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Biphasic Intermittent Positive Airway Pressure Ventilation versus Conventional Ventilation in Acute Respiratory Distress Syndrome and Acute Lung Injury

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ABSTRACT

This study was designed to evaluate the effectiveness, value and safety of biphasic positive airway pressure ventilation in comparison to conventional mode of ventilation (ARDS net low tidal volume strategy) in patient with Acute Respiratory Distress Syndrome (ARDS) and Acute Lung Injury (ALI). This present work was conducted on 32 patients, (22 males and 10 females) with their ages ranging between 20 to 75 years. These patients were admitted to intensive care Department, at Al-Azhar University hospitals from August 2010 to April 2011, they all had documented acute lung injury and ARDS of different etiologies and required invasive mechanical ventilation. The patients were randomized using a concealed allocation approach with sealed envelopes. Patients were randomized to one of two protocol groups consisting of two different ventilatory strategies with identical general ventilatory measures and general care. BiPAP Group (group A): It included sixteen patients in this group who ventilated with BiPAP. Lung Protective Strategy protocol group (Group B): It included sixteen patients in this group who were subjected to Synchronized Intermittent Mandatory Ventilation (SIMV) mode with lung protective strategy protocol. The main results of this study were high statistically significant reduction of the Peak Airway Pressure in BiPAP group. BiPAP group is associated with better results than lung protective strategy group as regard Hypoxic Index. No statistically significant difference between both groups as regard hemodynamic parameters was observed; BiPAP group had shorter duration of ventilation, shorter duration of ICU stay and high statistically significant decrease of the sedation dosage requirement.

Key words: BiPAP, conventional ventilation, ARDS, acute lung injury

INTRODUCTION

Acute Lung Injury (ALI) and its more severe form Acute Respiratory Distress Syndrome (ARDS), are life-threatening conditions. This syndrome is characterized by an acute onset of hypoxemia with bilateral pulmonary infiltrates seen in the chest radiograph consistent with pulmonary edema that cannot be explained by left heart failure (Steinberg *et al*., 2006).

Because no effective pharmacologic therapy has been identified, treatment is primarily supportive. Intubation and mechanical ventilation are often required to ameliorate the derangements in gas exchange, lung compliance and work of breathing. Multiple mechanical ventilation strategies have been researched to determine the optimal method to maximize gas exchange with minimal lung damage in patients with acute lung injury (Raoof *et al*., 2010).

Over the last two decades, numerous modalities and strategies have been developed and advocated as improvements in ventilating patients with acute respiratory distress syndrome (ARDS). Virtually every aspect of mechanical ventilation has been examined in an effort to improve gas exchange or to avoid lung damage (Blum *et al.*, 2010).

Conventional modes of mechanical ventilation often fail to attain the goal of adequate gas exchange without increasing the risk of Ventilator Induced Lung Injury (VILI). This has led some investigators to explore unconventional modes of mechanical ventilation to determine if new techniques can oxygenate and ventilate the patient with less injury to the lung. Alternative and adjunct methods of ventilation continue to be attractive to investigators unhappy with the high rate of mortality in ARDS (Spronk and Schultz, 2010).

The use of low tidal volumes with appropriate levels of PEEP to ensure lung recruitment (ARDSNet) is the current standard of care in mechanical ventilation of patients with ARDS. However, ARDS net strategy is useless in some patients whose clinical end-points cannot be achieved via this strategy or may not be a candidate for this strategy. Well-known physiological and clinical disadvantages of full ventilatory support have an increased tendency of dependent atelectasis, worsening of ventilation-perfusion matching, decreased oxygen delivery and organ perfusion, increased need of sedation and muscle weakness (Wrigge *et al.*, 2005).

Biphasic positive airway pressure ventilation (BiPAP) is being used increasingly as alternative strategies to conventional assisted control ventilation for patients with acute respiratory distress syndrome and acute lung injury. BiPAP permits spontaneous breathing throughout the ventilatory cycle and hence, offers several advantages over conventional strategies to improve the pathophysiology in these patients, including gas exchange, cardiovascular function and reducing or eliminating the need for heavy sedation (Borges *et al.*, 2006).

This study aimed at assessing the effectiveness, value and safety of biphasic positive airway pressure ventilation in comparison to conventional mode of ventilation (ARDS net low tidal volume strategy) in patient with ARDS and ALI.

MATERIALS AND METHODS

After approval from the Hospital ethics committee, this present work was conducted on 32 patients, (22 males and 10 females) with their ages ranging between 20 to 75 years.

These patients were admitted to intensive care Department, at Al-Azhar University hospitals from August 2010 to April 2011, they all had documented acute lung injury and ARDS of different etiologies and required invasive mechanical ventilation. The diagnosis of acute lung injury and ARDS is based on the criteria proposed by the American European Consensus Conference ALI and ARDS. The diagnostic criteria for ARDS proposed by this committee were $PaO_2/FiO_2 \leq 200$, bilateral infiltrates on chest radiograph that need not be diffuse and pulmonary artery occlusion pressure ≤ 18 mmHg or no clinical evidence of left atrial hypertension when a pulmonary artery catheter was not used. The diagnostic criteria for acute lung injury (ALI) were similar except the PaO_2/FiO_2 ratio was ≤ 300.

Exclusion criteria for all participants selected for the study included: Patients with haemodynamic unstability, patients on inotropic support, cardiogenic pulmonary oedema, recent unstable angina or MI, COPD, intracranial abnormality, severe barotrauma, anatomic abnormality of chest wall and pregnancy.

All patients were submitted to a stabilization phase during which they were ventilated with Volume Assist-Control Mandatory Ventilation (VACMV) with protective lung strategy. During this stabilization phase, the monitoring was instituted and inclusion and exclusion criteria were confirmed.

The patients were randomized using a concealed allocation approach with sealed envelopes. Patients were randomized to one of the two protocol groups consisting of two different ventilatory strategies with identical general ventilatory measures and general care:

- **BiPAP group (group A):** It included sixteen patients in this group who ventilated with BiPAP
- **Lung protective strategy protocol group (group B):** It included sixteen patients in this group who were subjected to Synchronized Intermittent Mandatory Ventilation (SIMV) mode with lung protective strategy protocol

Ventilatory strategies includes:

- The ventilatory modes were studied for 24 h without interruption in all groups
- The physiological targets and basis for main ventilatory settings were similar during the stabilization period and thereafter in all groups

Biphasic positive airway pressure (BiPAP) parameters:

- Settings are chosen on the basis of the airway pressure, the breathing frequency and the I: E ratio. The airway pressure of the BiPAP ventilation are adjusted as follows:
    - "Plow" corresponds to the PEEP adjustment under Volume Assist-Control Mode of mechanical ventilation
    - The value of plateau pressure of prior ACMV serves as a basis for the choice of the value of "P high"
- T high and "T low" are adjusted in accordance with the I; E ratio. "T high" being inspiratory time and “T low" being expiratory time

Lung protective strategy (LPS): It included sixteen patients who were subjected to ventilation with SIMV with lung protective strategy protocol. (ARDS net lung protective strategy).

Tidal volume: Aim for tidal volume of 6 mL kg^{-1} IBW while not exceeding plateau pressure (Pplat) of 30 cm H_2O. May titrate up to 8 mL kg^{-1} IBW if plateau pressure$\leq$30 cm H_2O and evidence for breath stacking or airway pressure<PEEP. Titrate down to 4 mL kg^{-1} IBW if plateau pressure >30 cm H_2O.

Inspiratory flow target: inspiratory:expiratory ratio at 1:1 to 1:3
Plateau pressure target: <30 cm H_2O
PEEP and FiO_2 target: PaO_2 = 55-80 mm Hg or SaO_2 = 88-95%

Outcome measures

- **Circulatory (haemodynamic) parameters:** Heart rate (HR) (beat min^{-1}) and mean systemic arterial blood pressure (mmHg)

- Arterial blood gases (ABG): pH, PaO_2 (arterial oxygen tension), $PaCO_2$(arterial CO_2 tension), HCO_3, Hypoxic index (PaO_2/FiO_2) and Peripheral oxygen saturation (SpO_2)
- Peak airway pressure (cm H_2O)
- Need for sedation: Patients in this study were sedated using propofol, which is IV general anesthetic agent (available as an emulsion in a phospholipid vehicle), which possesses sedative, amnesic and hypnotic properties is administered as an initial bolus of 1 to 2 mg kg^{-1} followed by a continuous infusion at a rate of 0.3 to 3 mg/kg/hr
- Duration of MV and Length of ICU stay

Statistical analysis of data: The collected data was organized, tabulated and statistically analyzed using SPSS software statistical computer package version 17. For quantitative data, the mean and standard deviation were calculated. The difference between two means was statistically analyzed using the students (t) test; comparison between more than two means was done using one way analysis of variance (ANOVA) test.

For qualitative data the number and percent distribution was calculated. Chi square χ^2 or Mann Witney test were used as for comparison between groups. Significance was adopted at $p<0.05$ for interpretation of results of tests of significance.

RESULTS

The results of the present study proved that: No statistically significant difference between studied groups at any time (0, 2, 6, 12 and 24 h) as regard Circulatory (Haemodynamic) Parameters (Heart Rate and mean systemic arterial blood pressure) (Table 1).

On evaluating the acid-base balance, the Serum Bicarbonate level measurement and the partial pressure of carbon dioxide level measurement of all study patients from different groups, there was no statistically significant difference between studied groups at any time. As regard Hypoxic index and oxygen tension there was highly statistically difference between studied groups. There was a significant increase in Hypoxic Index when using BiPAP as compared to lung protective strategy group patients (Table 2).

On evaluating the peak airway pressure and the Mean airway pressure of all study patients, there was high statistically significant reduction of the Peak airway pressure and the mean airway pressure in BiPAP group (Table 3).

On evaluating the sedation dosage requirements of all study patients, there was high statistically decrease of the sedation dosage in BiPAP group as compared to lung protective strategy

Table 1: Comparison between studied groups heat rate (HR) and Mean BP at 0, 2, 6, 12 and 24 h

		HR (beat min^{-1})			BP		
Time (h)	Groups	Mean	SD	p value	Mean	SD	p value
0	BiPAP	92.81	22.18	0.054	92.37	15.55	0.725
	LPS	106.81	17.10		90.25	13.71	
2	BiPAP	94.75	22.46	0.060	92.37	14.09	0.931
	LPS	107.06	15.65		92.06	14.70	
6	BiPAP	94.94	18.11	0.065	92.87	12.97	0.740
	LPS	105.88	15.82		90.25	15.45	
12	BiPAP	94.38	17.56	0.080	93.06	13.91	0.956
	LPS	104.94	12.74		92.25	15.49	
24	BiPAP	92.56	15.79	0.074	93.31	13.17	0.969
	LPS	102.75	10.94		93.68	12.96	

Table 2: Comparison between studied groups at 0, 2, 6, 12 and 24 hours as regard arterial blood gases (PH, P_aCO_2 and hypoxic index)

		PH		$PaCO_2$		Hypoxic index	
Time (h)	Groups	Mean	p value	Mean	p value	Mean	p value
0	BiPAP	7.28	0.303	37.37	0.755	220.12	0.025 *
	LPS	7.32		35.68		157.06	
2	BiPAP	7.28	0.271	37.43	0.613	243.75	0.220
	LPS	7.33		36.93		199.88	
6	BiPAP	7.32	0.658	38.62	0.266	284.81	0.001 **
	LPS	7.34		37.87		196.88	
12	BiPAP	7.33	0.591	38.50	0.557	310.62	0.0001 **
	LPS	7.35		37.43		210.81	
24	BiPAP	7.32	0.435	39.56	0.103	221.06	0.0001 **
	LPS	7.36		37.43		334.69	

* Significant p<0.05 ** highly significant p<0.01

Table 3: Comparison of peak airway pressure (P_{peak}) between studied groups at 0, 2, 6, 12 and 24 h

		P_{peak} (cm H_2O)		
Time (h)	Groups	Mean	SD	p value
0	BiPAP	20.50	4.40	0.0001**
	LPS	33.63	5.86	
2	BiPAP	20.25	4.06	0.0001**
	LPS	33.63	5.86	
6	BiPAP	20.50	4.40	0.0001**
	LPS	32.63	7.03	
12	BiPAP	20.25	4.06	0.0001**
	LPS	32.13	7.09	
24	BiPAP	20.00	4.44	0.0001**
	LPS	32.94	6.86	

*Significant p<0.05 ** highly significant p<0.01

Table 4: Comparison of sedation requirements between studied groups at 0, 2, 6, 12 and 24 h

		Sedation requirements (mg kg^{-1} h^{-1})		
Time	Groups	Mean	SD	p value
0	BiPAP	1.51	0.49	0.132
	LPS	1.25	0.31	
2	BiPAP	1.53	0.51	0.146
	LPS	1.25	0.31	
6	BiPAP	1.04	0.51	0.002**
	LPS	1.60	0.50	
12	BiPAP	0.76	0.56	0.001**
	LPS	1.55	0.46	
24	BiPAP	0.64	0.77	0.002**
	LPS	1.53	0.51	

*Significant p<0.05 **highly siguificant p<0.01

group. This dramatic decrease in sedation requirements during BiPAP is due to capability of the patient to breathe spontaneously freely throughout the ventilator cycle of BiPAP allowing better patient-ventilator synchrony (Table 4).

Table 5: Comparison between studied groups as regard duration of ICU stay length and ventilation days

	ICU days			Ventilation days		
Groups	Mean	SD	p value	Mean	SD	p value
BiPAP	15.93	16.90	0.022*	10.31	9.11	0.01**
LPS	29.18	13.55		20.18	8.94	

*Significant $p<0.05$ **highly significant $p<0.01$

Regarding the duration of ICU stay and the duration of mechanical ventilation, there were statistically significant difference in duration of ICU stay and duration of mechanical ventilation in all study patients from different groups. Duration of ICU stay was much lower in BiPAP group when compared to lung protective strategy group (Table 5).

DISCUSSION

BiPAP is a pressure-limited, time-cycled, spontaneous mode of ventilation. The unique features of this ventilator mode in patients with acute lung injury include (1) Spontaneous breathing and (2) Tidal ventilation to accomplish CO_2 clearance occurs in reverse sequence from other conventional modes, starting from a higher "baseline" pressure and occurs as a decompression-reinflation tidal cycle or expiration-inspiration.

This study aimed at evaluating BiPAP effects on haemodynamic variables (mean blood pressure and heart rate), Arterial blood gases (PO_2, $PaCO_2$, pH and hypoxic index), Respiratory parameters (peak airway pressure), need for sedation and the outcome compared to conventional lung protective strategy ventilation.

On evaluating circulatory and haemodynamic changes; there were no statistically significant difference between studied groups at any time (0, 2, 6, 12 and 24 h) on measuring heart rate and mean arterial blood pressure. This study results go hand in hand with the study results concluded by Varpula *et al.* (2003), Varpula *et al.* (2004), Dart *et al.* (2005) and Yoshida *et al.* (2009) who reported that, there were no differences in the heart rate and mean blood pressure between different conventional ventilator modes and APRV/BiPAPmode.

On evaluating the acid-base balance of all study patients from different groups, there was no statistically significant difference between studied groups at any time (0, 2, 6, 12 and 24 h).

This study results go hand in hand with the study results concluded by Varpula *et al.* (2004), Yoshida *et al.* (2009), Walkey *et al.* (2011) and Gonzalez *et al.* (2010), who reported that, there were no differences in pH or Serum Bicarbonate level reading between different conventional ventilator modes and BiPAP mode in patients with ALI or ARDS.

On evaluating the partial pressure of carbon dioxide level measurement of all study patients from different groups, there was no statistically significant difference between studied groups at any time.

Similar results were reached during previous clinical studies conducted by Putensen *et al.* (2001), Varpula *et al.* (2004), Dart *et al.* (2005), Walkey *et al.* (2011) and Gonzalez *et al.* (2010), who reported that, there were no differences in partial pressure of carbon dioxide level measurement reading between different conventional ventilator modes and BiPAP mode in patients with ALI or ARDS.

As regard Hypoxic index, there was no statistically significant difference between studied groups as regard Hypoxic index at the start and at 2 h, while there was highly statistically difference at 6, 12 and 24 h. There was a significant increase 15% in Hypoxic Index when using BiPAP when compared to lung protective strategy group patients (p-value<0.05).

This finding was also confirmed by the study conducted by Walkey *et al.* (2011). Patients requiring mechanical ventilation for >48 h met criteria for pulmonary contusion were the basis for this study. They found that PaO_2/FiO_2 ratios were higher during APRV/BiPAP compared with conventional ventilation (p<0.001).

The conceptual advantage of BiPAP is thought to come from substantial mean airway pressure and preservation of spontaneous ventilation. Whereas numerous studies have shown that BiPAP without spontaneous ventilation did not affect gas exchange and was not different from conventional pressure-controlled M V. During BiPAP, patients can breathe spontaneously without a trigger and support in any phase and can control frequency and duration of spontaneous inspiration and expiration which is a unique mechanism that makes it possible to maintain a sinusoidal flow pattern similar to normal spontaneous breathing and to generate full diaphragmatic contraction. Therefore, the results showing that BiPAP improved oxygenation are mainly attributable to the above-mentioned spontaneous ventilation benefits (Walkey *et al.*, 2011; Myers and MacIntyre, 2007).

On evaluating the Mean airway pressure of all study patients, there was statistically significant difference between studied groups at base, 2, 6, 12 and 24 h. There was high statistically significant reduction of the Mean airway pressure in BiPAP group. The earliest human trial of APRV/BiPAP by Garner *et al.* (1988) found that peak airway pressures were reduced when compared with conventional positive pressure ventilation (11±2 vs.38±6 cm H_2O).

Significantly lower peak airway pressures were also found by Cane *et al.* (1991) after transitioning 18 patients to APRV/BiPAP from conventional intermittent positive airway pressure ventilation with PEEP (65±15 vs. 39±10 cm H_2O. p<0.01).

On the other hand, a retrospective study aiming at determining which mode, APRV/BiPAP or pressure support ventilation (PSV), decreases atelectasis more in patients with acute lung injury and acute respiratory distress syndrome (ARDS) was conducted by Yoshida *et al.* (2009) .They were found that The Paw, peak and Paw, mean in both groups were moderate and there were no significant differences during the study periods between the ventilatory modes. (p = 0.391 in Paw, mean and p = 0.334 in Paw, peak). As they noticed that airway pressures in both groups were similar and moderate, they claimed that the advantage of BiPAP seems to come from preservation of spontaneous ventilation rather than substantial mean airway pressure. The significant decrease in peak airway pressure is probably due to the nature of APRV/BiPAP as a pressure control mode of ventilation. This may explain this difference as Yoshida and colleagues compared APRV/BiPAP to Pressure Support Ventilation (PSV).

On evaluating the sedation dosage requirements of the study patients, there was no statistically significant difference between two studied groups at base and at 2 h. On the other hand, there was statistically significant difference between studied groups at 6, 12 and 24 h. There was high statistically significant decrease of the sedation dosage in BiPAP group as compared to lung protective strategy group. This dramatic decrease in sedation requirements during BiPAP is due to capability of the patient to breathe spontaneously freely throughout the ventilator cycle of BiPAP allowing better patient-ventilator synchrony.

As regard duration of ICU stay, there was statistically significant difference in duration of ICU stay in all study patients from different groups. Duration of ICU stay was much lower in BiPAP group when compared to lung protective strategy group (p = 0.022).

On evaluating the duration of mechanical ventilation in study patients, there was statistically significant difference in all study patients from different groups. Duration of mechanical ventilation was much lower in BiPAP group when compared to lung protective strategy group ($p = 0.01$).

In a retrospective study (2004) of over 600 heart surgery patients, a reduction in consumption of analgesics and sedatives was observed when patients were allowed to breathe spontaneously from an early stage with APRV/BiPAP. Preliminary data show that maintaining spontaneous breathing with APRV/BiPAP in patients with multiple trauma over an observation period of more than 10 days leads to significantly lower consumption of analgesics and sedatives than when controlled ventilation is used for 72 h followed by weaning (Grasso *et al.*, 2004).

In another pilot study by Kaplan *et al.* (2001) ARDS patients who were already paralyzed and sedated with inverse-ratio ventilation were transitioned to APRV/BiPAP, with an approximate 70% reduction in neuromuscular blockade and 30% reduction in sedation (benzodiazepines) needed to maintain a constant stimulated bispectral index (BIS) value of 70.

A Cohort Study (2009) conducted by Marik *et al.* (2009), Aiming at assessing the effect of APRV/BiPAP with low level Pressure Support (PS) on indices of oxygenation and ventilation in patients with severe ARDS. During the study period they recorded oxygenation and ventilation data as well as the use of sedative and vasopressor agents in patients with severe ARDS who we switched to APRV/BiPAP+PS from low tidal volume Assist-Controlled (AC) ventilation. Remarkably, they have found that APRV/BiPAP is extremely well tolerated by patients allowing sedation to be discontinued in many patients. The total daily dose of sedatives and vasopressor agents decreased by 46% after 24 h of APRV/BiPAP.

All the above results suggest that sedation/neuromuscular blockade requirements are dramatically reduced with BiPAP. Remarkably it was found that APRV/BiPAP modes are extremely well tolerated by patients allowing sedation to be discontinued in many patients. This is a very important issue as the increased use of sedation has been associated with a longer duration of mechanical ventilation as well as an increased incidence of ventilator associated pneumonia, delirium and an increased mortality. BiPAP use an active exhalation valve that allows spontaneous breathing throughout the respiratory cycle (Pandharipande *et al.*, 2006).

CONCLUSION

BiPAP ventilation is unique approach to ventilatory support in patients with acute lung injury, most exciting, BiPAP offer a potential way to limit sedation use and facilitate weaning from mechanical ventilation in patients with acute lung injury.

REFERENCES

Blum, J.M., D.M. Fetterman, P.K. Park, M. Morris and A.L. Rosenberg, 2010. A description of intraoperative ventilator management and ventilation strategies in hypoxic patients. Anesth. Analg., 110: 1616-1622.

Borges, J.B., V.N. Okamoto, G.F.J. Matos, MP.R. Caramez and P.R. Arantes *et al.*, 2006. Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. Am. J. Respir. Crit. Care Med., 174: 268-278.

Cane, R.D., W.T. Peruzzi and B.A. Shapiro, 1991. Airway pressure release ventilation in severe acute respiratory failure. Chest, 100: 460-463.

Dart, B.W., R.A. Maxwell, C.M. Richart, D.K. Brooks, D.L. Ciraulo, D.E. Barker and R.P. Burns, 2005. Preliminary experience with airway pressure release ventilation in a trauma/surgical intensive care unit. J. Trauma, 59: 71-76.

Garner, W., J.B. Downs, M.C. Stock and J. Rasanen, 1988. Airway pressure release ventilation (APRV). A human trial. Chest, 94: 779-781.

Gonzalez, M., A.C. Arroliga, F. Frutos-Vivar, K. Raymondos and A. Esteban *et al.*, 2010. Airway pressure release ventilation versus assist-control ventilation: A comparative propensity score and international cohort study. Intensive Care Med., 36: 817-827.

Grasso, S., V. Fanelli, A. Cafarelli, L. Dalfino, G. Ingenito and G. Ancona, 2004. Patient ventilator interaction during PSV at different levels of sedation in ALI patients. Intensive Care Med., 30: S13-S13.

Kaplan, L.J., H. Bailey and V. Formosa, 2001. Airway pressure release ventilation increases cardiac performance in patients with acute lung injury/adult respiratory distress syndrome. Crit. Care, 5: 221-226.

Marik, P., E.M. Delgado and B. Michael, 2009. Effect of airway pressure release ventilation (APRV) with pressure support (PS) on indices of oxygenation and ventilation in patients with severe ARDS: A cohort study. Crit. Care Shock, 12: 43-48.

Myers, T.R. and N.R. MacIntyre, 2007. Respiratory controversies in the critical care setting. Does airway pressure release ventilation offer important new advantages in mechanical ventilator support?. Respir. Care, 52: 452-460.

Pandharipande, P., A. Shintani, J. Peterson, B.T. Pun and G.R. Wilkinson *et al.*, 2006. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology, 104: 21-26.

Putensen, C., S. Zech, H. Wrigge, J. Zinserling, F. Stuber, T. Von Spiegel and N. Mutz, 2001. Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am. J. Respir. Crit. Care Med., 164: 43-49.

Raoof, S., K. Goulet, A. Esan, D.R. Hess and C.N. Sessler, 2010. Severe hypoxemic respiratory failure: Part 2--nonventilatory strategies. Chest, 137: 1437-1448.

Spronk, P.E. and M.J. Schultz, 2010. Mechanical ventilation in critically Ill patients with 2009 influenza A(H1N1). JAMA, 303: 939-940.

Steinberg, K.P., L.D. Hudson, R.B. Goodman, C.L. Hough and P.N. Lanken *et al.*, 2006. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N. Engl. J. Med., 354: 1671-1684.

Varpula, T., I. Jousela, R. Niemi, O. Takkunen and V. Pettila, 2003. Combined effects of prone positioning and airway pressure release ventilation on gas exchange in patients with acute lung injury. Acta Anaesthesiol. Scand., 47: 516-524.

Varpula, T., P. Valta, R. Niemi, O. Takkunen, M. Hynynen and V. Pettila, 2004. Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome. Acta Anaesthesiol. Scand., 48: 722-731.

Walkey, A.J., S. Nair, S. Papadopoulos, S. Agarwal and C.C. Reardon, 2011. Use of airway pressure release ventilation is associated with a reduced incidence of ventilator-associated pneumonia in patients with pulmonary contusion. J. Trauma-Injury Infect. Crit. Care, 70: E42-E47.

Wrigge, H., J. Zinserling, P. Neumann, T. Muders, A. Magnusson, C. Putensen and G. Hedenstierna, 2005. Spontaneous breathing with airway pressure release ventilation favors ventilation in dependent lung regions and counters cyclic alveolar collapse in oleic-acid-induced lung injury: A randomized controlled computed tomography trial. Crit. Care, 9: R780-R789.

Yoshida, T., H. Rinka, A. Kaji, A. Yoshimoto, H. Arimoto, T. Miyaichi and M. Kan, 2009. The impact of spontaneous ventilation on distribution of lung aeration in patients with acute respiratory distress syndrome: Airway pressure release ventilation versus pressure support ventilation. Anesthesia Analgesia, 109: 1892-1900.