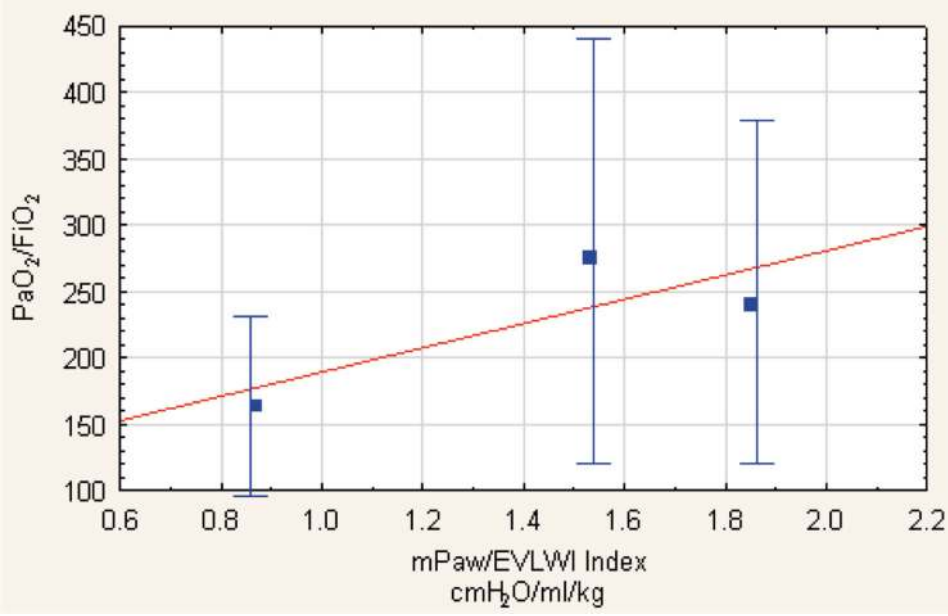
Legend: Squares express means; whiskers express standard deviation.

Figure 9B. Scatter plot diagram showing the relation between the EVLWI in ml/kg and the PaO2/FiO2



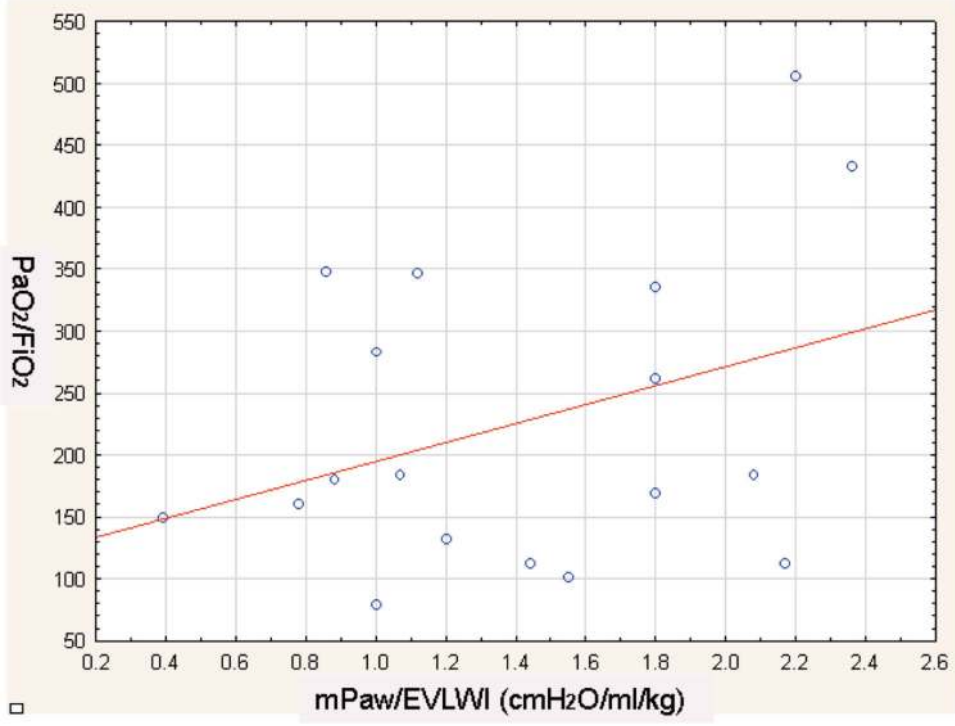
Legend: EVLWI=extra vascular lung water index; PaO2/FiO2=ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen.

Figure 10A. Positive correlation between the mPaw/EVLWI index in cmH2O/ml/kg and the PaO2/FiO2



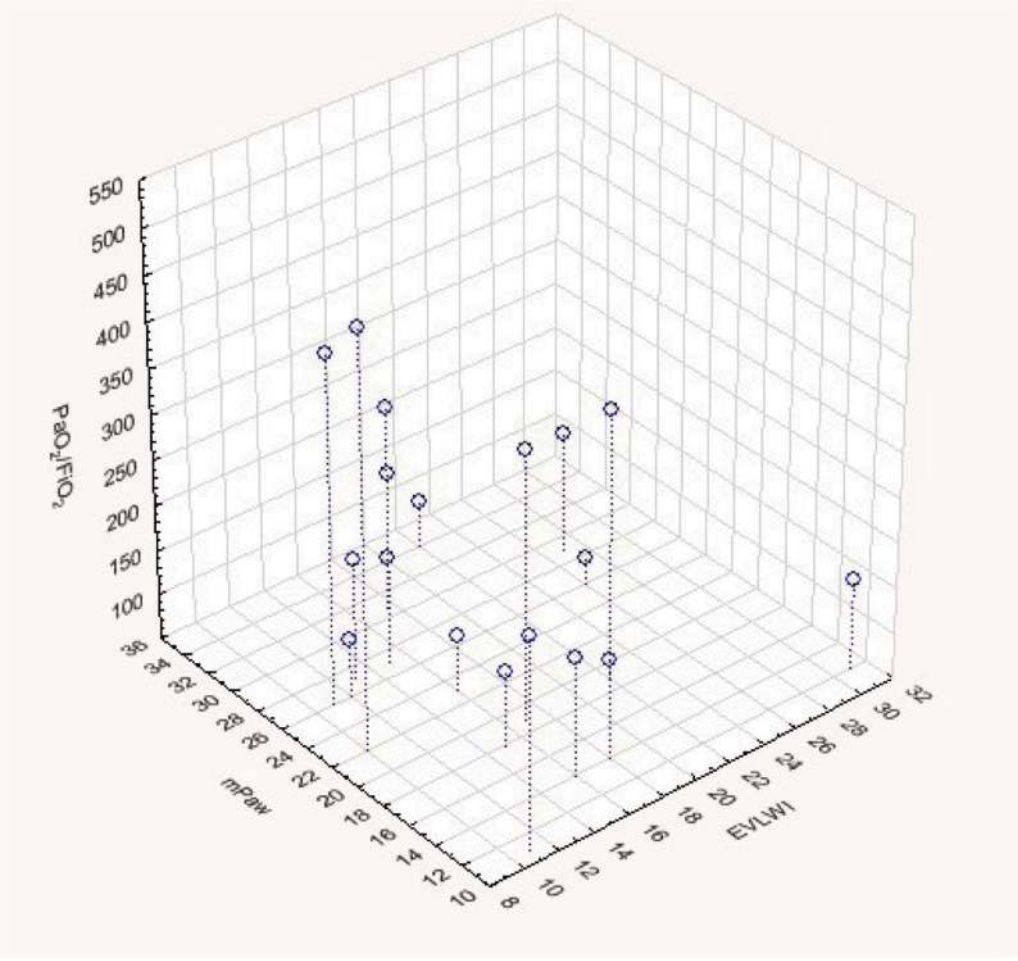
Legend: Squares express means; whiskers express standard deviation.

Figure 10B. Scatter plot diagram showing the relation between the mPaw/EVLWI in cmH2O/ml/kg and the PaO2/FiO2



Legend: mPaw/EVLWI=ratio of mean airway pressure to extravascular lung water index; PaO2/FiO2=ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen.

Figure 11. Three-dimensional scatter plot diagram summarizing all the measurements and the relationship between the mPaw in cmH2O, the EVLWI in ml/kg, and the PaO2/FiO2



Legend: mPaw=mean airway pressure; EVLWI=extra vascular lung water index; PaO2/FiO2=ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen.

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