ABSTRACT... farooq_ahrana@yahoo.com. Objectives: To assess the safety, potential efficacy, morbidity and mortality of a small tidal volume mechanical ventilation strategy designed to reduce stretch induced lung injury in ARDS. 

Design: A prospective interventional experimental Setting: CMH Rawalpindi: Period: 1st Sept 2001 to 30th June 2002. Material & Methods: ARDS is a disease associated with high rate of mortality. It was a prospective interventional experimental study of 50 patients who underwent ventilatory support at intensive care unit of a tertiary care teaching hospital Combined Military Hospital Rawalpindi. Results: In both the Traditional Tidal Volume (TTV) and Small Tidal Volume (STV) groups 15 of 26 patients [58%] achieved Reversal of Respiratory Failure (RRF). Of the patients who achieved RRF, the mean number of days on positive pressure ventilation were 11.9±1.9 and 11.3 ± 2.2 days for the TV and STV patients respectively [not significant]. The mean number of days from the first day that weaning from MV was allowed (when Fi O2 was <or= 0.50 and PEEP was <or= 5) to RRF was 5.2 ±1.1 and 5.1 ±1.0 in the TTV and STV groups respectively [p= .94].Mortality before hospital discharge was 46% in the TTV group and 50 % in the STV group. Conclusion The sample size was too small to discern small treatment effects. The differences in tidal volumes and plateau pressures were modest or reduced tidal volume ventilation is not beneficial.

Key words: Acute Respiratory Distress Syndrome(ARDS), Small Tidal Volume (STV), Traditional Tidal Volume(TTV), Reversal of Respiratory Failure (RRF), Multiple Organ Dysfunction Syndrome (MODS). 

INTRODUCTION
Mortality from acute respiratory distress syndrome (ARDS) remains high despite advances in treatments for the conditions that cause or are associated with this disorder. Mechanical ventilation may cause acute lung injury from over distention of lung tissue which could exacerbate or perpetuate respiratory failure. It has been suggested that recovery from acute respiratory distress syndrome would improve if gas exchange were maintained without over distending the lung. This comparison was necessary because of possible adverse effects of small tidal volume (STV) like requiring higher Fi O2 or positive end expiratory pressure to maintain arterial oxygenation. There may be respiratory acidosis, decreased contractility of the heart and altered distribution of systemic blood flow. Low tidal volume ventilation is correlated with improved oxygenation, hemodynamic status and acid base status as well as decreased alveolar permeability and contra lateral extra vascular lung water. The protective effect of plasma on
cotic pressure is lost as increased amounts of albumin leak in the pulmonary interstitium, capillary hydrostatic pressures are unopposed and result in transudation of fluid into the lungs. A.R.D.S represents the pulmonary manifestations of the systemic inflammatory response syndrome [SIRS]. The initial mediators include tumor necrosis factor (TNF), interleukins 1, 6, 8 (IL-1, IL6, IL8), platelet activating factor, various prostaglandins and leukotrienes. There is release of nitric oxide which is a potent vasodilator and myocardial depressant, it also causes norepinephrine unresponsiveness. It also causes the release of calcium independent form of inducible NO synthases which further produces nitric oxide. Subsequently there is activation of neutrophils and macrophage. Destruction of alveolar epithelial cells (type I and II) is prominent. Alveolar flooding as well as abnormalities in surfactant production result in collapse. The exudative phase of ARDS. may rapidly resolve or persistent for a varying period. It is often followed by a fibrotic phase which in some cases leads to permanent scarring. Patients present with severe dyspnea and labor respiration. Hypoxemia due to intrapulmonary shunting is a universal finding.

Although dead space ventilation is increased, arterial CO₂ tension is typically decreased because of a marked increase in minute ventilation. Ventilatory failure may be seen initially in severe cases or may eventually develop owing to respiratory muscle fatigue or marked destruction of the capillary alveolar membrane. Pulmonary hypertension and low or normal left ventricular filling pressure are characteristic hemodynamic findings. Multiple small filling defects on pulmonary angiography representing thromboemboli may occur and are associated with increased mortality rate.

**MATERIALS AND METHODS**

The study was prospective interventional therapeutic trial comparing traditional vs. reduced tidal volume ventilation in patients with acute respiratory distress syndrome. The intensive care unit of combined military hospital Rawalpindi comprises of nine beds. Each bed has provision of invasive as well as non invasive patient monitoring and artificial ventilation with ADULT STAR ventilator. Patients included in the study were randomly allocated to the following two groups.

**GROUP A.** This comprised of patients who were artificially ventilated with small tidal volume i.e 7-8 ml/ kg body weight with a positive end expiratory pressure as per requirement of the patient.

**GROUP B.** This comprised of patients who were artificially ventilated with traditional tidal volume i.e 10-12 ml/kg body weight with a positive end expiratory pressure as per requirement of the patient. PALL hydrophobic heat moisture exchanger was interposed between endotracheal tube and ventilator circuit for each of above patient. The following monitoring and investigations were carried out for each patient. Pulse oximetry, non invasive blood pressure monitoring, daily blood gas assessment, change in the peak inspiratory pressure and total lung compliance, daily x-ray chest, evidence of chest infection by analysis of volume, consistency, culture, sensitivity of sputum. The efficiency and efficacy of each method of ventilation was gauged from following observations. The highest daily mean PaCO₂ values for each patient, The highest daily mean PaO₂ values, Daily mean pH values, Daily mean positive end expiratory pressure and Fi O₂ values in both groups, Effects on circulation, Use of neuromuscular blockers (pancuronium) and sedatives (midazolam) in both groups. (The greater requirement of muscle relaxants was taken as a negative attribute to the particular mode of ventilation). Reversal of respiratory failure (RRF.) and successful weaning, barotraumas and mortality. The initial ventilator mode was CMV/ assisted/controlled. mode.

Ventilator rate was adjusted from 6 to 30 breaths per minute to achieve target of PaCO₂ 30 to 45 mm of Hg. The maximum ventilator rate of 30 breaths per minute was used to minimize air trapping. The patient was weaned off by using SIMV mode. Data was presented in tubular and graphical forms and was expressed as mean ± standard deviation. Univariate analysis was performed using chi square test, student “t” Test for normally distributed variables .P<0.05 was considered significant.

**INCLUSION CRITERIA**

Patients were eligible if they met the following criteria;
2. Age >18 years.
3. Patients receiving positive pressure ventilation via an endotracheal tube.
4. Patients having the duration of artificial ventilation more than 48 hours.
5. No suspicion of congestive cardiac failure.
6. No signs of atelectasis or effusions on radiograph.

**EXCLUSION CRITERIA**

Patients were excluded if any of the following conditions existed:
1. Age <18 years.
2. Pregnancy.
3. Lobectomy or pneumonectomy during current hospital stay.
4. Severe chronic obstructive or restrictive respiratory diseases.
5. Anticipated life expectancy from comorbid conditions <3 months.
6. Congestive cardiac failure.

**RESULTS**

Daily mean VT values in TTV and STV patients during the first five days were 621 ±8 and 462 ±10 ml, 10.2 ±0.1 ml/kg, 7.3 ±0.1 ml/kg, respectively (p<.001). The highest daily mean PaCO₂ values in TTV and STV patients during the first five days were 40.1 ±1.6 and 50.3 ±3.5 torr (5.3 ±0.2 and 6.7 ±0.5 kPa) respectively (p=.01). These corresponded to daily mean pH values in TTV and STV patients of 7.38 ±0.02, and 7.34 ±0.02 respectively (p=.12). Daily mean PO₂ values for the TTV and STV treatment groups for the first five days were 83.2 ±1.9 and 79.8 ±2.2 torr (1.1 ±0.3 and 10.6 ±0.3 kPa) respectively (p=.25). These exceeded the upper limit of the target range 75 torr (10 kPa) primarily because decreases in PEEP or FiO₂ were not required when PEEP was <5 and FiO₂ was <0.50.

The mean number of vasopressors used per patient ventilator day through day five were 0.40 ±0.13 and 0.47 ±0.13 in the TTV and STV groups respectively (not significant). The mean proportion of ventilator day's through day five on which a neuromuscular blocker was used was 0.16 ±0.06 and 0.31 ±0.07 in TTV and STV patients respectively (p=.13). The mean number of sedatives medication administered per patient ventilator day through day five was 1.23 ±0.13 and 1.37 ±0.16 in the TTV and STV groups respectively (p=.70).

**DISCUSSION**

ARDS is a condition of multiple etiologies, in spite of recent advances in its management the disease still remains a dilemma. Previous clinical trials including intravenous administration of vasodilator such as prostaglandin E1 and nitroglycerine failed to effectively treat ARDS since these agents worsened intrapulmonary shunts and induced systemic hypotension although they did induce small degree of pulmonary vasodilatation. Current treatments for ARDS include mechanical ventilation and extra corporeal membrane oxygenation (ECMO) which breath for the body while the lungs heal. Mechanical ventilation can cause additional injury to the lungs, while ECMO is complicated, expensive, and labor intensive. Recently percutaneous carbon dioxide removal (AVCO2R) has proved favourable in research trials. Progression of ARDS and SIRS into a spiraling process of progressive dysfunction in two or more related organ system led to the description of multiple organ system dysfunction (MODS).

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In this study, STV patients did not require greater PEEP and FI $O_2$ during the first five days of treatment, suggesting that gas exchange did not deteriorate with STV. In ARDS patients large amounts of endogenous NO are released via NO synthetase (NOS) which is induced by endotoxin and pro-inflammatory cytokines such as tumor necrosis factor and interleukin-1 in macrophage, endothelium and vascular smooth muscle. It improves the hypoxemia associated with ARDS as NO is a pulmonary vasodilator and decreases the required intensity of mechanical ventilation. This is how these patients can be ventilated with lower inspired oxygen fractions, lower airway pressure there by decreasing oxygen toxicity and barotraumas and preventing ventilator induced lung injury. There were no differences between the STV and TTV groups in fluid intake or output or requirements for vasopressors agents, suggesting that circulation was not impaired. The use of medications for sedation and neuromuscular blockade was similar in the TTV and STV groups. "A prospective randomized, clinical trial comparing traditional versus reduced tidal volume ventilation in A.R.D.S patients' was carried out in Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA$^{13}$. In that study there were no significant differences in two groups in requirements for PEEP or $FIO_2$, fluid intake/outputs, requirement for vasopressors, sedatives or neuromuscular blocking agents, percentage of patients that achieved unassisted breathing, ventilator days or mortality $^{18}$. Another study “Acute respiratory distress syndrome: Low-Stretch Ventilation Improves Survival” was carried out in the Department of Pulmonary and Critical Care Medicine, Cleveland Clinic, USA in which patients with ARDS or acute lung injury were randomly assigned to have their respirators set to deliver tidal volume of either 6ml/kg or a more traditional 12ml/kg. Mortality in the low tidal volume group was 31.01, compared with 39.81 in the traditional tidal volume group, 22% difference (P = .007). Together, these data suggest that STV was safe. However there are no encouraging trends with STV in the proportions of patients who achieved RRF, time to RRF or mortality before hospital discharge. A possible explanation for the apparent lack of beneficial effects from STV in this group was that over distention may not be an important cause of lung injury. Low tidal volume ventilation was correlated with improved oxygenation, hemodynamic status and acid-base status as well as decreased alveolar permeability and contra lateral extra vascular lung water $^{20}$. Although acute lung injury occurred in animal studies when high airway pressures and lung volumes were used, it was attenuated when higher PEEP values were added. This suggests that cyclic opening and closing of unstable airway may be a more important cause of lung injury than stretch. Beneficial reductions in exposure to stretch during each inspiration may have been counteracted by effects of more frequent inspirations over time. Another possible explanation for the absence of the effects of STV treatment is that beneficial effects were counteracted by deleterious effects for example, improved oxygenation from reduced stretch injury may have been counteracted by atelectasis. In STV patients with the smallest tidal volumes, hypercapnia and acidosis may have caused organ or system dysfunction that was not recognized.

In summary, the STV strategy used appeared to be safe as TTV, but there were no beneficial effects of STV on gas exchange, RRF, ventilator days, or mortality. Beneficial effects may occur with STV if tidal volume is reduced more aggressively to further reduce lung stretch or if STV is used only in the most severe cases of ARDS, in which stretch induced lung injury is most likely. However, much work and additional trials would be necessary to assess and ascertain the real advantage of STV. over TTV as in the present study there were no significant differences between two groups.

**CONCLUSION**

The reduced tidal volume strategy used in this study was safe. However failure to achieve beneficial effects of small tidal volume ventilation treatment in important clinical outcome variables may have occurred because;

a. The sample size was too small to discern small treatment effects.
b. The differences in tidal volumes and plateau pressures were modest or
c. Reduced tidal volume ventilation is not beneficial.
REFERENCES


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