

Research Article

Contributing Factors to Acute Respiratory Distress Syndrome after Cardiac Surgery: Role of Mechanical Ventilation-An Observational Prospective Study

Daniela Pasero^{1*}, Nerlep Kahur Rana¹, Gabriele Giovenale¹, Alessandra Davi¹, Sara Viberti¹, Claudia Filippini¹, Mauro Rinaldi² and Luca Brazzi¹

¹Department of Anaesthesia and Critical Care Medicine, University of Turin, Italy

²Department of Cardiothoracic and Vascular Surgery, University of Turin, Italy

***Corresponding author**

Daniela Pasero, Department of Anaesthesia and Critical Care Medicine, "Health and Science City" Hospital, University of Turin, Corso Bramante 88, 10126 Turin, Italy, Tel: 39-011633-6129; Fax: 39-011-696-0448; Email: daniela.pasero@unito.it

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Abstract

Objective: Patients undergoing cardiopulmonary by-pass (CPB) often require prolonged mechanical ventilation during the post-operative period. Several observational studies have shown that, in critically ill patients undergoing mechanical ventilation without acute respiratory distress syndrome (ARDS), high tidal volume was associated with the development of ARDS, while the role of mechanical ventilation in the development of ARDS in CPB patients remains unknown. This study hypothesized that injurious mechanical ventilation during the post-operative period of CPB was a risk factor to the development of acute respiratory distress syndrome.

Methods: A prospective observational study was conducted in the cardiac intensive care unit of a University Hospital, in Turin, between December 2010 and December 2012. Any patient admitted to cardiac intensive care unit, following cardiac surgery on CPB was enrolled. No intervention was required. Baseline, operative and post-operative variables were collected from each patient and the development of ARDS over 7 days was recorded. A multivariate logistic regressions analysis was performed to determine independent risk factor for the development of ARDS.

Results: One hundred sixty three patients met inclusion criteria and were enrolled into the study. Twenty patients developed ARDS, on day 3.4 ± 1.0 . Multivariate logistic regression analysis identified high tidal volume, respiratory rate (RR), euroSCORE and fresh frozen plasma transfusions (FFP) as risk factors for ARDS.

Conclusions: Injurious mechanical ventilation, characterized by high tidal volume and RR, together with high severity of the peri-operative conditions and transfusions, represent independent risk factors for ARDS in patients following CPB.

ABBREVIATIONS

ARDS: Acute Respiratory Distress Syndrome

INTRODUCTION

Post-operative pulmonary dysfunction is a major complication following cardiac surgery with cardiopulmonary by-pass (CPB)

and can often lead to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), which is associated with increased morbidity and mortality [1,2]. Several factors are thought to contribute to the development of lung injury, including the pre-operative inflammatory state, the type of surgery, time on CPB and CPB itself [3], aortic cross clamp time [3], blood transfusions and anesthesia management [4]. Mechanical ventilation is an

important therapeutic tool for the treatment of respiratory dysfunction, but some ventilation strategies with high tidal volume (TV) might worsen lung injury [5], with a mechanism known as ventilator-induced lung injury (VILI), which might increase morbidity and mortality in patients already affected by ALI/ARDS [5]. In addition, some observational studies have shown that, in mechanically ventilated patients without lung injury, high tidal volume and high peak inspiratory pressures were associated with the development of ALI/ARDS [6,7]. The underlying mechanisms of VILI includes the inflammatory state, as predisposing factor, and the alveolar stress and strain due to hyperinflation and to the opening/closing mechanism, that might worsen the inflammatory response and lead to multiple organ dysfunction syndrome [5].

Ventilator settings and the length of mechanical ventilation, during the post-operative period, play a role in the inflammatory response following cardiac surgery, since recent studies in CPB patients showed that the application of injurious mechanical ventilation (high tidal volume and low PEEP) was associated with increased cytokines in the lungs and systemic circulatory system [8]. In addition, *Holmes et al.*, found that the length of mechanical ventilation was longer in patients with a larger inflammatory response after CPB [9].

The present study examined the hypothesis that injurious mechanical ventilation represents a risk factor for acute respiratory distress syndrome in patients undergoing cardiopulmonary by-pass.

MATERIALS AND METHODS

Study design. We conducted a prospective observational study between December 2010 and December 2012 in the cardiac intensive care unit (ICU) at the City of Health and Science Hospital in Turin, Italy. The institutional review board approved the study (n. CEI/540). If the patient was incompetent at study entry, consent was delayed, and the family was informed of the study (although not required). Written permission for using collected data was hence obtained from the patient (if competent) or from the family (in case of death or if the patient remained incompetent).

Inclusion criteria: We enrolled all patients undergoing a cardiac surgery intervention on CPB with an ICU stay longer than 24 hours.

Exclusion criteria: age < 18 yrs, off pump surgery, heart or lung transplantation, mechanical ventilation before surgery, acute respiratory distress syndrome present at the admission to the ICU.

Study Protocol. Patients were screened and enrolled into the study following cardiac surgery with CPB after 24 hours from the admission to the ICU. Baseline variables of the peri-operative period were collected: age, gender, euro SCORE (European system for cardiac operative risk evaluation) [10], intra-operative basal PaO₂, necessity for emergency surgery, total surgery time, time on CPB, cross clamping time, and administration of red blood packed cells (RBC) and/or fresh frozen plasma (FFP) transfusions.

Post-operatively, all patients remained sedated, mechanically ventilated and underwent a chest radiograph, to confirm the

initial absence of ALI/ARDS or other pulmonary abnormalities. Patients were studied for seven days from ICU admission and the following ventilator and hemodynamic parameters were collected: tidal volume (TV), respiratory rate (RR), minute ventilation, positive end expiratory pressure (PEEP), blood gas analysis, catecholamine infusion, transfusions and fluid balance. Tidal volume was also calculated for Predictive Body Weight (TV/PBW).

During study period patients were monitored for the development of ARDS. Diagnosis of ALI/ARDS was made according with the American-European Consensus conference criteria [11], including acute onset, PaO₂/FiO₂ < 300 for ALI (< 200 for ARDS) regardless of PEEP level, bilateral and diffuse opacities on antero-posterior chest radiograph, absence of left ventricular failure, or history of lung disease. PaO₂/FiO₂ < 300 was confirmed in three consecutive blood gases. Chest radiographs for the presence of bilateral infiltrations were performed and evaluated by two investigators not involved in the patient's clinical management. To assess the level of agreement in the radiologic evaluation of ARDS, a chance-corrected agreement, using the K coefficient, was calculated [12].

Clinical predictors: All variables related to mechanical ventilation and respiratory function (TV, RR, PEEP, Pa CO₂ and PaO₂/FiO₂ ratio) were expressed as mean value for each day, until the day before ARDS onset; fluid balance as cumulative value until the day before the onset of ARDS; support with vasoactive drugs as the percentage of patients who required vasoactive support, at any time before the ARDS onset. Among patients who did not develop lung injury (Control group), ventilatory and hemodynamic parameters were expressed as mean values until the day before of the average day of the lung injury onset of the ARDS group. All variables clinically meaningful and significantly different at the univariate analysis were entered into a multivariable logistic regression model.

Outcome assessment

The duration of mechanical ventilation was calculated from the ICU admission until extubation. Ventilator free days (VFD) were calculated at seven days, minus the time on mechanical ventilation. ICU length of stay was calculated up to 28 days, and patients who died before were considered as having the maximum value.

Data analysis

Continuous data were expressed as mean ± SD or median (IQR). Comparison of continuous and categorical data between groups were performed using the unpaired Student's t-test or Mann-Whitney U-test and Fisher's exact test, respectively, and were considered significant for p < 0.05.

In order to assess independent risk factors for ARDS, a logistic regression model was created: when significant level for inclusion at the univariate analysis was p < 0.05, the variables were included in a forward conditional multivariable analysis and significant level for odds ratio estimation was p = 0.05. Statistical analysis was conducted with SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS AND DISCUSSION

Among 1302 patients admitted to the ICU after cardiac surgery on CPB, 163 were included into the study. Among these, twenty patients developed ALI/ARDS (four patients had a $\text{PaO}_2/\text{FiO}_2 < 300$ and 16 patients had a $\text{PaO}_2/\text{FiO}_2 < 200$), diagnosed on the third day (3.4 ± 1.0) following cardiac surgery. Regarding the diagnosis of ALI/ARDS, the K coefficient representing the agreement between the assessment for the presence or absence of bilateral infiltrates was equal to 0.67 (SE=0.11).

Demographic data were not significantly different in age, gender or baseline PaO_2 values between patients who did or did not develop ARDS (Table 1). However, patients who developed ARDS had a higher peri-operative risk according to the euroSCORE and more often required cardiac surgery in emergency condition compared to those who did not develop ARDS. In addition patients who developed ARDS received a significantly higher volume of packed red blood cells (RBC) and fresh frozen plasma (FFP) transfusions during the intra-operative period compare to those who did not develop ARDS, while there were no observed differences in the CPB duration and cross clamping time (Table 2). The types of intervention included in this study were: ascending aorta substitution (AAS) (26%), coronary artery by-pass grafting (CABG) (20%), valve surgery (45%) and combined valve and coronary by-pass surgery (9%).

During their ICU stay, patients who developed ARDS were mechanically ventilated with a significantly higher tidal volume, a higher level of PEEP and a higher respiratory rate ($p < 0.01$). Moreover, these patients required more vasoactive support, primarily with norepinephrine ($p = 0.02$), while there was no significant difference in fluid balance during the days preceding the development of ARDS (Table 3). No patients who were

mechanically ventilated for less than 24 hours developed ARDS (Figure 1). Moreover there was an increasing risk to develop lung injury over time and with the increase of TV. Among patients ventilated with a TV higher than 11,5ml/kg/PBW, ARDS developed earlier (Figure 2).

Risk factors

The following variables were included into a logistic regression model: mean TV/PBW, $\text{PEEP} > 5 \text{ cmH}_2\text{O}$, $\text{PEEP} < 5 \text{ cmH}_2\text{O}$, $\text{PEEP} = 5 \text{ cmH}_2\text{O}$, respiratory rate, vasoactive drugs, RBC and FFP transfusions, cardiac surgery in emergency, duration of surgical intervention and euroSCORE. The multivariable regression analysis found TV/PBW, RR, euroSCORE and FFP as predictors for ARDS (Table 4).

Outcome variables

Patients who developed ARDS were mechanically ventilated for a significant longer time, as expressed by shorter VFD (0 (0-4) vs. 6 (0-7) days, $p < 0.001$) and significantly longer ICU-LOS (22 (4-26) vs. 2 (1-26) days, $p < 0.001$).

Discussion

The incidence of acute lung injury after cardiac surgery was reported from 0.61% to 10%, in several large observational studies, with prospective and retrospective data, evaluating the pre and intra-operative predicting factors in different surgical setting [2,13-15] According with the American-European Consensus conference criteria, [11] in the present study acute lung injury occurred in approximately 1.5% of patients undergoing cardiac surgery with CPB, occurring on day 3 after surgery.

Table 1: Demographic and baseline data.

	ARDS (n= 20)	Control (n= 143)	p Value
Age (years)	69 ± 10	65 ± 14	0.28
Gender, n (M/F)	11/9	106/38	0.09
euroSCORE	10 ± 6	6 ± 3	0.004
EF>50%, N (%)	16 (80)	131 (91)	0.39
EF=50-30%, N (%)	4 (20)	11 (8)	0.19
EF<30%, N (%)	0 (0)	2 (1)	1.0
Pre-operative PaO_2 , mmHg (kPa)	72±16 (9.6±2.1)	75±14 (10±1.9)	0.4
Emergency	12(60)	31(21)	<0.001

Abbreviations: EuroSCORE: European System for Cardiac Operative Risk Evaluation; EF: Ejection Fraction; Data were expressed as mean ± SD or N (%)

Table 2: Intra-operative data.

	ARDS (n= 20)	Control (n= 143)	p Value
Total surgery time, min	434 ± 181	322 ± 119	0.01
CPB, min	153±63	144±80	0.65
Clamping time, min	96±51	94±55	0.9
Red blood cells transfusion, ml	1775 (0-3750)	800 (0-11000)	< 0.001
Fresh frozen plasma transfusion, ml	1000 (0-3000)	450 (0-3400)	0.001

Abbreviations: CPB: Cardiopulmonary Bypass; IQR: InterQuartile Range; Data are expressed as mean±SD or median and IQR or n (%).

Table 3: Ventilatory and hemodynamic parameters, during post-operative time before ARDS onset.

	ARDS (n = 20)	Control (n = 143)	p Value
Basal PaO ₂ /FiO ₂	254 ± 109	296±107	0.1
PaO ₂ /FiO ₂ at ARDS onset	147±53	288±107	<0.001
Tidal Volume/PBW, ml/kg	10.01 ± 1.0	8.9 ± 1.3	0.001
PEEP >5 cmH ₂ O, N (%)	8 (40)	11 (8)	
PEEP <5 cmH ₂ O, N (%)	1(5)	22 (15)	<0.001
PEEP =5 cmH ₂ O, N (%)	11 (55)	110 (77)	
Respiratory Rate, rate/min	14±2	13±2	0.001
PaCO ₂ , mmHg (kPa)	40±4 (5.3±0.5)	39,9±6 (5.3±0.8)	0.9
Vmin, l/min	8.64±1,92	7.16±1.37	<0.001
Vasopressors	17 (85%)	84 (58%)	0.02

Abbreviations: PEEP: Positive End Expiratory Pressure; Vmin: Minute Ventilation; MV: Mechanical Ventilation; Data are expressed as mean ± SD or median and IQR, interquartile range or N (%)

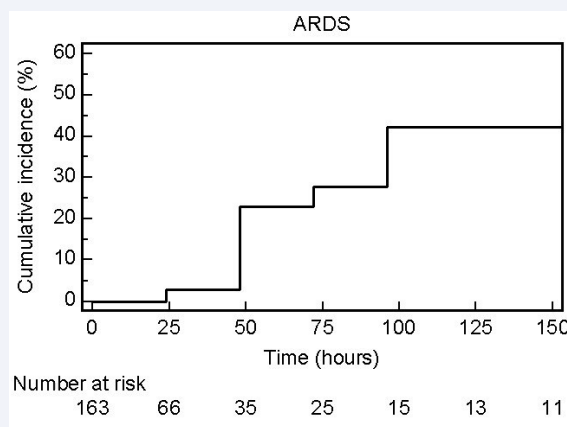


Figure 1 The graph represented the cumulative incidence and the risk to develop ARDS in relationship with the time on mechanical ventilation; patients ventilated for less than 24 hours had no risk to develop ARDS.

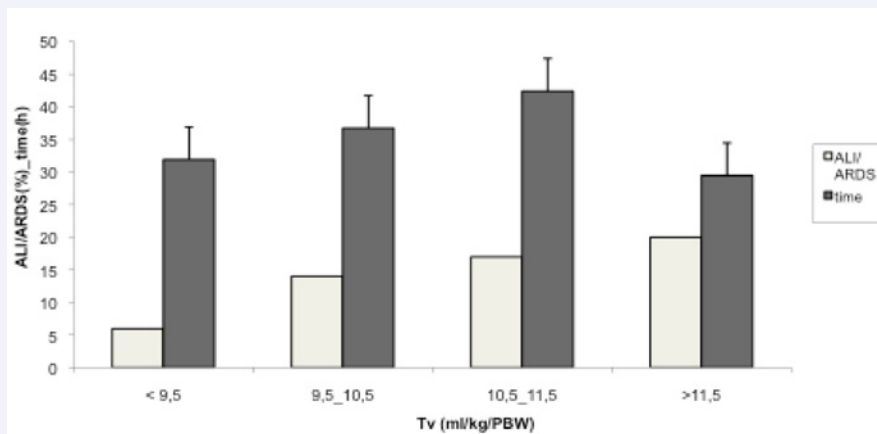


Figure 2 The graph represents the percentage of risk to develop ARDS with the increase of tidal volume and the time on mechanical ventilation; in patients ventilated with a TV > 11.5 ml/kg/PBW there is a greater risk to develop ARDS with a shorter duration of mechanical ventilation.

Recently the Berlin definition reclassified patients who developed ARDS, based on the timing of onset, the chest imaging, the origin of oedema and the severity of hypoxemia, with a PEEP level higher than 5 cm H₂O, removing the term ALI, which was included in one of the three subgroups of ARDS defined by

severity. According with this new definition the patients enrolled in the present study could be reclassified as mild to moderate ARDS [16]. To our knowledge no data are available with the new definition of ARDS in patients undergoing cardiac surgery.

The main findings of the present study were that mechanical

Table 4: Predictive factors for ARDS after cardiac surgery.

	OR (95% CI)	p Value
TV/PBW (ml/kg)	2.55 (1.50-4.35)	0.001
RR (rate/min)	1.53(1.10-2.12)	0.01
FFP (ml)	1.001 (1.000-1.002)	0.004
EuroSCORE	1.30 (1.11-1.53)	0.007

Abbreviations: OR: Odds Ratio; CI: Confidence Interval; TV: Tidal Volume; PBW: Predicted Body Weight; RR: Respiratory Rate; FFP: Fresh Frozen Plasma; EuroSCORE: European system for Cardiac Operative Risk Evaluation.

ventilation with high tidal volume and relatively high RR, together with higher euroSCORE and FFP transfusions represented the main predictors of increased risk of ARDS, in patients following cardiac surgery.

Several authors showed that mechanical ventilation with large tidal volume applied to patients without ALI/ARDS at the admission to the ICU significantly increased their risk to develop ARDS [6,7,17]. All previous studies included critically ill patients admitted for either medical and surgical reasons, who were mechanically ventilated for more than 48 hours, showing that the majority of patients developed ARDS approximately three days following the initiation of mechanical ventilation [6]. Our results confirm the predominant role of mechanical ventilation for the development of ARDS, independently from other risk factors and underline the precocity of lung damage caused by injurious ventilator settings. Differently from the previous studies, we analyzed all the patients that were mechanically ventilated upon admission to the cardiac ICU following an intervention on CPB, even those patients ventilated for less than 48 hours, since CPB itself is believed to increase pulmonary damage due to its ability to induce both a pulmonary and systemic inflammatory reaction.

There is wide evidence from both experimental and clinical studies that injurious ventilator settings, such as high tidal volume and low PEEP, can increase pulmonary and systemic inflammation in patients with ARDS [5]. This mechanism has been recently suggested in patients undergoing CPB, but with discordant results [8,9,18].

Three randomized clinical trials reported that protective mechanical ventilation with low tidal volume after CPB, during the post operative period, did not change cytokine levels, pulmonary function and time to extubation compared to injurious ventilator setting [18-20]. In contrast, there are two randomized clinical trials that have shown a significant increase of pulmonary and systemic inflammatory response (IL- 6 and IL-8) after CPB in patients ventilated with high tidal volume and low PEEP; however, no difference was found regarding the time on mechanical ventilation and no patients developed ARDS during the post-operative period [8,19]. Therefore, these studies suggested that CPB might play a marginal role in the development of lung injury but claims that injurious mechanical ventilation did increase the risk of lung injury; however, all these previous studies have examined small number of selected patients, such as low risk patients following elective surgery, hemodynamically stable with short CPB time and very few hours on mechanical ventilation after surgery [8,18-20]. Although our patients were not randomized, we enrolled higher risk patients undergoing mostly emergency surgery with longer CPB time and longer

post-operative mechanical ventilation. Differently from previous studies, Holmes et al. found that the length of mechanical ventilation during the post operative period was correlated with a larger inflammatory response after CPB [9], while *Rothenburger et al.*, observed that post-operative concentrations of IL-8 were higher in patients who were ventilated for more than 24 hours [21]. A recent prospective cohort study, evaluating intra-operative ventilator settings as risk factor for ALI, showed that injurious ventilation and specifically high tidal volume did not represent an independent risk for the development of ALI, in different kind of surgery, included cardiac patients [2]. Similarly, in our study, among patients ventilated for less than 24 hours, no patient developed ALI/ARDS, thereby confirming the importance of time on mechanical ventilation for the development of lung injury.

Moreover few experimental and clinical studies showed an increased injury in lung affected by ARDS when high tidal volume is associated with increased respiratory rate, especially in spontaneous breathing models, because of an increase in peak and plateau pressures [22,23], which exerted a negative effect also in critically ill patients without ARDS at onset of mechanical ventilation [6,7]. Similarly in our study we observed an increased risk to develop ARDS in patients ventilated with increasing respiratory rate and higher tidal volume and, since we did not collect peak and plateau pressures before ARDS onset, we can only speculate that these last variables might have a key role in the development of the lung injury.

Cardiac surgery patients present a higher risk to develop transfusion-related acute lung injury (TRALI), since during cardiac surgery procedures patients that are on CPB sometimes need a large amount of blood products. TRALI is defined as the acute injury, developed within six hours from transfusion and it is not strictly related to the quantity of transfusions [24]. Moreover, previous retrospective and prospective observational studies reported a significantly higher probability to develop ALI/ARDS in critically ill patients receiving a transfusion [6,24]. Additionally, a recent retrospective single centre study showed an increased risk to develop ALI/ARDS in patients receiving FFP and platelets more than RBC transfusion [25]. Similarly, in our study we observed a weak but significant association with an increase risk to develop ARDS in patients receiving an increasing quantity of FFP transfusions.

The present study had some limitations: first of all it is an observational and single centre study; moreover the number of patients developing the acute lung injury was low, suggesting that a small proportion of patients undergoing this kind of surgery have an increasing risk to develop such a complication.

CONCLUSION

In conclusion, the application of high tidal volumes and increasing respiratory rate, in patients with a greater severity of the perioperative condition and the need of great quantity of FFP transfusions are strongly associated with an increased risk to develop acute respiratory distress syndrome after cardiac surgery with CPB, suggesting that we should avoid injurious ventilator setting in the post-operative period, especially when a late extubation (>24 hours) is expected; however, more prospective multicenter trials with a larger number of patients are required to confirm these results.

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