Efficacy and safety of an open lung ventilation strategy with staircase recruitment followed by comparison on two different modes of ventilation, in moderate ARDS in cirrhosis: A pilot randomized trial

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Background: Mechanical ventilation in cirrhosis with acute respiratory distress syndrome (ARDS) is not widely studied. We aimed to study the effect of the staircase recruitment manoeuvre followed by two different modes of ventilation.

Methods: Thirty patients with cirrhosis with moderate ARDS underwent the staircase recruitment manoeuvre followed by randomisation to volume control or pressure control group.

Results: The PaO2/FIO2 ratio showed a significant improvement in both the groups after recruitment. The improvement was significantly higher in the pressure control ventilation (PCV) group at the end of the first hour as compared to the volume control ventilation (VCV) group. However, this difference was not significant at the end of 6 and 12 h. In the PCV group it improved from 118.47 ± 10.21 to 189.87 ± 55.18 12 h post-recruitment. In the VCV group it improved from 113.79 ± 13.22 to 180.93 ± 81.97. Static lung compliance also improved in both the groups significantly (P < 0.001). The PCV group showed an improvement from 25.42 ± 11.94 mL/cm H2O at baseline to 29.51 ± 14.58 mL/cm H2O. In the VCV group the lung compliance improved from 24.78 ± 4.87 mL/cm H2O to 31.31 ± 10.88 mL/cm H2O.

Conclusion: This study shows that stepwise recruitment manoeuvre is an effective rescue therapy to improve oxygenation in cirrhosis with moderate ARDS. PCV may have an advantage over VCV in terms of better oxygenation.

Key Words: cirrhosis; ARDS; recruitment; ventilation mode

INTRODUCTION

Patients with end-stage liver disease are at risk for developing acute respiratory failure and hypoxemia secondary to hepatopulmonary syndrome, portopulmonary hypertension [1]. The presence of an exaggerated inflammatory response with a relative immunocompromised state predisposes to acute lung injury and pneumonia [2]. Respiratory abnormalities like chest wall oedema and pleural effusions (hepatic hydrothorax) decrease thoracic compliance [3]. Presence of ascites results in cephalad displacement of the diaphragm. This also reduces the respiratory muscle efficiency and increases the work of breathing [4]. This results in atelectasis and worsening pulmonary gas exchange. Acute respiratory distress syndrome (ARDS) is one of the main reasons for intensive care unit admission and mortality [2]. Mechanical ventilation is a life-supporting intervention that aims to maintain gas exchange [5]. It allows time for the lungs to heal, but it is invasive and can result in lung injury [6]. It is uncertain whether the ventilator-related injury can be reduced if the pressure delivered by the ventilator with each breath is controlled or whether the volume of air delivered by each breath is limited [7].

A Cochrane review in 2018 has suggested that the current data are insufficient to recommend a particular mode. The authors have also called for more studies to provide reliable evidence.

Shear stress contributes to ventilator-induced lung injury (VILI) [8]; hence the “open lung” concept has been advocated to keep the lung open. It consists of a recruitment manoeuvre to open the lung followed by a high positive end expiratory pressure (PEEP) application to maintain alveolar stability [8]. It has been suggested that a pressure of 45–60 cm H2O is required to overcome the alveolar retractile force and the compressing force on the alveoli by surrounding lung tissue [9].

Metanalysis has concluded that recruitment manoeuvres result in improvement in oxygenation but may cause negative hemodynamic consequences in ARDS [10]. However, the data with regards to mechanical ventilation is nonexistent for patients with cirrhosis [11]. Therefore, the primary objective of the study was to assess the efficacy and safety of the staircase recruitment manoeuvre (SRM) in moderate ARDS in cirrhosis. The secondary objective was to study the impact of two different modes of ventilation on oxygenation post recruitment.

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METHODS
This prospective, pilot randomised controlled trial was conducted after approval by the Institutional Ethics Committee (Number: IEC/2017/51/NA07) from 1 October 2017 to 30 January 2018. All patients gave written informed consent, as per the declaration of Helsinki and good clinical practice guidelines. Thirty adult cirrhotic patients who received mechanical ventilation for the first time in our institute and who satisfied Berlin criteria for moderate acute respiratory distress syndrome with a requirement of FiO₂ >50% with pO₂ <85 mmHg after 6 h of intubation and mechanical ventilation were included. Patients were excluded in case of cardiogenic pulmonary oedema, history of arrhythmia, pre-existing chronic lung disease, hepatopulmonary syndrome, portopulmonary hypertension, anatomic chest wall abnormalities, and increased intracranial tension.

Both groups of patients underwent the following investigations on intensive care unit (ICU) admission: haemogram, renal and liver function tests, blood sugar fasting, arterial blood gas, and chest X-ray. In all 30 patients, SRM was initiated. All patients were ventilated with the Extend XT ventilator (Air Liquide medical systems, France). Prior to initiation of the SRM, all patients were on pressure control mode of ventilation. Since there is no standard technique, the technique reported by Hodgson et al. was followed [12]. Sedation was given as per ICU protocol. Thirty patients, SRM was initiated. All patients were ventilated with the Extend XT ventilator (Air Liquide medical systems, France). Prior to initiation of the SRM, all patients were on pressure control mode of ventilation. Since there is no standard technique, the technique reported by Hodgson et al. was followed [12]. Sedation was given as per ICU protocol. The patients were paralysed with and injection of atracurium. Recruitment was done once; however, if arterial blood gas (ABG) analysis showed a decrease in PaO₂ every 2 min and then reduced to 25, then 22, then 19, or then 15 cm H₂O every 3 min or until a decrease in SaO₂ > 1% from maximum SaO₂ was observed. This was defined as the derecruitment point. PEEP was then increased to 40 cm H₂O for 1 min and returned to a PEEP level 2 cm H₂O above the derecruitment point (which was then defined as optimal PEEP).

Immediately post-SRM, the patients were randomized to either volume control ventilation (VCV) or pressure control ventilation (PCV). The patients were randomly allocated to either group using computer generated, random numbers from a biostatistician not directly involved in the study. Patients were randomized to either of the two groups in 1:1 ratio. Blinding was not possible for technical reasons.

Both groups were continued on sedation. Patients were monitored for changes in oxygenation; lung compliance; vitals; vasopressor inotro- score (VIS) [13]; ventilator parameters 1 h, 6 h, and 12-h post-SRM and for length of mechanical ventilation; length of ICU stay; and mortality. The primary endpoint was improvement in oxygenation and static lung compliance lasting for at least 12 h post-recruitment on both the modes of ventilation.

Secondary endpoints were: failure of recruitment in terms of failure to improve oxygenation; adverse effects of recruitment like hypotension, arrhythmia, desaturation, tachycardia, bradycardia; pneumothorax requiring termination of recruitment manoeuvre; and duration of mechanical ventilation.

Statistical Package for the Social Science (SPSS) version 16, (SPSS-16, IBM, Chicago, USA) was used for analysing the data. Data were reported as proportions or mean ± SD. Chi-square test or Fisher exact test was used for categorical variables. Normally distributed continuous variables were compared using the Student t-test (unpaired data) to analyze the significant effect in patients. The sample size was one of convenience since this was a pilot study.

FIGURE 1
Participant flow in the study.
Efficacy and safety of an open lung ventilation strategy

RESULTS

The allocation of patients is shown in the CONSORT (Consolidated Standards of Reporting Trials) diagram (Figure 1). The baseline demographic, disease severity scores, blood gas values, ventilator, and hemodynamic parameters were comparable in both the groups (Table 1). Admitted patients had high MELD (model for end-stage liver disease) and SOFA (sequential organ failure assessment) scores in both the groups. No significant differences in terms of age, sex, oxygenation, ventilatory parameters, or hemodynamic parameters were present. The PaO$_2$/FiO$_2$ ratio was comparable at baseline in both groups (P > 0.29). The vasopressor support was comparable in both groups (P > 0.54). Presence of infection as a possible precursor to ARDS was present in 60% of patients in the PCV group and in 40% of patients in the VCV group, P = 0.28.

SRM showed a significant improvement in PaO$_2$ in the PCV and VCV group at the end of 12 h, but there was no difference between both groups (P = 0.73) (Table 2, Figure 2). Both groups showed a significant improvement in PaO$_2$/FiO$_2$ ratio at the end of 12 h. The improvement in PaO$_2}$/FiO$_2$ ratio was significantly higher in the PCV group at the end of the first hour as compared to the VCV group (Table 2, Figure 3). The PEEP requirement was significantly higher in the control group at the end of 6 h and 12 h as compared to the pressure control group. Both the groups required an increase in PEEP from the baseline after the recruitment maneuver, which showed a trend towards significance (P = 0.05) (Table 2, Figure 4). The plateau pressure also reduced significantly in both the groups, (P < 0.05) with no difference between the groups (Table 2, Figure 5). Likewise, the static compliance also improved in both the groups, which was sustained till the end of 12 h after recruitment; however, there was no difference between both groups (Table 2, Figure 6).

One patient developed severe hypotension and bradycardia during the recruitment manoeuvre, so it was abandoned. There were no significant changes in heart rate and mean arterial pressure between the two groups or over time (Table 3). There was no significant change in the vasopressor inotrope score seen after the recruitment. (Table 3). Also, there was no difference between both groups. There was no significant difference in the length of mechanical ventilation or outcome between the two groups (Tables 4, 5).

| TABLE 1 |
| Baseline demographic, clinical, blood gas, and ventilatory parameters of patients enrolled |

| Characteristics | PCV group (n = 15) | VCV group (n = 15) | P |
|-----------------|--------------------|--------------------|---|
| Age (years)     | 46.87 ± 12.72      | 50.20 ± 14.45      | 0.5 |
| BMI             | 26.65 ± 2.91       | 24.82 ± 3.77       | 0.14 |
| SOFA            | 12.27 ± 3.150      | 12.40 ± 2.796      | 0.90 |
| APACHE          | 39 ± 10.351        | 40.67 ± 6.73       | 0.60 |
| MELD            | 29.33 ± 0.217      | 24.6 ± 0.395       | 0.17 |
| CTP             | 12.87 ± 1.807      | 13.40 ± 5.316      | 0.71 |
| pH              | 7.35 ± 0.05        | 7.33 ± 0.10        | 0.53 |
| HCO$_3$ (mmol/L)| 19.52 ± 6.85       | 18.96 ± 4.66       | 0.81 |
| Na (mmol/L)     | 136.00 ± 0.72      | 132.73 ± 9.77      | 0.33 |
| K (mmol/L)      | 4,600 ± 0.93       | 4,227 ± 0.96       | 0.34 |
| Lactate (mmol/L)| 6.45 ± 6.15        | 6.173 ± 6.35       | 0.90 |
| FiO$_2$         | 50.36 ± 14.70      | 50.80 ± 14.45      | 0.93 |
| PaO$_2$/mm Hg   | 79.64 ± 12.55      | 71.06 ± 20.45      | 0.18 |
| PCO$_2$/mm Hg   | 39.32 ± 8.77       | 40.84 ± 8.66       | 0.64 |
| PaO$_2$/FiO$_2$ | 118.47 ± 10.21     | 113.79 ± 13.22     | 0.29 |
| PEEP (cm H$_2$O)| 6.60 ± 0.91        | 7.27 ± 1.71        | 0.19 |
| Tidal Volume (ml)| 470.20 ± 150.09    | 488.21 ± 47.37     | 0.87 |
| Plateau pressure (cm H$_2$O)| 25 ± 2.50    | 26.64 ± 2.46       | 0.08 |
| Vitals          |                    |                    |     |
| Heart rate (beats per minute) | 90.6 ± 5.83 | 87.33 ± 7.57 | 0.19 |
| MAP (mm Hg)     | 76.07 ± 22.42      | 83.18 ± 27.50      | 0.48 |
| VIS             | 12.10 ± 10.81      | 9.79 ± 10.98       | 0.54 |
| Presence of infection on day of intubation | 9/15 (60%) | 6/15 (40%) | 0.28 |

Data are n (%) or mean ± S.D.

Note: APACHE = acute physiology and chronic health evaluation; BMI = body mass index; CTP = Child Turcotte Pugh score; FiO$_2$ = fraction of inspired oxygen; HCO$_3$ = bicarbonate; cm H$_2$O = centimeters of water; K = potassium; MAP = mean blood pressure; MELD = model for end stage liver disease; mm Hg = millimeters of Mercury; Na = Sodium PaO$_2$ = partial pressure of arterial oxygen; PCO$_2$ = partial pressure of arterial carbon dioxide; Pplat = plateau pressure; PaO$_2$ = pressure controlled ventilation; PEEP = positive end expiratory pressure; SO = standard deviation; SOFA = sequential organ failure score; TV = tidal volume; VIS = vasopressor inotrope score; ABG = arterial blood gas; VCV = volume control ventilation.
TABLE 2
Ventilatory parameters before and after recruitment

|                        | 0 h                  | 1 h                  | 6 h                  | 12 h                 | P       |
|------------------------|----------------------|----------------------|----------------------|----------------------|---------|
| PaO₂ (mean ± SD)       | PCV 79.64 ± 12.55     | 109.07 ± 34.85       | 93.98 ± 24.82        | 97.55 ± 33.71        | <0.05   |
|                        | VCV 71.06 ± 20.45     | 93.20 ± 25.88        | 95.91 ± 22.29        | 115.29 ± 30.07       | <0.05   |
| PCO₂ (mean ± SD)       | PCV 39.32 ± 8.77      | 38.38 ± 7.92         | 38.26 ± 8.40         | 38.26 ± 8.89         | 0.63    |
|                        | VCV 40.84 ± 8.86      | 38.05 ± 10.29        | 41.43 ± 7.69         | 40.71 ± 8.05         | 0.69    |
| PaO₂/FiO₂ (mean ± SD)  | PCV 118.47 ± 10.218   | 185.67 ± 52.782      | 179.13 ± 48.264      | 189.87 ± 55.187      | <0.05   |
|                        | VCV 113.79 ± 13.221   | 129.29 ± 42.253      | 144.64 ± 50.118      | 180.93 ± 81.971      | <0.05   |
| Compliance (mean ± SD) | PCV 25.42 ± 11.94     | 25.96 ± 11.6         | 28.78 ± 13.61        | 29.51 ± 14.58        | <0.05   |
|                        | VCV 24.78 ± 4.87      | 27.05 ± 4.06         | 29.83 ± 5.12         | 31.31 ± 10.88        | <0.05   |
| PEEP (mean ± SD)       | PCV 6.60 ± 0.91       | 8.53 ± 0.83          | 8.47 ± 0.91          | 8.53 ± 1.12          | 0.05    |
|                        | VCV 7.27 ± 1.71       | 9.20 ± 1.65          | 9.60 ± 1.72          | 9.60 ± 1.72          | 0.05    |
| Plateau pressure (mean ± SD) | PCV 25.00 ± 2.50     | 26.13 ± 2.99         | 25.40 ± 4.23         | 24.67 ± 3.67         | <0.05   |
|                        | VCV 26.64 ± 2.46      | 27.21 ± 2.19         | 26.00 ± 2.85         | 25.14 ± 2.82         | <0.05   |
| Tidal Volume (mean ± SD) | PCV 470.20 ± 150.09  | 460.26 ± 111.32      | 468.66 ± 121.50      | 455.20 ± 124.68      | 0.53    |
|                        | VCV 488.21 ± 47.37    | 482.50 ± 42.09       | 480.35 ± 43.16       | 480.00 ± 43.36       | 0.53    |
| pH (mean ± SD)         | PCV 7.35 ± 0.05       | 7.37 ± 0.07          | 7.36 ± 0.08          | 7.35 ± 0.10          | 0.76    |
|                        | VCV 7.33 ± 0.10       | 7.33 ± 0.16          | 7.31 ± 0.11          | 7.3221 ± 0.12        | 0.76    |
| p                      | 0.29                 | <0.05               | 0.07                 | 0.73                 |         |
|                        | 0.19                 | 0.17                | <0.05               | 0.05                 |         |
|                        | 0.08                 | 0.28                | 0.66                 | 0.44                 |         |
|                        | 0.67                 | 0.48                | 0.73                 | 0.48                 |         |
|                        | 0.35                 | 0.17                | 0.17                 | 0.40                 |         |

Note: SD = standard deviation; PCV = pressure control ventilation; VCV = volume control ventilation; PEEP = positive end expiratory pressure; PaO₂ = partial pressure of arterial oxygen; PCO₂ = partial pressure of arterial carbon dioxide; FiO₂ = Fraction of inspired oxygen.

"0" h values are taken just before recruitment manœuvre.
1 h, 6 h and 12 h values at those at the respective time after recruitment.

FIGURE 2
Trend of partial pressure of oxygen (PO₂) in arterial blood gas after recruitment manœuvre in pressure control ventilation and volume control ventilation groups.
FIGURE 3
Trend in PaO$_2$/FiO$_2$ ratio after recruitment in both groups.

FIGURE 4
Trend of PEEP after recruitment.
FIGURE 5
Trend of plateau pressure in both groups.

FIGURE 6
Trend of static compliance in both groups after recruitment.
end of 6 and 12 h, but this was at the cost of higher PEEP requirement in the VCV group as compared to the PCV group. This could be because, compared with constant flow VCV, VCV favours gas distribution between regions with heterogeneous time constants and allows a more homogeneous share of tidal volume to the whole lung through its quicker alveolar filling and more laminar flow [19]. The initial high flow rate leads to rapid alveolar inflation and improves ventilation-perfusion mismatch [20]. These advantages of PCV over VCV can be accomplished with VCV with a decelerating flow waveform [21]. However, we have used the volume control mode with a constant flow, which could explain the difference.

Similar to early proning in ARDS, early SRM may probably recruit the collapsed alveoli in the early hyaline membrane phase of ARDS before fibroblastic cell activation [22]. We performed the manoeuvre as early as 6 h after intubation, which probably resulted in the improvement in oxygenation. However, along with improvement in oxygenation, adverse events like hypotension have been reported during the procedure, which is usually transient. Hodgson et al. [12] did not report any adverse hemodynamic events during their study. They performed the SRM once daily whereas King et al. [22] performed it every 8 h. Kung et al. [22] reported a 50% incidence of hypotension during the manoeuvre. They also increased the PEEP by 3 cm H₂O every 3 breaths, whereas Hodgson et al. [12] increased the PEEP by 10 cm H₂O every 2 min. Therefore, the rapid escalation of PEEP and increased frequency of SRM could have contributed to the high incidence of hypotension in their study.

Patients with liver disease exhibit intense arterial vasodilatation with a reduced central blood volume, mimicking hypovolemia, and vascular hyporeactivity. The frequency of vasopressor requirement is also high in patients with liver disease and ARDS [13]; therefore, the frequency was restricted to just once. The procedure had to be abandoned in one patient due to severe hypotension. The rest of the patients tolerated the procedure well, with no rise in vasopressor support after the procedure. The increase in pleural pressure secondary to the increase in airway pressure plays a major role in impeding venous return. However, the transmission of airway pressure to the pleural space may in part depend on the distensibility of the lungs. It has been found that in patients with lung compliance more than 45 mL/cm H₂O, 37% of the airway pressure is transmitted to the pleural space, whereas in patients with compliance less than 30 mL/cm H₂O only 24% of the airway pressure is transmitted to the pleural space [23]. This could be the reason we did not see an increase in vasopressor support despite a significant increase in PEEP after the SRM.

As evidenced by the high mortality in our study, the physiological improvements did not translate into clinically meaningful outcomes. However, it could have implications for use in patients with other critically ill patients with mild ARDS awaiting liver transplant or in immediate post-liver transplant patients who develop ARDS.

LIMITATIONS

The main drawback is the pilot study with small sample size. There was a lack of recording of other factors like effusions, degree of ascites, and the presence of hepatopulmonary syndrome that could have influenced the oxygenation and ventilator requirements in both groups.

CONCLUSION

This study shows that stepwise recruitment manoeuvre is an effective rescue therapy to improve oxygenation in cirrhosis with moderate ARDS. It should be performed as early as possible and even a single manoeuvre is effective. Pressure control ventilation may have an advantage over volume control ventilation in terms of better oxygenation with a lower PEEP requirement. However, a larger sample size could confirm this more substantially.

AUTHOR DISCLOSURES

Contributors
All authors contributed to the conception or design of the work, the acquisition, analysis, or interpretation of the data. All authors were involved in drafting and commenting on the paper and have approved the final version.

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Competing interests
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.
Ethical approval

This prospective, pilot randomised controlled trial was conducted after approval by the Institutional Ethics Committee (Number: IEC/2017/51/NA07) from 1st October 2017 to 30th January 2018. All patients gave written informed consent.

REFERENCES

1. Karcz M, Bankey B, Schwalberger D, Lachmann B, Papadakos PJ. Acute respiratory failure complicating advanced liver disease. Semin Respir Crit Care Med 2012;33:96–112. doi: 10.1055/s-0032-1301738
2. Olson C, Jody. Intensive care of the patient with cirrhosis. Hepatology 2011;54(5):964–72. doi: 10.1002/hep.24622
3. Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. New Engl J Med 1998;338:347–354. doi: 10.1056/NEJM199802053380602
4. Bajaj P. Ventilator-induced lung injury. Indian J Anaesth 2008;52:363.
5. Cipulli F, Vasques F, Duscio E, Romitti F, Quintel M, Gattinoni L. Atelectrauma or volutrauma: the dilemma. J Thorac Dis 2018;10:1258–64. doi: 10.21037/jtd.2018.02.71
6. Findlay JY, Fix OK, Paugam-Burtz C, et al. Critical care of the end-stage liver disease patient awaiting liver transplantation. Liver Transpl 2011;17(5):496–510. doi: 10.1002/lt.22269
7. Valla, Aat J, Kotecha AA et al. Development and performance of a novel vasopressor-driven mortality prediction model in septic shock. Ann Intensive Care 2018;8:112. doi: 10.1186/s13613-018-0459-6
8. Boente RD, Sheikh A, Bosslet GT, Ghahrell MS. Outcomes of acute respiratory distress syndrome in mechanically ventilated patients with cirrhosis. Crit Care 2019;Le5040. doi: 10.1186/cce.0000000000040
9. Donahoe M. Acute respiratory distress syndrome: a clinical review. Pulm Crit Care 2011;1:192–211. doi: 10.4103/2045-8932.83454
10. Hodgson CL, Tuxen DV, Davies AR, et al. A randomised controlled trial of an open lung strategy with staircase recruitment titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome. Crit Care 2011;15(3):R133. doi: 10.1186/cc10249
11. Grasso S, Stripoli T, Sacchi M, et al. Inhomogeneity of lung parenchyma during the open lung strategy: a computed tomography scan study. Ann J Respir Crit Care Med 2009;180:415–23. doi: 10.1164/ajcc.159.3.9802090
12. Findlay JY. Risks and benefits of mechanical ventilation in acute respiratory distress syndrome. Crit Care Med 2018;10(1):1258–64. doi: 10.21037/jtcsv2-18-02
13. Jardin F, Genevray B, Brun-Ney D, Bourdarias JF. Influence of lung and chest wall compliance on transmission of airway pressure to the pleural space in critically ill patients. Chest 1985;88:653–8. doi: 10.1378/chest.88.5.653