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Original Article

Higher positive end expiratory pressure guided by upper inflection point of pressure volume curve ameliorating respiratory function in acute respiratory distress syndrome pig models

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Abstract: Background: No optimal positive end expiratory pressure (PEEP) threshold has been established. Methods: Twenty-two healthy pigs were induced to ARDS models and were randomly divided into four groups according to inflection points: P_{LIP+2} (5), $P_{(LIP+UIP)/2}$ (6), P_{EIP} (6) and P_{UIP-5} (5). Parameters of extra-vascular lung water, gas exchange, hemodynamic parameters and respiratory mechanics were measured in the groups of different time point. Results: Values of P_{LIP+2}, $(P_{LIP}+P_{UIP})/2$, P_{EIP} and P_{UIP-5} were 9.1 ± 0.6 cmH_2O, 15.6 ± 1.1 cmH_2O, 17.8 ± 0.7 cmH_2O and 19.3 ± 1.8 cmH_2O respectively. Value of EVLW decrease with time significantly in group P_{EIP} and P_{UIP-5}. PaO_2 and oxygenation index (PaO_2/FiO_2) increased significantly in the group of $(P_{LIP}+P_{UIP})/2$, P_{EIP} and P_{UIP-5} in 2 hours after PEEP use. The increase in SaO_2 reached significance in group P_{EIP}. The effect of different PEEP on $PaCO_2$ was not significant. After PEEP was given, mean arterial pressure (MAP) and cardiac output (CO) were decreased, while the central venous pressure (CVP) was increased significantly in groups of P_{EIP} and P_{UIP-5} in comparison with baseline. The change in plat airway pressure (Pplat) in group P_{EIP} and P_{UIP-5}, static lung compliance (Cst) in group P_{EIP} reached significance in 2 hours after PEEP use. Conclusions: Higher PEEP could help obtain better oxygenation, improve pulmonary compliance and lung ventilation in ARDS pigs. PEEP guided by UIP of PV curve may be the optimal PEEP.

Keywords: PEEP, acute respiratory distress syndrome (ARDS), pressure volume (PV) curve, upper inflection point (UIP)

Introduction

Reduction of the tidal volume, and thus of the stress applied to the lungs, can protect the lungs from over inflation and unambiguously reduce acute respiratory distress syndrome (ARDS) mortality in a large multicenter randomized trial [1]. However, cyclic alveolar closure caused by small tidal volume (VT) may induce low efficiency of ventilation [2]. Therefore, a suitable positive end expiratory pressure (PEEP) to optimally balance recruitment and distention in each patient is necessary.

It is reported that proper PEEP can be determined by identifying pressure volume (PV) curve inflection points [3]. The lower inflection point (LIP) of the inflation limb has been shown to be the point of massive alveolar recruitment and therefore an option for setting PEEP [4]. But it is still under debate. Those much higher PEEP than LIP can still recruit lung [5] and in practice some patients need much higher PEEP to maintain saturation of oxygen [6], which manifests that PEEP deduced from LIP may be not optimal.

In the present study, we compared the effects of different PEEP pressure deduced from PV curve through ARDS pig models, established the safety range of PEEP, and brought convenience of PEEP setting.

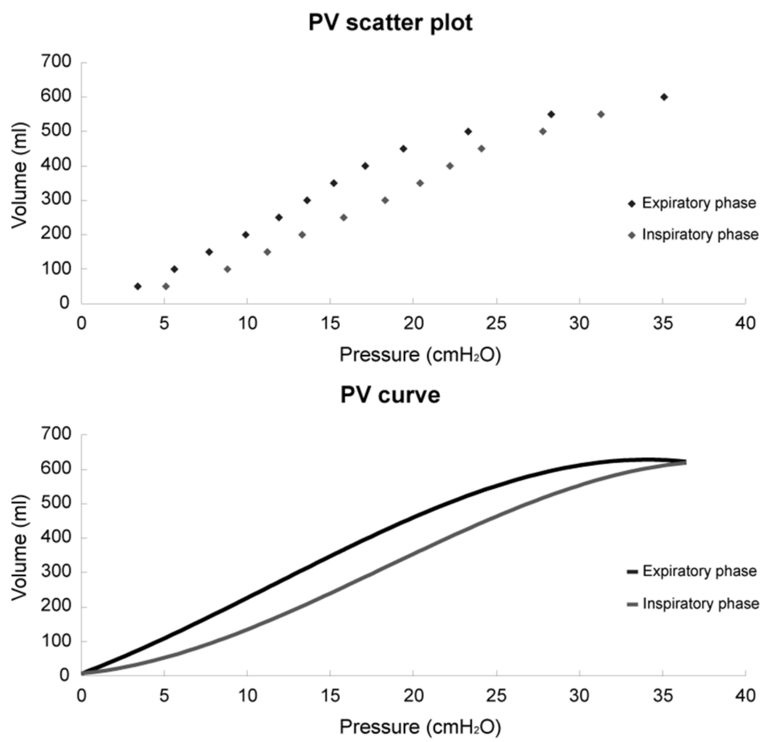

Figure 1. PV scatter plot was obtained using super-syringe and PV curve established, and inflection points were estimated by observing.

Methods

Animal preparation

Twenty-two healthy domestic pigs weighing 21 to 29 kg were enrolled in this study and were fed by professional staffs in the animal room. Prior to instrumentation, animals were premedicated with intramuscular sodium pentobarbital (30 mg) and maintained with sodium pentobarbital (2 $mg \cdot kg^{-1} \cdot h^{-1}$) and pancuronium bromide (0.1 $mg \cdot kg^{-1}$). Then they were placed supine on a heating pad to maintain the core temperature at 38°C [7].

Venous access was then established and secured in a jugular vein. To ensure adequate hydration, 500 mL of lactated Ringer's solution was infused rapidly followed by an infusion rate of 5 $ml \cdot kg^{-1} \cdot h^{-1}$ throughout the experiment. Animals were monitored with continuous electrocardiography and oximetry on multichannel monitors (IntelliVue MP20, M8001A, Philips Medizin Systeme Boblingen, Germany).

All animal-related procedures were approved by the Animal Care and Use Committee of The Tenth People's Hospital of Shanghai (permit number: 2011-RES1). This study was also approved by the Science and Technology Commission of Shanghai Municipality (ID: SYXK 2007-0006).

Surgical procedures and ventilation

The animals were tracheotomized, intubated with a 7.5 mm internal diameter cuffed tracheal tube, and ventilated (Servo 900, Siemens, Berlin, Germany) in a volume-controlled ventilation mode with a PEEP of 5 cmH_2O, an inspiratory/expiratory ratio of 1:2, and inspired O_2 fraction (FiO_2) of 0.4, a respiratory rate of 25 breaths per minute and tidal volume of 10 $ml \cdot kg^{-1}$ to maintain arterial partial pressure of CO_2 ($PaCO_2$) between 35 to 40 mmHg before HCl administration.

A 5 F catheter (PVPK2015L20, PULSIOCATH, Pulsion Medical Systems, Feldkirchen, Germany) was inserted into the right femoral artery for thermodilution measurements and pulse contour analysis and connected to the pulse index continuous cardiac output (PiCCO) plus hemodynamic monitor (PC8100, Pulsion Medical Systems). Blood samples were collected, extravascular lung water (EVLW), intrathoracic blood volume (ITBV) and global end diastolic volume (GEDV) was measured.

ARDS model establishment and experimental design

Initial lung injury was induced by instillation of 0.3 N HCl as a bolus through a feeding tube connected to the end of the tracheal tube. HCl was administered to each side (1.5 $ml \cdot kg^{-1}$) serially with the animal placed on one lateral side followed by the other (60 seconds each side). Arterial blood gases were monitored, and stable ARDS models were established when PaO_2/FiO_2 < 150 mmHg, maintaining 30 minutes [8].

PV curves were measured by super-syringe method. The pig was disconnected from the

Table 1. Effect of PEEP on EVLW in pigs with ARDS (mean ± SD)

Group	Time dot	n	EVLW ($ml \cdot kg^{-1}$)	ITBV (Pml)	GEDV (Pml)
P_{LIP+2}	0 h	5	16.6 ± 3.2	1031.8 ± 425.1	831.9 ± 343.1
	1 h		15.5 ± 4.7	1043.9 ± 365.0	841.8 ± 293.8
	2 h		14.9 ± 1.4	974.1 ± 345.6	786.0 ± 286.7
$(P_{LIP} + P_{UIP})/2$					
$(P_{LIP} + P_{UIP})/2$	0 h	6	15.8 ± 2.5	963.1 ± 254.2	798.4 ± 189.3
	1 h		14.7 ± 4.5	843.3 ± 237.4	677.3 ± 171.5
	2 h		12.7 ± 2.2*	803.6 ± 205.1	648.2 ± 165.1
P_{EIP}					
P_{EIP}	0 h	6	17.3 ± 1.6	1034.8 ± 466.3	838.0 ± 380.1
	1 h		15.1 ± 1.7*	911.4 ± 335.5	741.5 ± 265.1
	2 h		12.9 ± 1.5$^{*,\#}$	969.3 ± 401.8	781.7 ± 323.7
P_{UIP-5}					
P_{UIP-5}	0 h	5	18.4 ± 2.4	934.3 ± 346.3	827.0 ± 132.1
	1 h		14.7 ± 2.5*	971.4 ± 432.4	785.5 ± 136.4
	2 h		14.1 ± 2.8*	939.1 ± 301.4	731.9 ± 253.3

$^{*}P < 0.05$, compared with 0 h of same group; $^{\#}P < 0.05$. Compared with P_{LIP+2} group at the same time point.

ventilator and connected to a specifically designed super-syringe at the end of a 3-s expiration. A 3-L syringe (Model Series 5540; Hans Rudolph) was used for insufflating the lungs with pure O_2 in 50-ml steps until a volume corresponding to a plateau pressure of 35 cmH_2O was reached. Intervals between two steps lasted 3 s [9]. PV scatter plot was obtained using super-syringe and PV curve established, and inflection points were estimated by observing.

Twenty-two pigs were randomly divided into four groups: P_{LIP+2} (5), $P_{(LIP+UIP)/2}$ (6), P_{EIP} (6) and P_{UIP-5} (5) (UIP: upper inflection point; EIP: expiratory inflection point), and given protective mechanical ventilation with VT of 6 $ml \cdot kg^{-1}$, plateau pressure ≤ 30 cmH_2O, an inspiratory/expiratory ratio of 1:2, and FiO_2 of 0.4, a respiratory rate of 25 breaths per minute, PEEP of (LIP + 2), (LIP + UIP)/2, EIP and (UIP-5) cmH_2O respectively.

Statistical analyses

All quantitative data were shown as mean ± standard deviation (SD), as the data proved to be normally distributed. Data was analyzed by one-way analysis of variance (ANOVA). All analyses were performed using SPSS 15.0 (SPSS, Inc., Chicago, IL, USA) and differences were considered statistically significant at a probability level of less than 0.05 ($P < 0.05$).

Results

Mean (SD) animal weight was 22.3 (2.1) kg. Haemoglobin concentration was 103 ± 8 g/L. There were no significant differences between the measured parameters at baseline before and after ARDS model establishment during the randomized protocol.

PV scatter plots and PV curve

Values of (P_{LIP}, V_{LIP}), (P_{UIP}, V_{UIP}), ($P_{EIP,}$ V_{EIP}) were (7.3 ± 0.7 cmH_2O, 97.3 ± 18.7 ml), (24.7 ± 0.9 cmH_2O, 484.3 ± 94.8 ml), (17.8 ± 0.7 cmH_2O, 483.4 ± 72.9 ml) respectively. Values of (P_{LIP+2}), $(P_{LIP} + P_{UIP})/2$ and (P_{UIP-5}) were calculated, and were 9.1 ± 0.6 cmH_2O, 15.6 ± 1.1 cmH_2O, and 19.3. ± 1.8 cmH_2O respectively, and were increased gradually from the first to the last (**Figure 1**).

Effect of different PEEP on EVLW

Value of EVLW tended to decrease along with PEEP increasing. And the decrease with time was significant in group P_{EIP} and P_{UIP-5} ($P < 0.05$). There was no increase of EVLW in any time dot. No obvious changes of ITBV and GEDV were observed, when higher PEEP was used ($P >$ 0.05, **Table 1**).

Effect of different PEEP on gas exchange

PaO_2 and oxygenation index (PaO_2/FiO_2) increased significantly in the group of $(P_{LIP} + P_{UIP})/2$, P_{EIP} and P_{UIP-5} in 2 hours after PEEP use ($P < 0.05$). SaO_2 had a tendency to increase, and reached significance in group P_{EIP}, when PEEP value was increased ($P < 0.05$). But the effect of different PEEP on $PaCO_2$ was not significant ($P > 0.05$) (**Table 2**).

Effect of different PEEP on hemodynamic parameters

All the variables including mean arterial pressure (MAP), central venous pressure (CVP) and cardiac output (CO) were not significantly different among groups at baseline ($P > 0.05$). But after PEEP was given, MAP and CO were decreased, while the CVP were increased sig-

Table 2. Effect of PEEP on gas exchanges in pigs with ARDS (mean ± SD)

Group	Time dot	n	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	SaO_2 (%)	PaO_2/FiO_2 (mmHg)
P_{LIP+2}	0 h	5	52.50 ± 9.15	46.16 ± 7.62	79.29 ± 10. 61	104.15 ± 30.37
	1 h		54.23 ± 10.16	42.33 ± 8.61	80.33 ± 11.23	105.86 ± 19.57
	2 h		55.20 ± 9.79	41.58 ± 8.52	81.65 ± 10.51	95.73 ± 17.46
$(P_{LIP} + P_{UIP})/2$	0 h	6	51.60 ± 7.32	45.25 ± 8.72	80.75 ± 9.72	104.65 ± 15.67
	1 h		62.20 ± 8.79*	39.45 ± 9.65	87.54 ± 7.68	125.45 ± 16.32*
	2 h		69.05 ± 8.36*,#	37.67 ± 7.22	87.67 ± 2.12	126.56 ± 15.56*
P_{EIP}	0 h	6	49.50 ± 7.39	44.79 ± 5.08	78.80 ± 10.97	106.50 ± 19.27
	1 h		66.50 ± 9.78*	39.17 ± 6.56	89.17 ± 12.56*	134.86 ± 16.37*,#
	2 h		78.45 ± 9.35*,#	38.42 ± 9.37	89.42 ± 12.37*	136.81 ± 17.43*,#
P_{UIP-5}	0 h	5	51.23 ± 6.67	45.67 ± 8.72	79.67 ± 5.72	102.36 ± 21.57
	1 h		67.80 ± 7.52*,#	39.26 ± 7.34	88.26 ± 9.34	133.18 ± 18.36*,#
	2 h		85.78 ± 11.32*,#	38.52 ± 7.25	90.36 ± 7.11*	143.65 ± 23.29*

*P < 0.05, compared with 0 h of same group; #P < 0.05. Compared with P_{LIP+2} group at the same time point.

nificantly in groups of P_{EIP} and P_{UIP-5} in comparison with baseline (P < 0.05). In groups of $(P_{LIP} + P_{UIP})/2$ and P_{UIP-5}, decreases were corrected fluids and inotropic agents (**Table 3**).

Effect of different PEEP on respiratory mechanics

Baseline peak airway pressure (PIP), plat airway pressure (Pplat) and static lung compliance (Cst) showed no significant difference (P > 0.05). After PEEP was given, PIP, Pplat and Cst tented to increase in comparison with baseline, but only the change in Pplat in group P_{EIP} and P_{UIP-5}, Cst in group P_{EIP} reached significance in 2 hours after PEEP use (P < 0.05, **Table 4**).

Discussion

In the present study, the upper inflection point of the deflation limb of the PV curve appeared to represent the point of optimal PEEP, with decreased EVLW, better condition of gas exchange, hemodynamic parameters and respiratory mechanics with time.

Many critically ill patients require and benefit from invasive mechanical ventilation because of acute lung injury (ALI) and ARDS, secondary injury occurring as well [10]. The secondary injury resulted from mechanical ventilation is attributable largely to two mechanical stresses: excessive lung distention at peak inspiration, and repetitive opening and closure of lung units [2]. The injury attributable to over-distention can be minimized by reducing VT and limiting plateau pressure [1]. The second source of injury may be minimized by interventions that recruit the lungs to prevent cyclic alveolar closure, such as PEEP and alternative ventilation modes such as high-frequency oscillation [11].

The optimal low tidal volume (not above 6 ml/kg) has been achieved agreement, but the best way to set PEEP, to optimally balance recruitment and distention in each patient, remains elusive. In patients with ARDS, LIP has been shown to be the point of massive alveolar recruitment and therefore an option for setting PEEP. It has been suggested that setting PEEP above the LIP may be beneficial, and a randomized trial of a modified ventilatory strategy incorporating this approach as well as permissive hypercapnia showed a reduced mortality rate and reduced barotrauma. However, it is sometimes difficult to measure PV curve at the bedside in ventilated patients, so the prevention of end expiratory collapse with PEEP cannot easily be determined. Furthermore, the LIP is affected by superimposed pressure and threshold opening pressure, and do not accurately indicate PEEP required to prevent end expiratory collapse [5]. Although the PV curve has been used to individualize setting proper PEEP in patients with ARDS, the physiologic interpretation of the curve remains under debate [12]. Those facts that re-inflation of collapsed lung units continuing on the linear portion of the PV curve and lung recruitment happening far above the LIP remind that LIP is not the end of recruitment of lung, and accordingly, the PEEP guided by LIP has been challenged [13].

Table 3. Effect of PEEP on hemodynamic parameters in pigs with ARDS (mean ± SD)

Group	Time dot	n	MAP (mmHg)	CVP (mmHg)	CO (L·min^{-1})
P_{LIP+2}	0 h	5	99.60 ± 9.72	5.10 ± 0.62	4.81 ± 0.43
	1 h		86.50 ± 9.88	5.33 ± 0.61	4.65 ± 0.56
	2 h		85.20 ± 9.72	5.58 ± 0.52	3.86 ± 0.46
$(P_{LIP} + P_{UIP})/2$	0 h	6	92.90 ± 9.56	6.75 ± 1.72	4.65 ± 0.67
	1 h		87.50 ± 7.27	7.54 ± 1.68$^{\#}$	3.86 ± 0.57$^{\#}$
	2 h		83.50 ± 9.88	7.67 ± 2.12	3.85 ± 0.37*
P_{EIP}	0 h	6	97.50 ± 7.23	5.80 ± 0.97	4.76 ± 0.47
	1 h		78.40 ± 9.67*	9.17 ± 2.56$^{*,\#}$	4.05 ± 0.27*
	2 h		86.50 ± 8.25*	9.42 ± 2.37$^{*,\#}$	3.89 ± 0.57*
P_{UIP-5}	0 h	5	94.03 ± 8.42	5.67 ± 1.72	4.86 ± 0.37
	1 h		77.80 ± 5.55*	13.26 ± 2.34$^{*,\#}$	3.18 ± 0.36$^{*,\#}$
	2 h		81.26 ± 6.80*	14.06 ± 2.11$^{*,\#}$	3.65 ± 0.29*

$^{*}P < 0.05$, compared with 0 h of same group; $^{\#}P < 0.05$. Compared with P_{LIP+2} group at the same time point.

Table 4. Effect of PEEP on pulmonary mechanics in pigs with ARDS (mean ± SD)

Group	Time dot	n	PIP (cmH_2O)	Pplat (cmH_2O)	Cst ($ml·cmH_2O^{-1}$)
P_{LIP+2}	0 h	5	36.20 ± 4.75	24.13 ± 4.36	13.92 ± 6.16
	1 h	5	35.90 ± 7.78	25.67 ± 3.27	13.65 ± 5.15
	2 h	5	35.43 ± 8.63	27.76 ± 4.24	14.23 ± 4.07
$(P_{LIP} + P_{UIP})/2$	0 h	6	36.50 ± 9.78	26.19 ± 3.08	13.67 ± 6.42
	1 h	6	31.38 ± 10.16	29.33 ± 4.26	15.54 ± 5.86
	2 h	6	29.50 ± 4.87	29.58 ± 2.52	15.75 ± 4.72
P_{EIP}	0 h	6	34.22 ± 9.15	25.24 ± 3.73	13.27 ± 4.56
	1 h	6	32.18 ± 5.16	31.18 ± 3.56*	18.26 ± 3.34
	2 h	6	31.23 ± 7.32	31.42 ± 2.73*	19.32 ± 2.41$^{*,\#}$
P_{UIP-5}	0 h	5	37.80 ± 13.28	27.43 ± 4.43	13.32 ± 8.37
	1 h	5	38.45 ± 11.35	33.26 ± 3.34*	15.34 ± 4.32
	2 h	5	35.78 ± 12.34	34.06 ± 2.13*	14.67 ± 2.92

$^{*}P < 0.05$, compared with 0 h of same group; $^{\#}P < 0.05$. Compared with P_{LIP+2} group at the same time point.

UIP is conventionally hypothesized to represent initial alveolar over-distension, and is utilized to set an upper limitation during mechanical ventilation in patients with ARDS. Nonetheless nowadays, it is becoming widely accepted that the UIP of the deflation limb of the PV curve represents the point of optimal PEEP [3]. In the present study, our aim is to compare different PEEP value between the different inflection points of the PV curve in ARDS pigs, and to assess the range of PEEP, and to study the effect of different PEEP on respiratory function following its use.

In the present study, values of PEEP from P_{LIP+2} to $P_{(LIP+UIP)/2}$, P_{EIP} and P_{UIP-5} cmH_2O increased gradually. Accompanying with PEEP increase, pressure of airway, compliance of lung and oxygenation index increased, but EVLW not increased. And pigs treated with higher level PEEP had better respiratory functions than those lower's, the higher, the better. In P_{LIP+2} group, oxygenation index decreased, although, has no significance, when ventilation continued without recruitment. But in the other three groups, higher PEEP values can maintain oxygenation index. It may be partially due to higher PEEP value may allow gradual recruitment of lung units, without the need for excessive increase in airway pressures [14].

In the study, the hemodynamic effects of increased airway pressure were managed with fluids and inotropic agents, when necessary, and did not limit the application of PEEP to reach the defined end point of treatment.

Conclusion

PEEP deduced from UIP of PV curve is higher than those from LIP. The upper inflection point of the deflation limb of the PV curve represents the point of optimal PEEP. Suitable higher PEEP (EIP or UIP-5, etc.) does not exacerbate respiratory function, but will bring convenience to set PEEP at the bedside. However, we should remember that accompanying with ARDS advancing, the parameter should be reset as the lung injury evolves.

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Disclosure of conflict of interest

None.

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