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Influence of respiratory rate on gas trapping during low volume ventilation of patients with acute lung injury

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Abstract *Objective:* Reduction in tidal volume (Vt) associated with increase in respiratory rate to limit hypercapnia is now proposed in patients with acute lung injury (ALI). The aim of this study was to test whether a high respiratory rate induces significant intrinsic positive end-expiratory pressure (PEEPi) in these patients. *Design:* Prospective crossover study. *Setting:* A medical intensive care unit. *Interventions and measurements:* Ten consecutive patients fulfilling criteria for severe ALI were ventilated with a 6 ml/kg Vt, a total PEEP level at 13±3 cmH_2O and a plateau pressure kept at 23±4 cmH_2O. The respiratory rate was randomly set below 20 breaths/min (17±3 breaths/min) and increased to 30 breaths/min (30±3 breaths/min) to compensate for hypercapnia. External PEEP was adjusted to keep the total PEEP and the plateau pressure constant. PEEPi was computed as the difference between total PEEP and external PEEP. The lung volume retained by PEEPi was then measured. *Results:* Increase in respiratory rate resulted in significantly higher PEEPi (1.3±0.4 versus 3.9±1.1 cmH_2O, $p<0.01$) and trapped volume (70±43 versus 244±127 ml, $p<0.01$). External PEEP needed to be reduced from 11.9±3.4 to 9.7±2.9 cmH_2O ($p<0.01$). PaO_2 was not affected but the alveolar-arterial oxygen tension difference slightly worsened with the high respiratory rate ($p<0.05$). *Conclusions:* An increase in respiratory rate used to avoid Vt reduction-induced hypercapnia may induce substantial gas trapping and PEEPi in patients with ALI.

Keywords Acute lung injury · Mechanical ventilation · Positive end-expiratory pressure · Dynamic hyperinflation

Introduction

Ventilator-induced lung injury (VILI) is directly influenced by ventilatory settings and is now recognized as a major determinant of outcome in patients with acute lung injury (ALI) [1, 2, 3]. Experimental studies have demonstrated that VILI may result from high distending trans-alveolar pressure at the end of inspiration, or from insufficient pressure at the end of expiration and possible opening-closing repeated phenomenon resulting from insufficient recruitment that occurs at the end of expiration [4, 5, 6]. To prevent both mechanisms, plateau pressure (Pplat) should be limited and positive end-expiratory pressure (PEEP) maintained at a sufficient level [7]. The results of the National Institute of Health (NIH) recently reported study demonstrated that a strategy based on tidal volume (Vt) reduction associated with a PEEP individually set according to oxygenation and a high respiratory rate (RR) to avoid respiratory acidosis, is beneficial in terms of mortality [1]. Whether a high RR could be responsible for gas trapping and intrinsic PEEP (PEEPi) in ALI patients, despite the reduction in Vt, remains to be demonstrated. In such a case, repeated measurements of total PEEP (PEEPtot) could

be recommended for routine practice. The present study was therefore designed to test the impact of RR on gas trapping and oxygenation when Vt is set at 6 ml/kg in patients with severe ALI or acute respiratory distress syndrome (ARDS).

Methods

Patients

Patients ventilated without any form of chronic lung disease and fulfilling the criteria for ALI or ARDS were candidates for inclusion [7]. The ethics committee of Rouen University Hospital approved the protocol and informed consent was obtained from patients' next of kin.

Ten sedated and paralyzed patients, ventilated (inner diameter of the endotracheal tube ranging from 7 to 8 mm) in the supine position and in the volume-controlled mode (Servo Ventilator 900C; Siemens-Elema, Solna, Sweden), were studied. Low compliance circuits (2 ml/cmH_2O) were used with a heat and moisture exchanger (HME: Hygrobac; DAR, Mirandola, Italy: dead space =84 ml and resistance =1.0 cmH_2O/l/s at 0.5 l/s) in five patients, and a heated humidifier (MR 730; Fisher & Paykel Healthcare, Auckland, New Zealand) in the other five patients.

Equipment

Flow, pressure and volume were recorded from the Servo 900C transducers, digitized and stored in a computer for subsequent measurements and calculations.

Experimental procedure

Each patient was ventilated with a low Vt (6 ml/kg of predicted body weight) with conventional RR (15–20 breaths/min) and high RR (up to 35 breaths/min) successively. Both strategies were randomly applied for 45 min each. The conventional RR was set as chosen by the attending physician, while high RR was set to keep pH between 7.35 and 7.45.

To obtain a similar PEEPtot and a similar end-inspiratory recoil pressure with both strategies, external PEEP (PEEPe) was individually adjusted taking PEEPi into account. The present design was proposed to assess the effect of RR per se on gas trapping for a given elastic recoil (i.e. by keeping PEEPtot constant). We wanted to assess what manipulations of external PEEP are needed to reach the same PEEPtot. In each patient, PEEPtot was predefined as approximately 2 cmH_2O above the lower inflexion point (LIP) determined on a pressure-volume curve (PV curve) recorded from zero end-expiratory pressure (ZEEP) using the low flow inflation technique [8]. FIO_2 as well as inspiratory to total respiratory time ratio (set at 33%) were also kept constant throughout the study.

Measurements and definitions

Intrinsic positive end-expiratory pressure and total positive end-expiratory pressure level

Intrinsic positive end-expiratory pressure was computed as the difference between PEEPtot (measured after a 2 s end-expiratory occlusion) and PEEPe.

Trapped volume related to intrinsic positive end-expiratory pressure (V_{PEEPi})

The V_{PEEPi} was computed as the difference between expiratory volumes measured during a normal expiration corresponding to the tested RR and a 6 s long expiration with the same set PEEPe [8]. An end-expiratory lung volume (EELV) variation related to PEEPtot ($V_{PEEPtot}$) was measured during a 6s long expiration from PEEPtot to ZEEP.

Pressures, resistance and static compliance

For each condition tested, three breaths were analyzed. Maximal inspiratory pressure (Pmax), plateau pressure (Pplat1) corresponding to the beginning of the end-inspiratory occlusion (first point of zero flow) and end-inspiratory pressure (Pplat2) corresponding to the elastic recoil pressure measured after 2 s long end-inspiratory occlusion were measured as previously described [9, 10]. Static compliance (Cstat) was computed as follows: Vt/(Pplat–PEEPtot) [11]. Minimal resistance (Rmin) was calculated as (Pmax–Pplat1)/flow [9] and total resistance (Rtot) as (Pmax–Pplat2)/flow. Additional resistance due to stress relaxation (ΔRrs) was computed as the difference between Rtot and Rmin (ΔRrs = Rtot–Rmin).

Gas exchange

Alveolar-arterial oxygen tension difference ($P(A–a)O_2$) was computed according to the equation of alveolar gases: $P(A–a)O_2$= ((Patm-47)×FIO_2–($PACO_2$/0.8))–PaO_2, where Patm is 760 mmHg and $PACO_2$ is $PaCO_2$, $PaCO_2$ and PaO_2 expressed in mmHg.

Statistics

Values are given as means ± standard deviation (SD). Pressures, volumes, ventilatory settings, hemodynamic parameters and arterial blood gases (ABG) were compared with Wilcoxon test for paired samples. Differences were considered significant for *p* less than 0.05. Regression analysis was computed with a Spearman rank correlation and *p* less than 0.05 was considered significant.

Results

The characteristics of the patients included in the present study are presented in Table 1. A PV curve recorded from ZEEP was obtained in all patients and the mean LIP was 9.9±3.7 cmH_2O.

Ventilatory settings and arterial blood gases

Ventilatory settings during the two strategies tested are presented in Table 2. RR ranged from 14 to 22 breaths/min for the conventional RR strategy and from 27 to 35 breaths/min for the high RR strategy. As expected, $PaCO_2$ was significantly decreased by the increase in RR (Table 3). PaO_2 was not influenced by the change in RR but the $P(A\text{-}a)O_2$, calculated at a similar FIO_2 in each patient, was significantly greater in the high RR strategy (Table 3). SaO_2 was slightly, but significantly, higher with high RR (Table 3).

Table 1 Patients characteristics (*PBW* predicted body weight, *LIS* lung injury score, *P/F* PaO_2/FIO_2 ratio, *ARF* acute respiratory failure, *ALI* acute lung injury, *M* male, *F* female, *S Shock* septic shock, *Asp* aspiration, *CAP* community-acquired pneumonia, *D* died, *S* survived)

Patients	Age (years)	Sex	PBW (kg)	LIS	P/F (mmHg)	Cause of ARF	Days of ALI before study	Outcome
1	39	M	75	3.0	142	S Shock	1	D
2	66	M	66	2.3	128	S Shock	1	S
3	46	F	62	1.8	220	Asp	1	S
4	35	F	66	2.5	150	CAP	1	S
5	56	M	75	2.5	170	Asp	6	S
6	42	M	71	2.8	169	CAP	5	S
7	27	M	80	2.3	158	Asp	2	S
8	72	M	71	2.0	178	S Shock	1	D
9	43	M	66	2.8	111	Asp	1	S
10	41	F	61	1.8	191	Asp	1	S
Mean ± SD	47±14		69±6	2.4±0.4	162±31		2±2	

Table 2 Ventilatory settings used in both strategies (*RR* respiratory rate, *Vt* tidal volume, V_E minute ventilation, *Ti/Ttot* inspiratory time on total respiratory time ratio (inspiratory time set on the ventilator was unchanged))

	Conventional RR	High RR	*p* value
RR (breaths/min)	17±3	30±3	<0.01
Vt (ml/kg)	6.3±0.8	6.4±0.8	NS
V_E (l/min)	7.4±2.1	13.4±2.7	<0.01
Ti/Ttot	0.36±0.01	0.39±0.01	<0.01

All results are presented as means ± SD

Table 3 Gas exchange with conventional and high respiratory rate (*RR*) ($P(A\text{-}a)O_2$ alveolar-arterial oxygen tension difference)

	Conventional RR	High RR	*p* value
PaO_2 (mmHg)	103±25	104±25	NS
SaO_2 (%)	96±1	98±1	<0.05
$PaCO_2$ (mmHg)	61±19	43±15	<0.01
pH	7.26±0.08	7.39±0.11	<0.01
$P(A\text{-}a)O_2$ (mmHg)	231.3±132.2	252.7±140.4	<0.05

All results are presented as means ± SD

Table 4 Influence of increase in respiratory rate (*RR*) on airway pressures and pulmonary volumes (*PEEPe* external positive end-expiratory pressure, *PEEPi* intrinsic positive end-expiratory pressure, *PEEPtot* total positive end-expiratory pressure, *Pplat* plateau pressure, V_{PEEPi} volume related to PEEPi, $V_{PEEPtot}$ volume related to PEEPtot)

	Conventional RR	High RR	*p* value
PEEPe (cmH_2O)	11.9±3.4	9.7±2.9	<0.01
PEEPi (cmH_2O)	1.3±0.4	3.9±1.1	<0.01
PEEPtot (cmH_2O)	13.2±3.2	13.5±3.0	NS
Pplat (cmH_2O)	23.6±4.2	23.2±3.9	NS
V_{PEEPi} (ml)	70±43	244±127	<0.01
$V_{PEEPtot}$ (ml)	811±275	832±199	NS

All results are presented as means ± SD

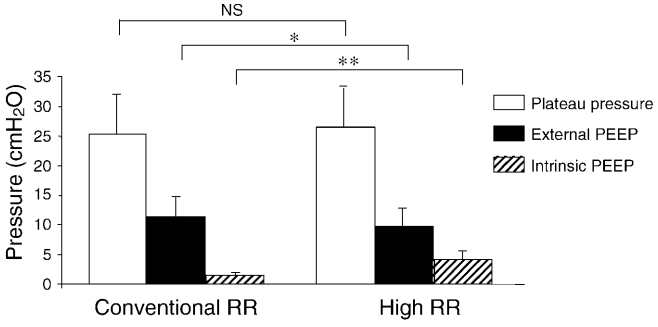

Fig. 1 Mean values and standard deviation of external positive end-expiratory pressure (PEEP), intrinsic PEEP and plateau pressure corresponding to the two respiratory rates (*RR*) tested (conventional RR and high RR). Note the significant increase in intrinsic PEEP at constant total PEEP

Effect of respiratory rate increase on intrinsic positive end-expiratory pressure and lung volumes

The change in RR was clinically well tolerated in all patients. As expected from the study design, Pplat and PEEPtot measured with conventional RR did not differ from those measured with high RR (Fig. 1). To achieve this goal, PEEPe was individually adjusted (Table 4) in order to compensate for the systematic and significant increase in PEEPi related to RR change (Table 4). PEEPi observed with high RR was associated with a substantial trapped gas volume (Table 4). The volume associated with PEEPi (V_{PEEPi}) ranged from 11 to 40% (mean 28±12%) of EELV variation due to PEEPtot ($V_{PEEPtot}$). PEEPi was significantly correlated with RR (p=0.0001, r=0.89).

Effect of respiratory rate increase on respiratory mechanics

Static compliance, taking into account PEEPi, calculated with conventional and high RR, respectively, did not sig-

nificantly differ (45±12 versus 47±9 ml/cmH_2O). Rmin was significantly higher with high RR (9.5±2.4 versus 11.4±2.6 cmH_2O/l/s, $p<0.05$), while Rtot (13.9±3.8 versus 15.2±3.5 cmH_2O/l/s) and ΔRrs (4.3±2.7 versus 3.7±1.6 cmH_2O/l/s) did not significantly differ between the two strategies.

Discussion

The present study demonstrates, in a group of patients with severe ALI (all but one had criteria for ARDS), that an increase in RR at approximately 30 breaths/min proposed to limit hypercapnia induced by the currently recommended Vt reduction, could be responsible for subsequent gas trapping as well as concomitant increase in PEEPtot. In addition, the replacement of external PEEP by PEEPi was not associated with improvement in oxygenation, contrary to several studies which have suggested a beneficial effect of PEEPi in terms of oxygenation [12, 13].

Justification and limits of the study

Recently the NIH study clearly demonstrated, in a large group of patients with ALI, that a protocol based on a complex ventilatory settings combination might affect morbidity and mortality [1]. To what extent the high RR used in the NIH low Vt arm was beneficial, by avoiding acidosis or by exerting a protective effect due to higher PEEP level, remains questionable. In fact, many data do not support a systematic limitation of hypercapnia. Carvalho et al. reported a beneficial impact on hemodynamics and gas exchange of acute hypercapnia in ARDS patients [14]. In experimental conditions, Laffey et al. suggested that hypercapnic cellular acidosis could be beneficial [15]. However, the three negative clinical trials designed to test the reduction in Vt used similar PEEP and RR levels, whereas the positive studies used either a higher level of PEEP or a higher RR in the protective ventilation groups [1, 3]. It is likely that a high RR strategy will be used in the future, and testing its consequence on gas trapping is thus of great importance in the settings of ALI and ARDS.

The present study was specifically designed to test the hypothesis that the increase in RR currently proposed in hypercapnic ARDS patients ventilated with reduced Vt, might induce consistent PEEPi. The experimental procedure as well as the strict conditions under which measurements were performed allowed an accurate evaluation of high RR-related gas trapping. However, the design of this study differed from the NIH procedure in several points, including patient selection and proportion of ALI/ARDS, PEEP titration, humidification system (heat and moisture exchanger might subsequently increase $PaCO_2$ when Vt is reduced) as well as oxygenation goals. For all these reasons, strictly speaking, this physiological study does not allow a conclusion to be drawn about the potential difference in the level of PEEPi between the two arms of the NIH study [1]. Moreover, due to the lack of a third 10 ml/kg-Vt strategy, we could not investigate the effect of RR independently of any change in minute ventilation.

Physiological mechanisms leading to intrinsic positive end-expiratory pressure

Since low compliance and high resistance characterize the respiratory mechanics of patients with ALI, the effects on PEEPi of a strategy associating low Vt and short expiratory time are difficult to predict. The rate of passive lung deflation is a determinant of PEEPi and depends on the elastic recoil pressure stored during the preceding inflation and the opposing flow resistance of the respiratory system including external expiratory apparatus. Richecoeur et al. found, in six patients with severe ARDS, that increasing RR to 30 breaths/min could optimize PCO_2 elimination without generating gas trapping [16]. These patients were studied after several days of ALI (14±9 days) at a late stage of ARDS with severe hypercapnia and low compliance that may have limited gas trapping. In a series of 57 mechanically ventilated patients with miscellaneous diagnosis (only two patients with chronic obstructive pulmonary disease), PEEPi varying from 1 to 6 cmH_2O (2.4±1.4 cmH_2O) was observed in 47% of cases [17]. PEEPi was observed in 100% of patients ventilated with a RR above 27 breaths/min, in 69% when the RR was between 20 and 27 breaths/min but also in 33% of patients with a RR below 20 breaths/min.

Recently, Koutsoukou et al. tested the hypothesis that expiratory flow limitation exists in ARDS [10]. In a group of ten ARDS mechanically ventilated patients, these authors observed a PEEPi level ranging from 0.4 to 7.7 cmH_2O (4.1±2.4 cmH_2O) at ZEEP. Expiratory flow limitation, assessed by means of the negative expiratory pressure technique, was found in 80% of these patients. These results suggest that substantial levels of PEEPi can be observed in ARDS patients and that this phenomenon may be due, at least in part, to expiratory flow limitation. Using the same methodology, Armaganidis et al. observed that 12 out of 32 patients ventilated for acute respiratory failure exhibited expiratory flow limitation. PEEPi was significantly higher in these patients, compared to those without expiratory flow limitation (7.1±2.8 cmH_2O versus 1.2±0.9 cmH_2O) [18].

The positive correlation between RR and PEEPi found in the present study suggests that the increase in RR was the main determinant of dynamic hyperinflation. This hypothesis was specifically tested by

De Durante et al. [19]. Considering the same minute ventilation, the authors increased RR stepwise in order to test different Vt and expiratory time combinations on PEEPi. For a similar minute ventilation (12.4±1.7 l/min), PEEPi measured during an end-expiratory occlusion ranged from 6.0±2.9 cmH_2O for a RR between 25 and 35 breaths/min, to 3.0±1.8 cmH_2O for a RR between 20 and 25 breaths/min. In this study, PEEPi was significantly higher in patients exhibiting high respiratory resistances and low Pplat. The amount of PEEPi observed in our patients (3.9±1.1 cmH_2O) with a RR around 30 breaths/min approximately corresponds to what is expected at the same RR in the study reported by De Durante et al. [19]. These results, consistent with our findings, strongly suggest that PEEPi should be routinely monitored, especially when increasing RR is considered to limit hypercapnia. In fact, an underestimation of PEEPtot may lead to deleterious and hidden hemodynamic effects.

Effects of intrinsic positive end-expiratory pressure on gas exchange

It has been suggested that PEEPi associated with dynamic hyperinflation obtained by an inverted inspiratory-expiratory ratio in ALI patients may be beneficial through inducing a more homogeneous lung-volume distribution [12, 13]. However, several authors have more recently demonstrated that inverse ratio ventilation does not improve PaO_2 compared to conventional ventilation when PEEPtot is maintained constant [20, 21]. By comparing two strategies based on different RR but similar Pplat and PEEPtot levels, the present study allowed us to demonstrate that PEEPi did not improve PaO_2. Moreover, the significantly larger $P(A\text{-}a)O_2$ observed with high RR, confirmed the lack of beneficial effect on oxygenation, specifically related to gas trapping.

In conclusion, the substantial amount of PEEPi induced by high respiratory frequency in this group of patients with ALI and ARDS, despite the use of a small Vt, suggests that dynamic hyperinflation should be systematically evoked when RR is increased to approximately 30 breaths/min to limit hypercapnia. Therefore, repeated measurements of PEEPtot should probably be considered in addition to the recommendations regarding the monitoring of Pplat. Moreover, replacement of external PEEP by PEEPi did not lead to an improvement in gas exchange.

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