Time to reach a new steady state after changes of positive end expiratory pressure.

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ABSTRACT

Purpose. To assess the time interval required to reach a new steady state of oxygenation-, ventilation-, respiratory mechanics- and hemodynamics-related variables after decreasing/increasing positive end expiratory pressure (PEEP).

Methods. In 23 patients (group 1) with acute respiratory distress syndrome (ARDS) PEEP was decreased from 10 to 5 cmH_2O and, after 60', it was increased from 5 to 15 cmH_2O. In other 21 ARDS patients (group 2) PEEP was increased from 10 to 15 cmH_2O and, after 60', decreased from 15 to 5 cmH_2O. Oxygenation, ventilation, respiratory mechanics and hemodynamic variables were recorded at time 5', 15', 30' and 60' after each PEEP change.

Results. When PEEP was decreased, PaO_2, PaO_2/FiO_2, venous admixture and arterial oxygen saturation reached their equilibrium after 5'. In contrast, when PEEP was increased, the equilibrium was not reached even after 60'. The ventilation-related variables did not change significantly with PEEP. The respiratory system compliance, when PEEP was decreased, significantly worsened only after 60'. Hemodynamics did not change significantly with PEEP. In the individual patients the change of oxygenation-related variables and of respiratory system compliance observed after 5' could predict the changes recorded after 60'. This was not possible for $PaCO_2$.

Conclusions. We could not find a unique equilibration time for all the considered variables. However, in general, a decremental PEEP test requires far lower equilibrium time than incremental PEEP test, suggesting a different time course for derecruitment and recruitment patterns.

KEYWORDS

ARDS, PaO_2/FiO_2, respiratory system mechanics, positive end expiratory pressure (PEEP)

INTRODUCTION

Positive end expiratory pressure (PEEP) is frequently applied in Intensive Care, either to improve oxygenation [1] or to protect the lung [2,3]. However the selection of the "optimum" PEEP level [4] for an individual patient is still an unresolved problem in clinical practice [5]. Incremental or decremental PEEP [6] tests are frequently performed to find out the best compromise between recruitment and overdistension with tolerable hemodynamic changes. Therefore, the evaluation of changes following the increase and decrease in PEEP level is a frequent requirement in intensive care units (ICU). The equilibration time for oxygenation has been described after setting PEEP 2 cmH_2O higher than inflection point of the pressure-volume curve [7]. The equilibration time for other oxygenation-related variables, respiratory system compliance and hemodynamics, during both incremental and decremental PEEP tests is not well-established, although in clinical practice 20 to 30 minutes are allowed as "equilibration period". Consequently, a considerable long time may be required if more than one level of PEEP is tested. In patients with acute respiratory distress syndrome (ARDS) we aimed to assess the equilibrium time required for the variables most commonly used in clinical practice, both after incremental or decremental PEEP test.

MATERIALS and METHODS

Study population

The study was approved by the institutional review board of our hospital, and informed consent was obtained according to the Italian national regulations. Mechanically ventilated patients, fulfilling the diagnostic criteria of ARDS (American European Consensus Conference definition [8]), admitted to the intensive care unit of our Institution, were enrolled in this study from January 2006 to April 2008. Exclusion criteria were age lower than 18 years, hemodynamic instability, documented barotrauma, pulmonary emphysema and pulmonary fibrosis.

Study protocol

All enrolled patients were sedated with propofol and midazolam and paralyzed with vecuronium to assure muscle relaxation. A recruitment manoeuvre was performed to normalize lung volumes just before to begin with study procedures: patients were ventilated for two minutes in pressure controlled ventilation at an inspiratory plateau pressure of 45 cmH_2O, a positive end expiratory pressure (PEEP) of 5 cmH_2O, a respiratory rate (RR) of 10 breaths per minutes and a 1:1 ratio of inspiration to expiration (I:E). Thereafter patients were ventilated for 60' with a PEEP level of 10 cmH_2O and tidal volume (Vt) of 6-8 mL per kilogram of actual body weight with I:E ratio 1:1. During this period, inspired oxygen fraction (FiO_2) was adjusted to maintain arterial saturation between 90% and 100% and the RR was adjusted to maintain arterial partial pressure of carbon dioxide ($PaCO_2$) between 35 and 50 mmHg. After this period the ventilatory setting (FiO_2, minute ventilation, I:E ratio, Vt, RR) was maintained unchanged throughout the study, while the PEEP was increased or decreased according to the protocol.

Forty-four patients were randomized in two groups. In the 23 patients of group 1, PEEP was changed from 10 to 5 cmH_2O and afterwards from 5 to 15 cmH_2O, while in the 21 patients of group 2, PEEP was changed from 10 to 15 cmH_2O and afterwards from 15 to 5 cmH_2O. Each level of PEEP was maintained for 60'.

Measurements and data collection

Respiratory and hemodynamic parameters were recorded at time 0', that is before PEEP changes, and time 5', 15', 30' and 60' after each PEEP change. At each time we collected/computed the following variables (see Supplementary Appendix for details and computations):

Oxygen- related variables: arterial and central venous oxygen partial pressure (PaO_2 and PvO_2), PaO_2/FiO_2, arterial and central venous oxygen saturation (SaO_2 and SvO_2) and venous admixture.

Ventilation-related variables: $PaCO_2$, the end tidal partial pressure of carbon dioxide ($EtCO_2$) and expired CO_2 in one minute ($PECO_2$) were measured by means of continuous expiratory air sampling (CO2SMO PLUS 8100; Novametrix Medical System Inc., Wallingford, CT). The physiologic and alveolar dead spaces fraction (Vd/Vt physiol. and Vd/Vt alveolar) were computed according to standard formulas

Respiratory mechanics-related variables: minute ventilation, peak pressure, inspiratory plateau pressure and mean airway pressure were recorded. Respiratory system compliance was also computed.

Hemodynamic related variables: heart rate, central venous pressure (CVP), mean arterial pressure were recorded in every patient. Values of cardiac output were measured when pulmonary catheter was in place (7 patients in group 1 and 5 patients in group 2).

Statistical analysis

Results are presented as mean ± standard deviation. Comparison of clinical variables, respiratory and physiological variables was performed by one-way or two-way analysis of variance on repeated measures or Student's t-test in the case of variables that were normally distributed; by one-way or two-way analysis of variance on repeated measures on ranks or the Wilcoxon test in the case of variables that did not appear normally distributed. The chi-square test was used in case of qualitative variables. When analysis of variance revealed a significant difference, Bonferroni's t-test or Tukey's test was used. Linear regression was used to assess the relationship between early and late changes of the considered variables. $P<0.05$ was accepted as significant. Analysis was performed with SigmaPlot 11.0 (Systat Software, Inc.).

RESULTS

The baseline characteristics of the study population are summarized in table 1. The two groups did not show any difference in all variables but the respiratory rate, which was slightly lower in group 2.

Decreasing PEEP

The effects of decreasing PEEP from 10 to 5 and from to 15 to 5 cmH_2O on PaO_2 (upper panel), $PaCO_2$ (middle panel) and respiratory system compliance (lower panel) are shown in figure 1. For completeness we reported in the supplementary appendix, table E1, the response of oxygenation-ventilation-, respiratory mechanics- and hemodynamic-related variables to PEEP decay at different times. As shown, we found that PaO_2 values recorded from 5' to 60' are different from the ones recorded at time 0', but we could not find any difference in values recorded from time 5' to 60'after decreasing PEEP. This indicates that, when PEEP is decreased, the equilibration time for arterial oxygenation is reached within 5'. PaO_2/FiO_2, Venous admixture and arterial saturation similarly worsened at time 5' and remained stable thereafter. In contrast, the $PaCO_2$ did not change until time 15' after PEEP decrease, and significantly increased at time 30' and 60'. The $EtCO_2$ significantly decreased in both groups at time 5' and returned to the baseline level between time 15' and 60'. Interestingly, however, physiological and alveolar dead space did not show any statistical significant change throughout the whole observation period.

According to respiratory system mechanics, the significant decrease in plateau pressure at time 5' matched the decrease of PEEP, as the respiratory system compliance was unmodified. At time 60', however, plateau pressure increased and respiratory system compliance decreased significantly compared to time 5'. For what hemodynamic-related variables concerns, no changes in mean arterial pressure and heart rate occurred from baseline to time 60', while cardiac output increased significantly at time 30'and time 60' only when PEEP was decreased from 15 to 5 cmH_2O. The central venous pressure significantly decreased at time 5' and thereafter remained stable. The decrease of SvO_2 was statistically significant at time 5' when PEEP was decreased from 10 to 5 cmH_2O, and matched the decrease of the SaO_2. Thereafter the SvO_2 remained stable throughout the whole observation period.

Increasing PEEP

The effects of increasing PEEP from 10 to 15 and from to 5 to 15 cmH_2O on PaO_2 (upper panel), $PaCO_2$ (middle panel) and respiratory system compliance (lower panel) are shown in figure 2. For completeness we reported in the supplementary appendix, table E2, the response of oxygenation-ventilation-, respiratory mechanics- and hemodynamic-related variables to PEEP increase at different times. As shown, the PaO_2 values progressively raised from time 5' to time 60' and no equilibrium was reached within this 60-minutes interval, as indicated by the statistically significant difference between non-contiguous values. The venous admixture, after a significant improvement at time 5', remained stable throughout the observation period, while arterial saturation and PaO_2/FiO_2 continuously increased with time as PaO_2 did. Both $PaCO_2$ and $EtCO_2$ significantly decreased at time 5' and, thereafter, returned to values equal or significantly greater than baseline.

Physiological and alveolar dead space did not change with PEEP increase, and remained unmodified throughout the observation period.

The plateau pressure increased significantly at time 5', matching the PEEP increase, being the respiratory system compliance unmodified. However, in the patients in which PEEP raised from 5 to 15 cmH_2O the plateau pressure showed an increasing trend up to time 60', but without reaching the statistical significance. The respiratory system compliance showed a similar but opposite behavior. Mean arterial pressure, cardiac output and SvO_2 were not affected by PEEP increase, CVP significantly increased, while the heart rate remained stable.

Individual patients variability

Data reported in table E1 and E1 and in figures 1 and 2 are expressed as mean and standard deviation. The standard deviation values, however, showed great variability of the values recorded before and after the PEEP change in the study population. Therefore, for completeness, we reported in the online supplementary appendix (from page E9 to E39), the individual patients time-courses of the analyzed variables. As shown, the single patients behavior is consistent with the average values in the majority of the cases.

Equilibration time and ARDS severity

When the response to incremental or decremental PEEP changes were examined after stratifying the patients in less and more severe ARDS according to the median FiO_2 (median 50% IQR 40-60), we could not find any difference in equilibration time in any of the considered variables. A detailed report of the time courses of the considered variables in patients with different ARDS severity is presented in the supplementary appendix.

Relationship between early and late response to PEEP change

In figure 3, upper panel, we represent the changes (d) between time 0' to time 60' of PaO_2, respiratory system compliance and $PaCO_2$ as a function of the changes of the same variables observed between time 0' and time 5'. As shown, the relationship indicates that nearly 87% of the late changes are explained by the early changes of PO_2 (($dPaO_2$ from 0' to 60') = -9.58 + 1.13*($dPaO_2$ from 0' to 5'), $P<0.001$, $r^2= 0.87$). In contrast, as shown in the middle panel, the changes of $PaCO_2$ after 60' are less predictable from its early changes (($dPaCO_2$ from 0' to 60') = -1.68 + 0.93*($dPaCO_2$ from 0' to 5'), $P<0.001$, $r^2= 0.37$). In the lower panel the late changes of respiratory mechanics appear well predicted by the early changes ((dCrs from 0' to 60') = 1.94+ 0.92*(dCrs from 0' to 5'), $P<0.001$, $r^2= 0.87$)).

DISCUSSION

It is a common practice in intensive care, before assessing the effects of changes of the ventilator setting on relevant variables, to wait for an "equilibration time". As an example, it was found that after changing FiO_2 the oxygenation reaches its equilibrium in less than 10' [9,10], while, when total ventilation is increased, the $PaCO_2$ falls exponentially, reaching its equilibrium in 10-20'. In contrast, when ventilation is decreased the rate of change of $PaCO_2$ is far lower and equilibration time requires up to 45-60' [11,12]. The present study has been designed to describe the equilibration time of oxygenation-, ventilation- and respiratory mechanics-related variables after incremental or decremental PEEP. We arbitrarily set the time 60' as the longest time allowed for equilibration, assuming that a longer period could imply, in some patients, a dramatic change of the underlying pathophysiological conditions of the lung , which may confound the effects of PEEP alone. Tugrul et al., after setting PEEP values according to the inflection point of the pressure volume curve, found that 20' were sufficient to reach 90% of the PaO_2 recorded at time 60', which was assumed as a "full equilibration time" [7]. In contrast, in our study, we found that each group of variables reached its equilibrium at different times, moreover we noted that some variables did not reach the equilibrium even at 60'. Finally, the time to equilibrium of the same variable was sometimes different when PEEP was decreased or increased and, interestingly, the severity of ARDS, and, by inference, the lung recruitability, did not affect the equilibration time in any of the considered variables.

Oxygenation-related variables

When PEEP was *decreased*, the PO_2 and the other oxygenation-related variables significantly decreased within 5' and stay unmodified in the following 55', suggesting that the oxygenation equilibrium was reached almost immediately. The PaO_2 decrease is likely due to the immediate collapse of the most dependent lung regions, as observed by CT scan [13], which remain perfused. The initial collapse is primarily due to the gravity dependent closure of the small airways ("loose" atelectasis). If the inspiratory pressure is sufficient to open them, opening/closing phenomenon is generated [14]. With time the "loose" atelectasis may become "sticky" due to the gas reabsorption, and the opening pressure become greater [15]. This phenomenon may affect the lung mechanics but is probably irrelevant for oxygenation, which is impaired in presence either of loose or sticky atelectasis, provided that atelectatic regions are perfused. It is also possible that, when atelectasis shift from opening/closing to always close status, which should lead to a further deterioration of oxygenation, more blood flow is diverted to aerated regions limiting the PO_2 fall (*hypoxic vasoconstriction*) [16,17]. Independently from causative mechanism, however, the PO_2 values after 5' are highly representative of the values observed up to 60' (see figure 3).

In contrast, when PEEP was *increased*, the PO_2 continuously rose, suggesting that equilibrium was not reached even at time 60'. In our setting the PO_2 rise was likely due to recruitment of previously collapsed and perfused pulmonary units , as FiO_2, minute ventilation and hemodynamics were unchanged. The slow PaO_2 rise confirms that, although most of the recruitment occurs rapidly, the remaining opening is a "slow" phenomenon [18]. In fact recruitment depends on the interaction between the increase of opening pressure (the plateau pressure raised proportionally to the PEEP value) and the increased threshold for closing pressure (higher PEEP maintains open regions which would collapse at lower PEEP) [14,19,20]. Whatever is the mechanism underlying the recruitment, it is obvious that its early assessment by observing PO_2 variations during incremental PEEP, may

be misleading, due to the slow equilibration time of the oxygenation-related variables. However, the PO_2 values obtained after 5', although not in equilibrium, may be sufficient to indicate the oxygenation trend (see figure 3).

Ventilation-related variables

When PEEP is decreased we did not observe significant changes of $PaCO_2$ throughout the observation period, compared to basal values. To discuss the $PaCO_2$ behavior it is important to recall that the amount of CO_2 in the body is very high (about 20 fold than oxygen) and that it is distributed within fast compartment (the blood) and intermediate and slow compartments (extracellular and intracellular). Due to this physiological characteristics, whatever change in the fast compartment induced by changes of ventilation/perfusion ratio, is "buffered" with time by the re-equilibration between fast compartment and the other body compartments. The practical consequence is that the equilibrium CO_2 requires time to be established [21].

When PEEP is increased the lung volume increases and the alveolar $PaCO_2$ (and $EtCO_2$) immediately decreases, as we observed at time 5'. Afterwards, the $PaCO_2$ returns to its baseline values. It must be noted, however, that an unmodified $PaCO_2$ may reflect the coexistence of two opposite phenomena, a regional decrease of dead space, due to recruitment of perfused units, and the regional increase of dead space, due to the hyper-distention. It must be also noted, however, that the rate of $PaCO_2$ increase, due to alveolar hypo-ventilation, is far slower than its rate of decrease during hyper-ventilation [11,12]. Moreover, we must also consider that the changes of 1 or 2 mmHg of $PaCO_2$, although physiologically important, are in the range of the errors of measurements either of blood gas analyzer or capnography. All these facts account for the long "equilibration" time of $PaCO_2$. Consequently late $PaCO_2$ changes cannot be reliably predicted by its early changes (see figure 3).

Respiratory mechanics-related variables

When PEEP was decreased the respiratory system mechanics was unchanged at time 5'. However, with time, the respiratory system compliance tended to decrease, reaching the statistical significance at time 60'. In this case referring to an equilibration time may be inappropriate, as the changes of compliance likely reflect a progressive change of the underlying lung pathology. In fact, when PEEP is decreased, the pulmonary units, in which the superimposed pressure is higher than PEEP, will collapse. These units can reopen only if the lower plateau pressures (due to the lower PEEP) is still sufficient to overcome the opening pressures of the collapsed units. If so these pulmonary units will undergo an intra-tidal opening/closing phenomenon. Initially the respiratory system compliance is not affected, as plateau pressure and PEEP are, on the average, equally decreased. With time, however, the regions undergoing opening and closing phenomenon may undergo complete collapse, due to gas reabsorption, and the inspiratory pressures are no longer sufficient to open these sticky atelectasis [15]. This time-dependent mechanism, leading to a decrease of the "baby lung" size will result in a progressive decrease, with time, of respiratory system compliance, as we observed at time 60'.

When PEEP was increased from 10 to 15 cmH_2O we did not observe significant changes in respiratory system compliance. In this setting, as the oxygenation continuously increases with time, it is possible that the increase in respiratory system compliance associated with recruitment of new

pulmonary units is offset by the hyper-inflation of other regions, as observed in animal models [20] or in CT studies [19]. When PEEP was increased from 5 to 15 cmH_2O, the lung recruitment likely prevailed on the over-inflation and at time 5' and 15' the respiratory system compliance increased significantly compared to the baseline. In summary, as the variations of compliance are likely associated with recruitment/derecruitment phenomenon, not surprisingly they do not reach an immediate equilibrium.

Hemodynamic-related variables

Changes of PEEP are usually associated to a change of hemodynamics. In this series of patients, they were of minor entity, but, when occurring, they were immediately observed after 5', as documented by the central venous pressure.

Conclusion

In our study we could not find a unique equilibration time for the variables we studied. For the oxygenation the equilibrium was fast after decremental PEEP but unreachable after incremental PEEP. Ventilation-associated variables required long time to reach their steady state, due to the physiological characteristics of CO_2 and its different patterns of elimination and retention. Respiratory system mechanics required long time to modify and, more than an equilibrium the changes likely reflect a progressive modification of the lung underlying pathology. Therefore, the different dynamics of the considered variables may be taken into account when evaluating the effects of PEEP changes

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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Table 1. Baseline Characteristic of the Study Population.

	Overall Population (n 44)	**Group 1** (n 23)	**Group 2** (n 21)	*P value*
Age (years)	61.1±16.8	60.7±15.6	61.6±18.5	0.872
Sex M (% tot)	29 (66)	15 (65)	14 (67)	0.828
Weight (kg)	81.5±21.7	78.5±21.5	84.9±21.9	0.289
Height (m)	1.7±0.1	1.7±0.1	1.7±0.1	0.865
BMI (kg/m^2)	27.3±6.6	26.3±6.4	28.4±6.7	0.222
Elapsed days before study	2.8±2.8	3.6±3.5	1.9±1.6	0.125
Respiratory rate (bpm)	15.8±3.5	16.8±3.6	14.8±3.07	0.032*
Tidal Volume (mL/kg actual)	7.1±1.5	7.1±1.6	7.0±1.4	0.816
Ve (L/min)	8.8±1.6	9.0±1.8	8.5±1.3	0.298
Ppeak (cmH_2O)	32.8±5.2	32.1±5.5	33.6±4.9	0.336
Pplat (cmH_2O)	24.1±3.3	23.7±3.3	24.5±3.4	0.477
Paw (cmH_2O)	14.5±1.2	14.5±1.3	14.5±1.2	0.940
Compliance (mL/cmH_2O)	42.0±13.7	42.0±14.9	42.0±12.6	0.944
PaO_2 (mmHg)	87.7±19.2	90.1±20.7	85.0±17.4	0.417
$PaCO_2$ (mmHg)	43.8±7.3	45.6±8.5	41.7±5.1	0.086
SaO_2 (%)	96.2±3.1	95.8±2.2	96.0±1.9	0.655
PaO_2/FiO_2 ratio	179.8±66.4	177.2±71.2	182.8±62.1	0.792
FiO_2 (%)	53.3±15.9	56.5±19.3	49.8±10.8	0.400
$EtCO_2$ (mmHg)	36.4±5.6	37.0±6.3	35.7±4.8	0.467
$PECO_2$ (mmHg)	19.6±4.5	19.3±4.9	20.0±3.9	0.606
VCO_2	166.6±49.2	165.0±47.3	168.1±52.4	0.847
Venous admixture	0.316±0.134	0.338±0.153	0.291±0.108	0.502
Vd/Vt physiol	0.535±0.119	0.562±0.122	0.507±0.113	0.152
Vd/Vt alveolar	0.160±0.126	0.176±0.128	0.143±0.125	0.355
CO (L/min)	7.5±2.1	8.3±2.3	6.3±1.3	0.144
MAP (mmHg)	80.6±10.7	82.6±9.0	78.6±12.3	0.219
HR (bpm)	88.4±20.4	89.4±21.7	87.3±19.4	0.737
CVP (mmHg)	11.8±3.2	11.4±2.3	12.3±4.0	0.361
SvO_2 (%)	76.0±6.6	77.0±6.2	74.9±6.9	0.327
pH	7.37±0.06	7.36±0.06	7.39±0.06	0.127
T (°C)	36.7±1.1	36.8±0.8	36.7±1.4	0.724

Cause of lung injury n° (%)				0.796
Pneumonia	11 (25)	4 (17.4)	7 (33.3)	
Sepsis	15 (34)	9 (39.2)	6 (28.6)	
Aspiration	7 (16)	4 (17.4)	3 (14.3)	
Trauma	6 (14)	3 (13.0)	3 (14.3)	
Other	5 (11)	3 (13.0)	2 (9.5)	

Table 1 summarizes the main demographic and physiological data standardized at PEEP 10 cmH_2O in the overall population and in the 2 groups.
Data are presented as mean ± standard deviation. Categorical variables are presented as number and percentage.
Physiological parameters were compared between group 1 and 2 by Student's t-test or Wilcoxon test for continuous variables and chi-square test to compare categorical variables. $P<0.05$ accepted as significant.
Elapsed days were counted from ICU admission to the PEEP test execution.
Other causes of acute lung injury included post-anoxic coma, cardio-circulatory shock, malingnancy, recent surgery.
BMI indicates body mass index; *Ve* minute ventilation; *Ppeak* airway peak pressure; *Pplat* airway plateau pressure, *Paw* mean airway pressure; PaO_2 arterial oxygen partial pressure; $PaCO_2$ arterial carbon dioxide partial pressure; SaO_2 arterial oxygen saturation; PaO_2/FiO_2 the ratio between arterial oxygen partial pressure and inspired oxygen fraction; FiO_2 inspired oxygen fraction; $EtCO_2$ end tidal partial pressure of carbon dioxide; $PECO_2$ expired carbon dioxide; VCO_2 carbon dioxide production, *Vd/Vt* dead space; *CO* cardiac output; *MAP* mean arterial pressure; *HR* heart rate; *CVP* central venous pressure; SvO_2 venous oxygen saturation; *T* indicates temperature.

FIGURE LEGENDS

Figure 1 shows the response of PaO_2 (upper panel), $PaCO_2$ (middle panel) and respiratory system compliance (Crs) (lower panel) to PEEP decay at different times. Black dots represent PEEP decay from 10 to 5 cmH_2O; white dots represent PEEP decay from 15 to 5 cmH_2O. P values resulting from one-way analysis of variance on repeated measures (on ranks when required): PEEP decay from 10 to 5 cmH_2O, PaO_2 $P<0.001$, $PaCO_2$=0.025, Crs $P<0.001$; PEEP decay from 15 to 5 cmH_2O, PaO_2 $P<0.001$, $PaCO_2$ =0.010, Crs $P<0.001$. Symbols refer to post-hoc analysis. * $P<0.05$ vs time 0'; # $P<0.05$ vs time 5'.

Figure 2 shows the response of PaO_2 (upper panel), $PaCO_2$ (middle panel) and respiratory system compliance (Crs) (lower panel) to PEEP increase at different times. Black dots represent PEEP increase from 10 to 15 cmH_2O; white dots represent PEEP increase from 5 to 15 cmH_2O. P values resulting from one-way analysis of variance on repeated measures (on ranks when required): PEEP increase from 10 to 15 cmH_2O, PaO_2 $P<0.001$, $PaCO_2$ =0.043, Crs P=0.494; PEEP increase from 5 to 15 cmH_2O, PaO_2 $P<0.001$, $PaCO_2$ <0.001, Crs $P<0.001$. Symbols refer to post-hoc analysis. * $P<0.05$ vs time 0'; # $P<0.05$ vs time 5'; ° $P<0.05$ vs time 15'; § $P<0.05$ vs time 30'.

Figure 3 shows the relationship between changes (d) recorded at 5' and changes recorded at 60' of 3 variables representative of oxygenation (PaO_2, first panel), ventilation ($PaCO_2$, middle panel) and respiratory mechanics (respiratory system compliance (Crs), lower panel). Black dots indicate PEEP decay from 10 to 5 cmH_2O, black squares indicate PEEP rise from 10 to 15 cmH_2O. white dots indicate PEEP rise from 5 to 15 cmH_2O and white squares indicate PEEP decay from 15 to 5 cmH_2O. Solid lines represent the linear regression:
($dPaO_2$ from 0' to 60') = -9.58 + 1.13*($dPaO_2$ from 0' to 5'), $P<0.001$, r^2= 0.87
($dPaCO_2$ from 0' to 60') = -1.68 + 0.93*($dPaCO_2$ from 0' to 5'), $P<0.001$, r^2= 0.37
(dCrs from 0' to 60') = 1.94+ 0.92*(dCrs from 0' to 5'), $P<0.001$, r^2= 0.87