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Effects of inspiratory pause on CO_2 elimination and arterial P_{CO_2} in acute lung injury

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Abstract

A high respiratory rate associated with the use of small tidal volumes, recommended for acute lung injury (ALI), shortens time for gas diffusion in the alveoli. This may decrease CO_2 elimination. We hypothesized that a post-inspiratory pause could enhance CO_2 elimination and reduce $PaCO_2$ by reducing dead space in ALI. In 15 mechanically ventilated patients with ALI and hypercapnia, a 20% post-inspiratory pause (Tp20) was applied during a period of 30 min between two ventilation periods without post-inspiratory pause (Tp0). Other parameters were kept unchanged. The single breath test for CO_2 was recorded every 5 minutes to measure tidal CO_2 elimination ($VtCO_2$), airway dead space (V_{Daw}) and slope of the alveolar plateau. PaO_2, $PaCO_2$, physiological and alveolar dead space (V_{Dphys}, V_{Dalv}) were determined at the end of each 30 minute period. The post-inspiratory pause, 0.7±0.2 s, induced on average less than 0.5 cm H_2O of intrinsic PEEP. During Tp20, $VtCO_2$ increased immediately by 28±10% (14±5 ml per breath compared to 11±4 for Tp0) and then decreased without reaching the initial value within 30 minutes. The addition of a post-inspiratory pause decreased significantly V_{Daw} by 14% and V_{Dphys} by 11% with no change in V_{Dalv}. During Tp20, the slope of alveolar plateau initially fell to 65±10 % of baseline value and continued to decrease. Tp20 induced a 10±3% decrease in $PaCO_2$ at 30 minutes (from 55±10 to 49±9 mmHg, $p<0.001$) with no significant variation in PaO_2. Post-inspiratory pause has a significant influence on CO_2 elimination when small tidal volumes are used during mechanical ventilation for ALI.

Keywords:

Gas Exchange, Dead Space, Mechanical Ventilation, ARDS

After transport of inspired gas through conducting airways, gas mixing in the respiratory zone by diffusion is time dependent. Therefore, a pause following gas insufflation may enhance gas exchange. Mechanical ventilators allow setting of a post-inspiratory pause time (Tp), often in percent of the breathing cycle.

During mechanical ventilation, prolonged Tp has been shown to enhance CO_2 elimination (8, 10-12, 14, 21). In healthy pigs, a prolonged Tp increases CO2 elimination per tidal breath (VtCO2), by decreasing airway dead space (V_{Daw}) (20). It was suggested that a prolonged Tp increased the mean distribution time of inspired gas (MDT), so as to allow more time for diffusion of CO_2 towards more central airways (7). MDT, further explained below, expresses the time available for enhanced diffusion between inhaled tidal volume and resident alveolar gas (2).

In pigs at health and with acute lung injury (ALI), Aström et al. recently found that a certain prolongation of MDT achieved with a longer Tp or with a longer inspiratory insufflation time had similar positive effects on CO_2 exchange (4). They noted that a prolonged Tp had a larger effect on MDT than a similar prolongation of inspiratory insufflation time.

Recently Aboab et al. showed that a longer Tp enhances CO_2 exchange evaluated from volumetric capnography in ALI and acute respiratory distress syndrome (ARDS) (2). Positive effects were observed both with regards to a reduced V_{Daw} and an elevated alveolar plateau. In their study Tp was only changed for one breath at a time and $PaCO_2$ was not measured. The question was left open if the beneficial effect of Tp was of temporary nature. In pigs, Aström et al. showed that a shortened MDT led to an increase in $PaCO_2$ that was nearly stable after 30 minutes. The study by Lessard et al. assessing CO_2 elimination in patients with ARDS was not controlled for the eventual increase in auto-PEEP and hemodynamic effects induced by the extension of inspiratory time (12). Mercat et al. did so and found that in ARDS an extended

end-inspiratory pause led to lower $PaCO_2$ by reducing physiological dead space but did not lead to improved PaO_2. (14).

In this study, we hypothesized that in patients with ALI or ARDS ventilated with small tidal volume, a post-inspiratory pause applied over a sufficient period of time would enhance CO_2 elimination and reduce $PaCO_2$ by reducing airway dead space and ventilation/perfusion non-homogeneity at the alveolar level. By applying volumetric capnography during the whole study we aimed at increased understanding about mechanisms behind effects of a prolonged Tp and dynamics of CO_2 exchange in ARDS.

PATIENTS AND METHODS

Material

Fifteen consecutive hypercapnic mechanically ventilated patients ($PaCO_2 \geq 45$ mmHg, Table 1), were studied within 48 hours after they fulfilled criteria for ALI or ARDS (5).

Sedation was achieved by continuous infusion. Neuromuscular blockade was used in 3 patients. The level of sedation (modified Ramsay score≥5) and the absence of respiratory effort on the flow-time curve during an end-expiratory pause of 6 seconds were checked before the beginning of the study. The patients were studied in semi recumbent position when stable with respect to ventilation, hemodynamics and metabolism (constant temperature). Hemodynamic stability was defined as <15% variation of heart rate and mean arterial pressure between two sets of measurements performed 60 minutes and 10 minutes before the beginning of the study. During the study, ten patients were receiving vaso-active drugs (dobutamine and/or epinephrine) at constant infusion rates. No fluid administration was made during the measurements.

If needed, endotracheal suction was performed well before the study and was not repeated during data collection. Clinically applied humidification/warming of inspired gas was maintained (heat/moisture exchanger in 10 patients, heated humidifier in 5). All patients had an arterial line.

Exclusion criteria were: age<18 years, presence of a chest tube, intracranial disease, Pa_{O_2}/Fi_{O_2}<75 mmHg, [HCO_3^-]<18 mmol/l, known severe COPD (FEV_1<50% predicted) or chronic respiratory insufficiency with long term oxygen therapy. High age of the patients and, as will be shown, high V_{Dphys} indicate a group of patients with a poor prognosis, in accordance with a 53% mortality rate (15).

Patients were ventilated in volume controlled mode with a constant flow (ServoVentilator 900C with a mainstream CO_2 Analyzer 930, Siemens-Elema, Solna, Sweden). Tidal volume (V_T) was 7±1 ml/kg of predicted body weight. At baseline, set inspiratory time (Ti) was 20% and Tp 0%. Applied positive end expiratory pressure (PEEPe) varied from 5 to 14 cmH_2O (Table 2). The ventilator/computer system used for data recording has previously been described (16, 19). Signals representing airway flow, pressure and CO_2 were fed to the A/D converter of a personal computer and sampled at 100 Hz. Compliance of the ventilator tubing was 1.7 ml/cmH_2O. Tracheal tube, CO_2 analyzer and heat and moisture exchanger dead space were measured in vitro (apparatus dead space volume was 86 ml if a heat and moisture exchanger was used, 41 ml for a heated humidifier). The Ethics Committee of French Intensive Care Society approved the protocol. Patients' next of kin were informed of the study protocol and gave their consent.

Procedure

Before the study, it was ensured that the extended Tp from 0% to 20% of total breathing cycle duration did not increase intrinsic PEEP by more than 1 cmH_2O. Insufflation time (20%), inspiratory flow, respiratory rate, V_T, FiO_2 and PEEPe were kept constant throughout the study.

Three periods were recorded. During the initial period of 30 min, Tp was set to 0%. Tp was changed to 20% for the second period. During the last period Tp was reset to 0 %. The periods were denoted $Tp0_{init}$, Tp20 and $Tp0_{late}$, respectively. Referring to Fig. 3, at 35 minutes, the knob on the ventilator panel for setting Tp was reset from 0 to 20 %. Thereby, a postinspiratory pause was introduced already for the ensuing inspiration. At 70 minutes, the knob was turned back to 0 % for recording of data for further 30 minutes. Signal recordings were performed during every 5 minutes. At 35 and 70 minutes the very first breaths during Tp20 and $Tp0_{late}$ were recorded. Ten breaths were analyzed during each recording. Blood gas analysis was performed using GEM Premier 3000 (Instrumentation Laboratory, Barcelona, Spain). Measurements during $Tp0_{init}$ are denoted baseline values.

Data analysis

Data for airway flow, pressure and CO_2 were transferred to a spreadsheet for Excel 2002 (Microsoft Corp., Redmond, WA, USA) and analyzed according to Uttman et al. (19). The expiratory flow signal was normalized by a correction factor so that expired tidal volume equaled the inspired measured at normal breaths. Flow rate and its integral volume were then corrected for gas compression in tubing and adjusted to body temperature and pressure, saturated with water vapor (BTPS). Accordingly, tidal volume was measured as the volume really delivered to the patient, corrected for gas compression in tubing. An unforeseen problem, further discussed below, was that during Tp20, the pressure drop at the end of insufflation caused redistribution from tubing to the lung. Thereby, V_T increased by about 13 ml or 2.6 %. Partial pressure of CO_2 at airway opening was calculated at actual barometric pressure.

Distribution and diffusion of tidal gas in the lung periphery starts at the moment when the interface between ‘fresh’ inspired gas and ‘used’ alveolar gas reaches the respiratory zone of the lung. It ends abruptly when the interface is pushed back into the airways at the start of expiration. Therefore, MDT is the interval from mean time of arrival of partitions of tidal volume in the respiratory zone until start of expiration. It expresses the time available for enhanced diffusion between inhaled tidal volume and resident alveolar gas, as mathematically described by Aboab et al. (2).

Further analysis was based upon the complete single breath test for CO_2 (SBT-CO_2), which is a loop comprising an expiratory and an inspiratory limb (6). $VtCO_2$ corresponds to the area within the loop (Fig. 1).

Different parameters related to dead space (V_D) were calculated from the SBT-CO_2. Mean values of 10 breaths were used. Physiologic dead space (V_{Dphys}) was calculated as follows.

$$V_{Dphys}\% = (Pa_{CO_2} \cdot V_T - \text{loop area A}) / (Pa_{CO_2} \cdot V_T) \cdot 100$$

V_{Dphys}% was calculated from signal recordings at the end of each period and simultaneous blood gas tests. Airway dead space distal to the CO_2 sensor (V_{Daw}) was calculated as the volume at which maximum slope of the SBT-CO_2 was measured. Carbon dioxide re-inspired from airway dead space proximal to the CO_2 sensor ($V_{Daw,prox}$) corresponds to area C (Fig. 1).

$$V_{Daw,prox}\% = \text{area C} / (Pa_{CO_2} \cdot V_T) \cdot 100$$

Alveolar dead space, V_{Dalv}, was calculated as follows.

$$V_{Dalv} = V_{Dphys} - (V_{Daw,prox} + V_{Daw})$$

The slope of the alveolar plateau (Slope) was determined at the midpoint of the alveolar from a logarithmic equation describing P_{CO_2} over volume (Fig. 1) (3).

Upon adding the post-inspiratory pause, the change during the very first 8 breaths in $VtCO_2$, Slope, MDT and V_{Daw} are denoted in $\Delta VtCO_2$, ΔSlope, ΔMDT and ΔV_{Daw}, respectively. The change of $PaCO_2$ between the ends of $Tp0_{init}$ and Tp20 periods is denoted $\Delta PaCO_2$.

Statistical methods

Data are presented as mean and SD or SE as specified. Friedman's non parametric test was used to study the relationship between the quantitative variables at different periods. Differences at the level of $p<0.05$ were considered statistically significant. For statistically significant differences, a Wilcoxon matched pairs signed-rank test was done to compare variables at $Tp0_{init}$ or $Tp0_{late}$ and Tp20. Spearman correlation coefficient was used to compare ΔVtCO2, ΔSlope, ΔMDT, ΔV_{Daw} and $\Delta PaCO_2$. Correlation coefficients were considered statistically significant at the 0.05 level and linear regression was used to establish the relationship between ΔV_{Daw} and $\Delta PaCO_2$.

RESULTS

Ventilation and hemodynamics

V_T was 489±63 ml, corresponding to 7±1 ml/kg of predicted body weight. Peak inspiratory flow rate was 0.7±0.2 l/s. During Tp20, airway pressure fell by 9.6 cmH_20 during the pause (from peak pressure to plateau pressure, Table 2). Then, tube decompression led to an increase of V_T, on average by 13±6 ml (2.6%) (Table 2). MDT changed from 0.21±0.07 s during $Tp0_{init}$ and $Tp0_{late}$, to 0.88±0.24 s during Tp20.

Mean airway pressure was at Tp0 12.4±2.7 cmH_2O and at Tp20 15.1±2.9 cmH_2O ($p<0.01$). Total PEEP increased by on average 0.4 cmH_20 during Tp20 because of a slight but significant increase in intrinsic PEEP (Table 2). Resistance and compliance of the respiratory system was

at Tp20 13.5±2.8 $cmH_2O/(l/s)$ and 44.0±11.4 ml/cmH_2O, respectively, yielding an average time constant of 0.59 s. The expiratory time for those 7 subjects who had a respiratory rate above 18 was at Tp20 1.8±0.2 s, i.e. about 3 time constants. Accordingly, expiration was long enough to allow near cessation of expiratory flow and low values of auto-PEEP also during Tp20 (Fig. 2). Hemodynamics remained constant during all periods (Table 2).

CO_2 elimination and dead space

During Tp20, $VtCO_2$ increased immediately by 28% (14±5 ml) compared to baseline during $Tp0_{init}$ and then decreased without reaching baseline within the Tp20 period (Fig. 3). During $Tp0_{late}$, $VtCO_2$ first fell suddenly to below baseline and then returned to baseline.

During the whole Tp20, V_{Daw} was reduced by 28 ml ($p<0.0001$, Table 2, Fig. 3). The decrease was 2.2 times higher than the increase in V_T. During $Tp0_{late}$, V_{Daw} equaled that during $Tp0_{init}$ (Fig. 3). At the end of Tp20, V_{Dphys} was 11±4% lower than at Tp0 while V_{Dalv} was unchanged (Table 2).

During Tp20, the slope of the alveolar plateau fell immediately to 65±10 % of baseline value (35±19 *vs* 53±23 mmHg/L) and then slowly decreased further to 32 ±17 mmHg/L (Fig. 3 and 4). During $Tp0_{late}$ the slope returned to baseline.

Arterial blood gases

During Tp20, $PaCO_2$ fell by 10±3% (from 55±10 to 49±9 mmHg; $p<0.0001$) (Fig. 5, Table 2). During $Tp0_{late}$, it returned to baseline. No significant change in PaO_2 was observed.

The change in $PaCO_2$ from baseline until end of Tp20 ($\Delta PaCO_2$, mmHg) correlated with the immediate change in V_{Daw} when the pause was instituted (ΔV_{Daw}, ml) (rho =0.60, $p<0.02$).

$$\Delta PaCO_2 = 0.15\Delta V_{Daw} - 1.49$$

No correlations were found between $\Delta PaCO_2$ and $\Delta VtCO_2$, ΔSlope or ΔMDT.

A comparison was made between 8 patients with respiratory rate ≤18 and 7 patients with rates >18. During Tp20, in both groups, PEEPtot increased by 0.4 cmH_2O, $PaCO_2$ decreased by 6 mmHg and V_{Daw} by 28 ml.

DISCUSSION

During volume controlled ventilation with small tidal volume and constant inspiratory flow in hypercapnic patients with ALI or ARDS, this study shows that a 20% post-inspiratory pause time leads to a 10% decrease in $PaCO_2$ after 30 minutes, secondary to enhanced CO_2 elimination. The main explanation of increased CO_2 elimination is lower V_{Daw}.

Our results agree with previous findings that a post-inspiratory pause enhances CO_2 elimination in healthy or surfactant depleted animals (4, 10, 11, 20) and with those obtained in surfactant depleted pigs in which inspiration at pressure controlled ventilation was prolonged (13). They also agree with results in patients with ALI/ARDS (2, 8, 12, 14).

The main effect of the post-inspiratory pause on CO_2 elimination reflects an instantaneous and continuous reduction of V_{Daw} that was immediately abolished during $Tp0_{late}$. According to the MDT concept this reflects enhanced diffusion of CO_2 from alveoli towards airways during the pause. As the decrease of V_{Daw} was more than two times larger than the small increase in V_T, the effect on $PaCO_2$ was about two thirds caused by the change in V_{Daw}. As further discussed below the ultimate changes in $PaCO_2$ could not be estimated during the test periods of 30 minutes. During Tp20, decompression of gas in the tubing during the pause reflects the product between (Ppeak-Pplat) and tube compliance and was calculated to 16 ml. The increase in V_T during Tp20 can accordingly be fully explained by gas decompression. The lower slope of the alveolar plateau during Tp20 indicates that a more even alveolar ventilation/perfusion

relationship may have contributed to enhanced CO_2 elimination. The slope of the alveolar plateau mainly reflects non-synchronous emptying of lung compartments with different ventilation/perfusion ratios (7). The immediate and nearly stable drop in slope during Tp20, Fig. 3, suggests more even alveolar ventilation due to diffusion within the alveolar zone that may have further contributed to enhanced CO_2 elimination during Tp20. In humans, equilibration through collateral channels may play a role in this. However, Uttman et al. made similar observations in healthy pigs, which do not have collaterals (20).

$VtCO_2$ at constant respiratory rate returned during $Tp0_{late}$ towards baseline as a sign of constant metabolic rate. Then, during Tp20, $VtCO_2$ should, after the initial increase, return towards the baseline that represents metabolic rate. In patients without significant cardiopulmonary disease, when ventilation was decreased by 10%, a new steady state was established along a mono-exponential path with a time constant of about 35 minutes (17). In the present study, the return towards baseline during Tp20 was far from complete (Fig. 3). Initially during that period $VtCO_2$ fell rapidly and then very slowly. The reasonable explanation is that CO_2 stores in the body of this group of patients are large and distributed among compartments with very different time constants for equilibration of CO_2. Severe cardiopulmonary disease, increased extravascular liquid space and poor circulation in peripheral edematous regions are likely causes of slow equilibration of CO_2. Similar conclusions have previously been drawn by Henneberg et al. (9).

During Tp20, the fall in $PaCO_2$ of 10 % is the result of enhanced CO_2 elimination as expressed by enhanced $VtCO_2$. However, the full effect on $PaCO_2$ of a change in efficient alveolar ventilation can not be observed until CO_2 stores in the body have been equilibrated as discussed by Taskar et al. (17). At completely steady state, the change in $PaCO_2$ should equal the change in initial effect on rate of CO_2 elimination, in this study represented by change in $VtCO_2$ by 28 %. That $VtCO_2$ did not return to baseline indicates that a steady state was not achieved

during Tp20, as discussed. Accordingly, the observed change in $PaCO_2$ probably underestimates the full effect of a post-inspiratory pause of 20%. In order to limit confounding factors due to spontaneous changes of metabolism, hemodynamic and other physiological parameters, the study periods were limited to 30 minutes as a compromise against a desirable steady state during each period. Aström et al. observed in pigs at health and with a model of ALI that after 30 minutes of ventilation with a different MDT, $PaCO_2$ changed by 0.75 of what was expected on the basis of immediate change in $VtCO_2$ (4). In the present study this fraction was only 10/28 i.e. 0.36. The difference may represent a much slower equilibration time in the gravely sick patient population. In the study of Mercat et al. $PaCO_2$ changed by only 5 % when the pause was prolonged although an equilibration time of 1 hour left more time available for equilibration of CO_2 stores in the body (14). In their study we estimate that MDT doubled from about 0.6 s to 1.3 s at prolonged Tp, while MDT in ours increased more than fourfold, from 0.21 to 0.88. The lower change in $PaCO_2$ in Mercat's study can be explained by the lower relative change in MDT considering that the effect of variable MDT according to Aström et al. is non-linear, i.e. more important towards lower MDT values.

At Tp20, shortening of expiration time from 80 % to 60 % led to a small but significant increase in intrinsic PEEP (<0.5 cmH_2O). PEEP tends to increase V_{Daw} and may hamper CO_2 elimination through hemodynamic effects. Increased PEEP increases in itself V_{Daw} due to airway distension (6, 18). Accordingly, the small increase in total PEEP might have attenuated the observed decrease in V_{Daw} and enhanced CO_2 elimination at Tp20. In spite of higher total PEEP at Tp20, peak pressure remained unchanged. This might indicate that some recruitment took place during Tp20. However, PaO_2 did not increase as was also observed in the study of Mercat et al. (14). One may speculate that positive effects of recruitment were balanced by negative effects caused by diversion of blood flow to collapsed lung, thereby increasing shunt.

The two groups with RR≤18 and RR>18 showed equal response to a prolonged pause which finding may reflect a low variation in RR in the present material.

In this experimental study, we aimed at unchanged tidal volume and used CO_2 turnover $PaCO_2$ as indicators of more efficient ventilation caused by a postinspiratory pause. In clincal practise, the utility of more efficient gas exchange would rather be to decrease tidal volume for enhanced lung protection. This could, depending on circumstances, be applied so as to either reduce peak pressure to limit barotrauma or to increase PEEP to stabilize lung recruitment. Notably, a postinspiratory pause is one of several options to lower V_T. One is an increase in respiratory rate. At high rates, MDT becomes shorter. Aström showed a steep decline in CO_2 exchange at low MDT values (4). At high respiratory rates, it may, therefore be important to use a pause to adequately prolong MDT.

In conclusion:

Post-inspiratory pause has a great influence on CO_2 exchange not only for breaths immediately following resetting. A prolongation of Tp leads to a decrease of $PaCO_2$ as hypothesized. The effects of Tp are mostly due to diffusion of CO_2 into airways but also to a more homogenous ventilation/perfusion at the alveolar level. The mode of inspiratory gas delivery should be taken into account e.g. in the context of low tidal volume ventilation (1). The ancillary observation of a long equilibrium time for $PaCO_2$ in ALI, indicating that 30 minutes is too short for full appreciation of the effect on $PaCO_2$ of a change in ventilation, merits further studies.

GRANTS

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Figure legends

Fig. 1. The single breath test for carbon dioxide (SBT-CO_2) depicts partial pressure of CO_2 at airway opening and $PaCO_2$ (horizontal dotted line) versus volume. Area A within the loop represents the amount of CO_2 eliminated during the breath ($VtCO_2$). Vertical interrupted line indicates airway dead space distal to the CO_2 sensor (V_{Daw}). Area C reflects CO_2 re-inspired from y-piece and tubing and represents proximal airway dead space ($V_{Daw,prox}$). Area B between the alveolar plateau and $PaCO_2$ illustrates alveolar dead space. The alveolar plateau was characterized by the equation $PCO_2 = b + m(\ln V)$. Its slope was determined at its mid-point.

Fig. 2. Representative tracings from single breaths of airway flow, pressure (Paw) and partial pressure of CO_2 at the y-piece in mainstream CO_2 analyzer, PCO_2. Thin black lines represent Tp0 and thicker grey lines Tp20.

Fig. 3 Diamonds represent mean values for the 15 patients at 5 minutes interval throughout the study. At 35 min the knob on the ventilator panel for setting Tp was reset from 0 to 20 % to start Tp20. At 70 minutes $Tp0_{late}$ was started by turning the knob back to 0 %. Times for resetting are indicated with vertical interrupted lines. Data at 35 and 70 minutes represent the first breaths during Tp20 and $Tp0_{late}$.

Panel A. Tidal elimination of CO_2 ($VtCO_2$) against time. For the 15 patients, diamonds and thin lines represent percent of mean value during $Tp0_{init}$ ±2 SE.

Panel B. Airway dead space (V_{Daw}) against time in each subject, patients ventilated with heated humidifiers (continuous lines) or heat and moisture exchangers (broken lines). Diamonds shows mean V_{Daw}.

Panel C. Slope of the alveolar plateau against time. For the 15 patients diamonds and thin lines represent percent of mean value during $Tp0_{init}$ ±2 SE.

Fig. 4. Single breath test for CO_2 from a representative patient (n° 2) with and without pause recorded at the end of initial period of zero pause ($Tp0_{init}$, continuous line) and after 10 and 30 min at Tp20, (dotted and interrupted lines, respectively). At $Tp0_{init}$, airway dead space (V_{Daw}, vertical lines) was larger and the slope of the alveolar plateau steeper, while the area within the loop representing $VtCO_2$ was smaller.

Fig. 5. Individual values and mean ± SE of $PaCO_2$ after mechanical ventilation with or without a post-inspiratory pause of 20% ($Tp0_{init}$, Tp20, and $Tp0_{late}$).

Table legends

Table 1. Characteristics of the 15 study patients with acute lung injury/acute respiratory distress syndrome.

Table 2. Ventilatory and respiratory mechanical parameters, dead spaces, blood gas and hemodynamic parameters (mean±SD) at the end of each study period.

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No	Age years	SAPS II	Cause ALI/ARDS	Underlying disease	Pa_{O_2}/Fi_{O_2} mmHg	Outcome
1	78	37	Pneumonia	Ischemic cardiopathy	160	alive
2	78	74	Pneumonia	Ischemic cardiopathy	147	alive
3	38	22	Septic shock	Cirrhosis	121	alive
4	57	40	Septic shock	Alcoholism	146	dead
5	76	47	Pneumonia	Cachexy	174	dead
6	58	52	Pneumonia	Ischemic cardiopathy	97	alive
7	91	56	Pneumonia	Epilepsy	154	dead
8	81	57	Pneumonia	Hypertension	83	dead
9	82	99	Septic shock	Hypertension	248	alive
10	39	55	Inhalation	Cachexy	193	dead
11	50	57	Inhalation	Cirrhosis	92	dead
12	71	41	Pneumonia	Leukemia	146	dead
13	44	40	Pneumonia	Aortic dissection	101	alive
14	75	60	Tumor infiltration	Lymphoma	170	alive
15	86	33	Pneumonia	Atrial fibrillation	196	dead
Mean ± SD	67±18	51±18	-	-	148±45	-

SAPS – simplified acute physiology score; ALI – acute lung injury; ARDS – acute respiratory distress syndrome

Table 2. Ventilatory and respiratory mechanical parameters, dead spaces, blood gas and hemodynamic parameters (mean±SD) at the end of each study period.

	$Tp0_{init}$	Tp20	$Tp0_{late}$	Friedman Test
V_T (ml)	489±63	502±63*	489±63	<0.0001
RR (min^{-1})	18±4	18±4	18±4	
Ti (s)	0.7±0.2	1.4±0.3	0.7±0.2	
Te (s)	3.0±0.6	2.3±0.5	3.0±0.6	
(Ti+Tp)/Ttot (%)	20	40	20	
Ppeak (cmH_2O)	31.5±5.7	31.3±5.4	31.3±5.6	0.4
Pplat (cmH_2O)		21.7±4.5		
PEEPe (cmH_2O)	8.8±2.5	8.8±2.5	8.8±2.5	
PEEPtot (cmH_2O)	9.1±2.5	9.5±2.6 *	9.1±2.5	<0.0001
V_{Dphys}% (%V_T)	68.2±7.4	60.8±8.8*	67.6±7.6	<0.0001
V_{Daw}% (%V_T)	40.3±8.8	33.4±8.8*	40.4±8.7	<0.0001
V_{Daw} (ml)	194±40	166±41*	195±39	<0.0001
V_{Dalv}% (%V_T)	23.8±9.1	22.8±10.1	22.9±8.6	0.4
FiO_2	0.8±0.2	0.8±0.2	0.8±0.2	
pH	7.27±0.07	7.31±0.08*	7.27±0.08	<0.0001
$PaCO_2$ (mmHg)	55±10	49±9*	55±10	<0.0001
PaO_2 (mmHg)	113±32	110±32	116±34	0.2
PaO_2/FiO_2 ratio (mmHg)	148±45	145±48	151±45	0.2
MAP (mmHg)	69±7	73±11	70±6	0.6
HR (min^{-1})	85±20	87±18	89±18	0.2

Values are mean±SD, *p=0.001 Tp20 vs $Tp0_{init}$ or $Tp0_{late}$, V_T – tidal volume, RR – respiratory rate, Ti–inspiratory time including post-inspiratory pause, Te–expiratory time; Ti+Tp – insufflation and post-inspiratory pause as percent of the breathing cycle, PEEPe – external positive end expiratory pressure, PEEPtot – external positive end expiratory pressure + intrinsic positive end expiratory pressure, V_{Dphys}% – physiological dead space in percent of V_T, V_{Daw}% – airways dead space in percent of V_T, V_{Dalv}% – alveolar dead space in percent of V_T, FiO_2 – fraction of inspired oxygen, MAP – mean arterial pressure, HR- heart rate.

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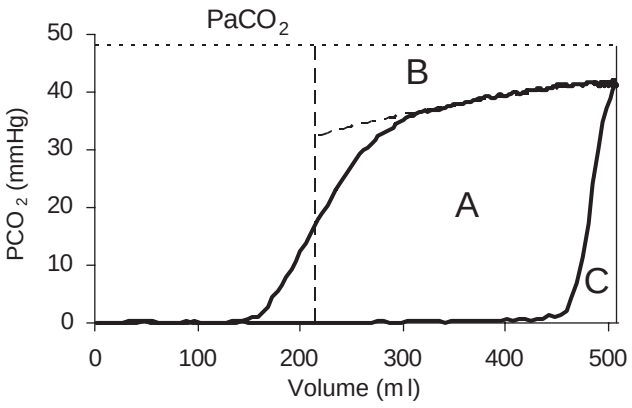
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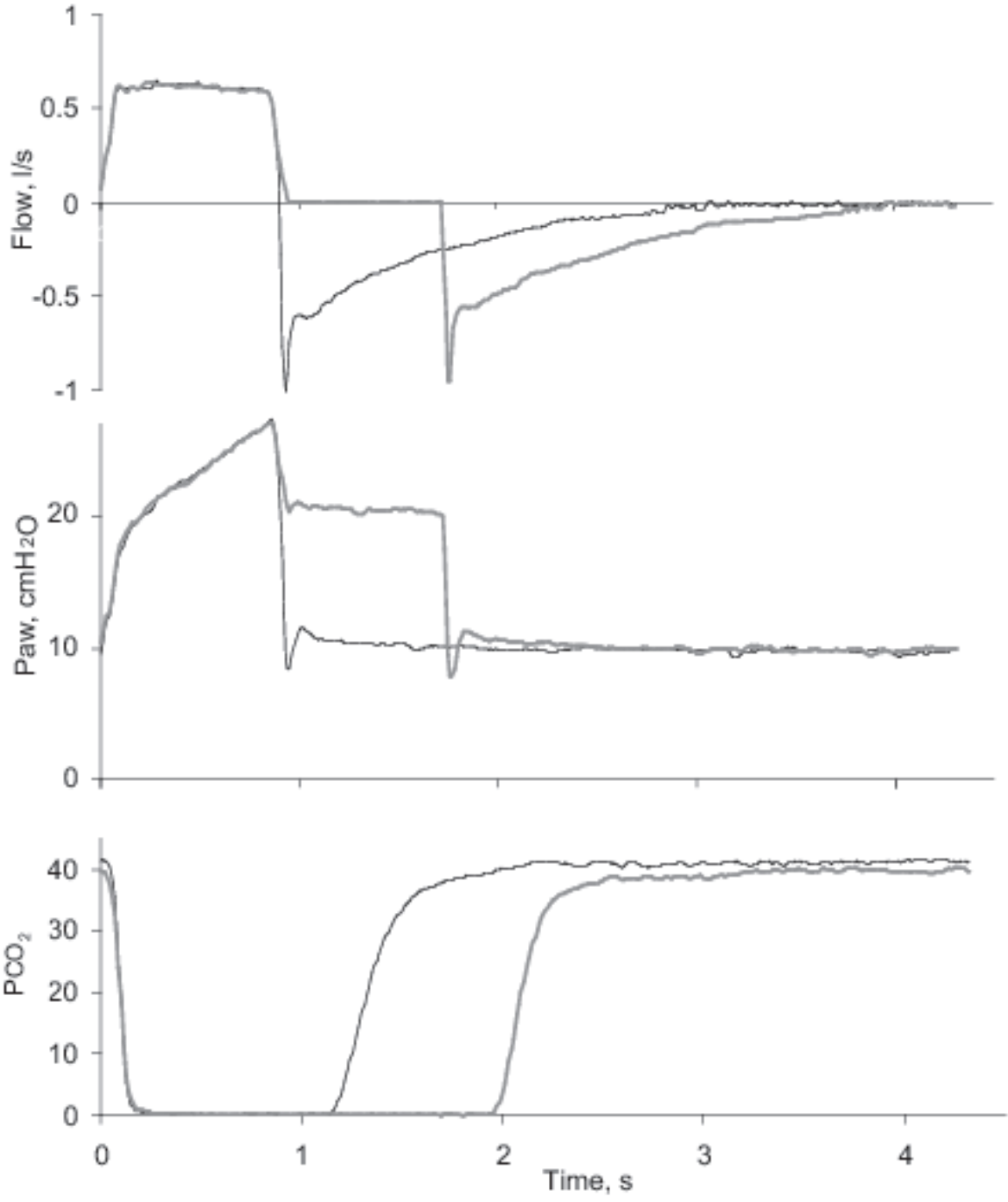
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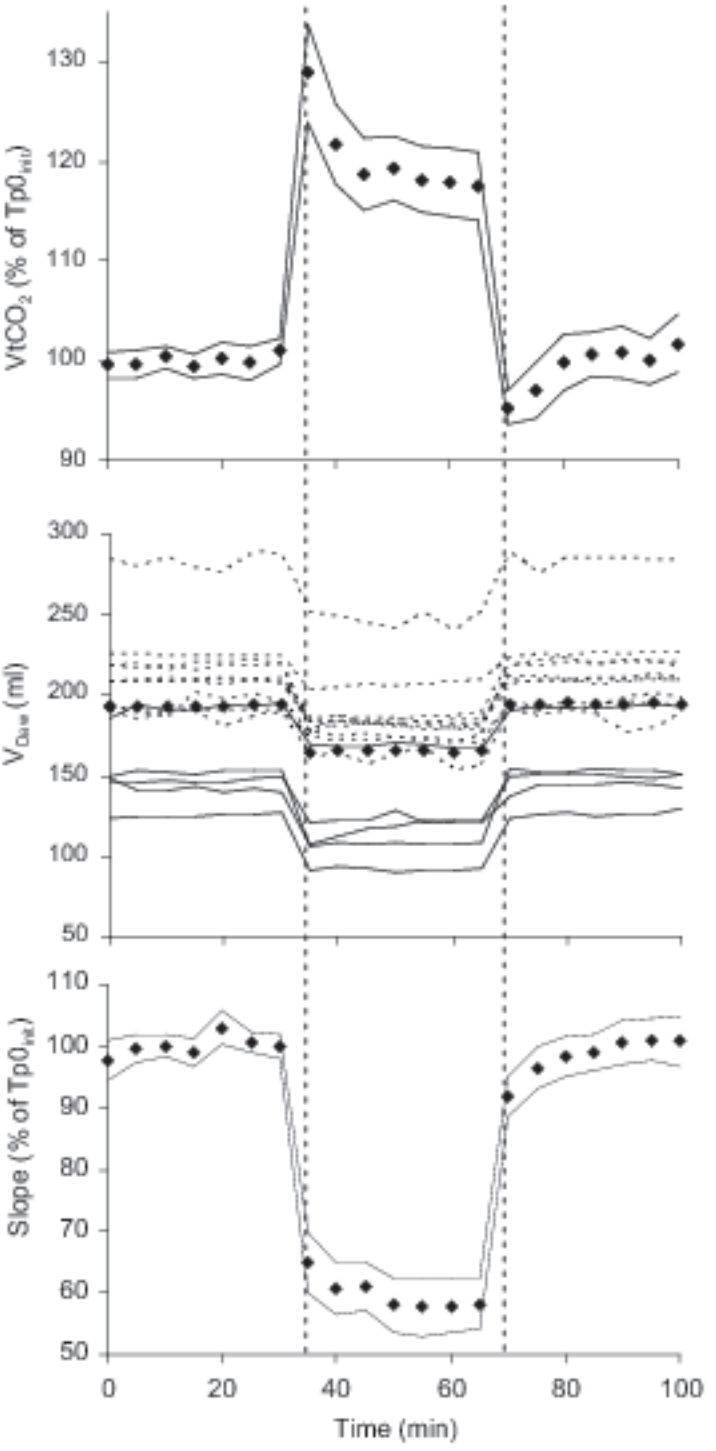
Table 2.

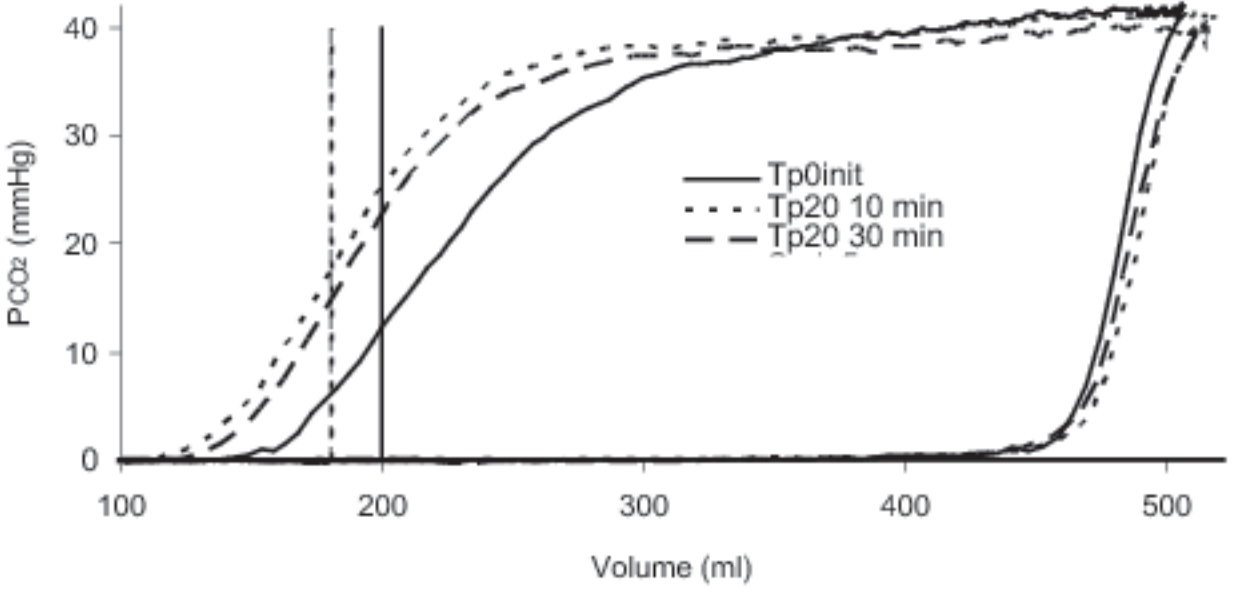
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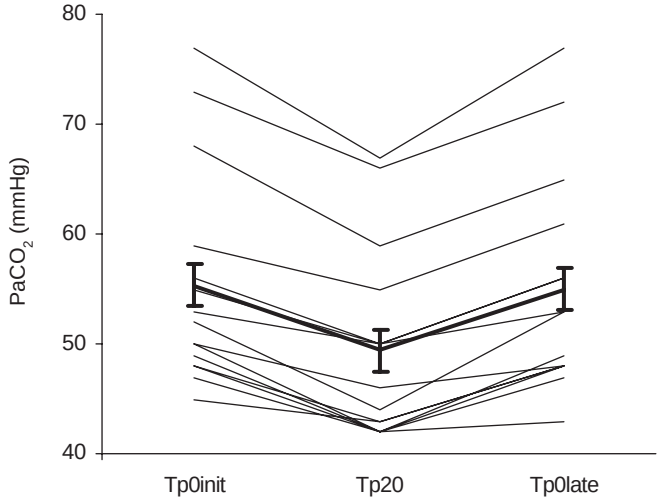
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PaCO2
50
40
30
20
10
0
PCO2 (mmHg)
B
A
C
0
100
200
300
400
500
Volume (ml)


1
0.5
0
-0.5
-1
Flow, l/s
20
10
0
Paw, cmH2O
40
30
20
10
0
PCO2
0
1
2
3
4
Time, s


VtCO2 (% of Tp0init)
130
120
110
100
90
VDaw (ml)
300
250
200
150
100
50
Slope (% of Tp0init)
110
100
90
80
70
60
50
0
20
40
60
80
100
Time (min)


40
30
20
10
0
PCO2 (mmHg)
100
200
300
400
500
Volume (ml)
Tp0init
Tp20 10 min
Tp20 30 min


80
70
60
50
40
PaCO2 (mmHg)
Tp0init
Tp20
Tp0late