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ARDS in Aged Patients: Respiratory System Mechanics and Outcome

Antonia Koutsoukou¹, Maria Katsiari², Stylianos Orfanos³, Nikoletta Rovina¹, Christina Dimitrakopoulou⁴, Anastasia Kotanidou⁵ and Antonia Koutsoukou¹

¹Department of Respiratory Medicine, Sotiria Hospital for Diseases of the Chest, Medical School, National and Kapodistrian University of Athens, Athens, Greece

²Konstantopouleio - Patission General Hospital of Nea Ionia, GR, Athens Greece

³Department of Critical Care, Attikon Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

⁴Errikos Ntynan Hospital Centre, Athens, Greece

⁵Department of Critical Care, Evangelismos Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Corresponding author: Antonia Koutsoukou, Department of Respiratory Medicine, Medical School, National and Kapodistrian University of Athens, Sotiria Hospital, 152 Mesogion Ave, 115 27 Athens Greece, Tel: +30 2107763718; Fax: +302107781250; E-mail: koutsoukou@yahoo.gr

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Abstract

Background: Aging is associated with physiological changes in respiratory mechanical properties. In elderly patients an increased incidence of Acute Respiratory Distress Syndrome (ARDS) resulting in increased number of elderly patients treated in Intensive Care Units (ICUs), along with increased mortality has been reported. Aim of the present study was to identify potential age-related differences in respiratory mechanics, gas exchange and ventilator settings in patients with early ARDS. The relationship between age and ICU mortality was additionally assessed.

Methods: In 58 consecutive early ARDS patients demographic and anthropometric characteristics, ventilatory settings, pulmonary physiologic measurements (arterial blood gases and static respiratory mechanics) and outcome within ICU setting were recorded. Patients were divided into three age groups, those <45 yrs old (Group A, n=16), those 45-65 yrs old (Group B, n=24) and those ≥ 65 yrs old (Group C, n=18).

Results: Ventilatory settings did not differ among the three ARDS age groups studied. Arterial blood gases and static respiratory mechanics were also comparable. Similarly, alveolar to arterial oxygen gradient (A-aDO₂) did not differ significantly between the three groups. The middle-aged and elderly patients compared to younger ones had significantly longer length of ICU stay (p=0.018) and higher, although not significant, ICU mortality (Group A: 25%; Group B: 41.67%; Group C: 61.1%).

Conclusions: An overt impact of age on respiratory system mechanics and gas exchange in early ARDS patients was

not detected in our cohort. Nevertheless, elderly patients demonstrated a trend for higher mortality, along with significantly longer hospitalization in the ICU.

Keywords: ARDS; Respiratory mechanics; Elderly; Mechanical ventilation

Introduction

The incidence of acute respiratory failure requiring mechanical ventilation increases 10-fold from the ages of 55 to 85 years, resulting in increased number of elderly patients treated in Intensive Care Units (ICUs) [1,2]. Aging is associated with physiological changes in respiratory mechanical properties, namely, increased lung compliance, due to decreased elastic recoil pressure of the lung, and reduced chest wall compliance, due to increased chest wall rigidity [3]. Age-related alterations in lung connective tissue and structural changes of the thoracic cage have been implicated as underlying mechanisms [4]. Loss of lung recoil pressure and reduction in supporting tissue may lead to homogeneous enlargement of airspaces and premature closure of small airways during tidal breathing resulting in air trapping and hyperinflation, a condition usually characterized as “senile emphysema” [5] and regional ventilation–perfusion mismatching with concurrent diminished efficiency of gas-exchange [6,7].

The above described age-related alterations might diminish elderly subjects’ reserve in cases of serious respiratory disorders. In elderly patients an increased incidence of Acute Respiratory Distress Syndrome (ARDS) along with increased mortality have been reported [8,9]. Alveolar instability, reduction of functional lung units and atelectasis, the major pathophysiological derangements in ARDS, might further

deteriorate the already existing age-related decline of respiratory system function in these patients. On the other hand, age-associated changes in the respiratory system properties may protect the elderly from potential disease-associated consequences; for instance, in the presence of small airways closure, gas can be trapped behind the closed airways, thus preventing atelectasis formation. In this respect, possible alterations in respiratory system mechanics encountered in ARDS could be expressed differently between younger and older patients. In addition, a possible age-related bias in ventilator settings selection may explain the differences in ventilatory settings that have been detected between ARDS age groups [10]. The objectives of our study were to identify potential age-related differences in respiratory mechanics, gas exchange and ventilator settings in patients with early ARDS. The relationship between age and ICU mortality was additionally assessed.

Materials and Methods

Study population

We studied fifty eight consecutive patients with acute respiratory failure resulting from ARDS. The diagnosis was made according to the American-European Consensus Conference [11]. Data acquired in the course of each patient's management were recorded for this study. The protocol for data collection was approved by the institutional review board and informed consent was not required. Exclusion criteria were documented history of chronic obstructive lung disease, pneumothorax, asthma and pulmonary fibrosis.

All patients were prospectively studied at early ARDS (within the first 3 days) while being in the semi-recumbent position. Sedation was performed with continuous intravenous infusion of propofol or midazolam.

Data compiled for each patient included demographic and anthropometric characteristics, ventilatory settings and pulmonary physiologic measurements (arterial blood gases and static respiratory system mechanics). Disease and lung injury severity were estimated by assessing Acute Physiology and Chronic Health Evaluation (APACHE) II [12], Simplified Acute Physiology II (SAPS) [13], Sequential Organ Failure Assessment (SOFA) [14] and Lung Injury [15] Scores. Calculation of LIS was based on chest x-ray (number of injured quartiles), total positive end-expiratory pressure (PEEP_{tot}) and the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO₂/FiO₂). Anthropometric and clinical characteristics of study population are presented in **Table 1**.

Table 1 Anthropometric and clinical characteristics of study population.

	Group A	Group B	Group C
	(n=16)	(n=24)	(n=18)
Age (years)	32 ± 7	56 ± 6*	74 ± 6*#
Sex (M/F)	15-Jan	15-Sep	10/8*

BMI (kg/m ²)	26.3 ± 1.5	28.8 ± 4.2	28.1 ± 3.1
ARDS origin (P/EP)	11-May	14-Oct	09-Sep
APACHE II	13.0 ± 4.0	20.7 ± 6.0*	23.4 ± 6.6*
SAPS II	34.1 ± 9.0	52.8 ± 12.0*	61.0 ± 10.7*#
SOFA	10.3 ± 3.5	9.6 ± 2.7	10.7 ± 4.0
LIS	2.5 ± 0.5	2.6 ± 0.6	2.6 ± 0.7
ICU LOS (days)	5 ± 3	14 ± 11*	14 ± 8*
ICU outcome (S/D)	12/4	14/10	7/11

* significantly different as compared to Group A; #: significantly different as compared to Group B

Values are mean + SD unless otherwise indicated; M: male, F: female; BMI: Body mass index; P: ARDS of pulmonary origin; EP: ARDS of extrapulmonary origin; APACHE II: Acute Physiology and Chronic Health Evaluation Score; SAPS II: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; LIS: Lung Injury Score; LOS: length of ICU stay; S: survived, D: died

Group A: younger (<45 yrs), Group B: middle-aged (45-65 years), Group C: the elderly (≥ 65 years) patients.

All patients were ventilated with the volume control modality. Fraction of inspired oxygen concentration and ventilatory settings (**Table 2**) were those prescribed by the patients' attending physicians and corresponded to the time that arterial blood gases were obtained. Airway pressure (Paw), tidal volume (V_T), and inspiratory flow (V) were recorded by using the ventilator display. Respiratory mechanics were assessed by the constant flow airway occlusion technique [16]. End-inspiratory plateau pressure (P_{plat}) was determined using an end-inspiratory pause for 3 secs, while total positive end-expiratory pressure (PEEP_{tot}: applied PEEP plus intrinsic PEEP) was assessed 3 sec after an end-expiratory occlusion. In all instances duplicate measurements were made and the mean values were used for the subsequent analysis. Static elastance of respiratory system (Est, rs) was calculated by dividing the difference between P_{plat} and PEEP_{tot} with the V_T, and maximal resistance of the respiratory system (R_{max,rs}) by dividing the difference between peak airway pressure (P_{peak}) and P_{plat} with inspiratory V. Maximal resistance of respiratory system (R_{max,rs}) was corrected for the resistance of the endotracheal tube [17].

Table 2 Ventilator settings of study population.

	Group A	Group B	Group C
	(n=16)	(n=24)	(n=18)
FiO ₂	0.71 ± 0.18	0.67 ± 0.16	0.64 ± 0.17
VT ml	604 ± 80	532 ± 67*	548 ± 83
VT/IBW ml/kg	7.9 ± 1.1	7.8 ± 1.1	8.5 ± 1.7
	62.5 ± 3.5	65.0 ± 7.7	65.5 ± 7.6
V I L/min			
f R min ⁻¹	20 ± 3	21 ± 6	17 ± 4
	11.6 ± 1.9	10.8 ± 3.1	9.7 ± 2.9
V E (L)			

TI s	1.01 ± 0.17	1.11 ± 0.30	1.06 ± 0.23
TI/TTOT	0.32 ± 0.04	0.36 ± 0.07	0.30 ± 0.06 [#]
PEEP cm H ₂ O	9.5 ± 3.0	9.5 ± 3.0	8.6 ± 3.0

*: significantly different as compared to Group A; #: significantly different as compared to Group B

Values are mean ± SD; FiO₂: fraction of inspired oxygen; VT: tidal volume; VT/BW: tidal volume per kilogram of ideal body weight; VI: inspiratory flow; FR: respiratory frequency; VE: Minute ventilation, TI and TTOT: inspiratory and total breathing cycle duration, Ppeak: airway pressure; Pplat: static end-inspiratory airway pressure; PEEP: applied PEEP

Group A: younger (<45 yrs), Group B: middle-aged (45-65 yrs), Group C: the elderly (≥ 65 yrs) patients.

Patients were divided into three age groups, those < 45 years old (Group A, n=16), those 45-65 years old (Group B, n=24) and those ≥ 65 years old (Group C, n=18). The outcome was defined as death or survival within the ICU setting.

Statistical analysis

Data are presented as means ± standard deviation (SD). Continuous variables were compared with one way analysis of variance. When analysis of variance revealed a significant difference, Holm-Sidak t-test was used to correct for multiple comparisons. Categorical variables were evaluated with the Chi-square test. All tests were 2-tailed and a p-value less than 0.05 was considered to indicate statistical significance.

Results

Clinical and epidemiological characteristics

Anthropometric and clinical characteristics of our cohort, after patients' allocation in three groups according to their age, are presented in **Table 1**. Younger patients (Group A) had mean age 32±7 years, the middle-aged (Group B) 56±6 years and the elderly (Group C) 74± 6 years (p<0.001). Although males were predominantly affected in all groups (93.7% vs. 62.5% vs. 55.5% respectively), the percentage of male affected was significantly higher in the Group A as compared to Group C (p=0.037). Body mass index (BMI) did not differ between the groups. Although younger patients presented with a predilection for pulmonary ARDS, the inter-comparison among the three age groups did not show significant difference in the ARDS origin (68.7% vs. 58.3% vs. 50%, p=0.55).

On ICU admission both APACHE II and SAPS II scores were significantly higher in middle-aged and elderly patients compared to younger ones (APACHE II: 13.0±4.0 vs. 20.7±6.0 vs. 23.4±6.6, p=0.002; SAPS II: 34.1±9.0 vs. 52.8±12.0 vs. 61.0±10.7, p<0.001, in groups A, B and C respectively). However, the number of organ failures, as assessed by the SOFA score, was not different between the groups. Severity of lung injury, based on LIS score, was also similar between the three age groups. The ICU length of stay was significantly longer in middle-aged and elderly patients compared to younger ones (5±3 days vs. 14±11 vs. 14±8, p=0.018, in groups A, B and C respectively). Intensive Care Unit mortality, although higher in middle-aged and elderly patients (Group A:

25%; Group B: 41.67%; Group C: 61.1%), was not significantly different between the three groups (p=0.106).

Ventilatory settings

No significant differences in FiO₂, inspiratory flow (V), respiratory rate (RR), minute ventilation (V_E), inspiratory time (Ti), and applied PEEP were identified in between the groups (**Table 2**). The inspiratory to total breathing cycle duration ratio was higher in Group B compared to Group C (0.36 ± 0.07 vs. 0.30 ± 0.07 sec, p=0.016). Although the tidal volume used in younger ARDS patients was higher as compared to middle-aged patients (604 ± 80 vs. 532 ± 67 mL, p=0.017), VT per kg of ideal body weight did not differ between the three groups.

Pulmonary physiologic measurements

Arterial blood gases and static respiratory mechanics and are shown in **Table 3**. Oxygenation, as estimated by PaO₂/FiO₂ ratio was similar between the three groups (126±44 vs. 139±50 vs. 127±40 mmHg, p=0.583, in groups A, B and C respectively). Partial pressure of carbon dioxide (PaCO₂), as surrogate for alveolar ventilation, was also comparable (44±4 vs. 40±8 vs. 42±9 mmHg, p=0.342). Similarly, alveolar to arterial oxygen gradient (AaDO₂) did not differ significantly between the groups. Although Group B had lower mean pH value (7.36±0.07) compared to Group A (7.39±0.05) and Group C (7.39±0.06), this difference was not significant.

Table 3 Pulmonary physiologic measurements of study population.

	Group A (n=16)	Group B (n=24)	Group C (n=18)
PaO ₂ (mmHg)	86 ± 27	89 ± 28	75 ± 12
PaCO ₂ (mmHg)	44 ± 4	40 ± 8	42 ± 9
pH	7.39 ± 0.05	7.36 ± 0.07	7.39 ± 0.06
PaO ₂ /FiO ₂ (mmHg)	126 ± 44	139 ± 50	127 ± 40
A-aDO ₂ (mmHg)	368 ± 125	336 ± 112	328 ± 119
Ppeak cm H ₂ O	44.5 ± 11.6	35.4 ± 9.3	35.9 ± 9.4
Pplat cm H ₂ O	30.9 ± 7.2	30.3 ± 5.9	29.3 ± 7.2
Est, rs (cmH ₂ O/L)	37.6 ± 17.2	40.7 ± 14.8	38.7 ± 15.8
Rmax, rs (cmH ₂ O/L/sec)	9.9 ± 5.8	8.9 ± 5.8	7.8 ± 3.9
PEEPi (cmH ₂ O)	0.5 ± 0.7	1.9 ± 2.4	1.4 ± 2.0

Values are mean ± SD; PaO₂: arterial partial pressure of oxygen; PaCO₂: arterial partial pressure of carbon dioxide; PaO₂/FiO₂: arterial partial pressure of oxygen to fraction of inspired oxygen ratio; A-aDO₂: Alveolar to arterial oxygen difference; Est, rs: static respiratory system elastance; Rmax, rs: total resistance of respiratory system; PEEPi: intrinsic PEEP

Group A: younger (<45 yrs), Group B: middle-aged (45-65 yrs), Group C: the elderly (≥ 65 yrs) patients.

Static elastance of respiratory system was similar in the three age groups studied (37.6±17.2 vs. 40.7±14.8 vs. 38.7±15.8 cm H₂O/L, p=0.820, in groups A, B and C

respectively,). Calculation of R_{max} , r_s did not reveal differences between the groups (9.9+5.8 vs. 8.9+5.8 vs. 7.8+3.9 cm H₂O/L/sec, $p=0.530$). Peak airway pressure and P_{plat} were also comparable. Similarly, the amount of PEEP_i was not significantly different between groups (0.5+0.7 vs. 1.9+2.4 vs. 1.4+2.0 cm H₂O, $p=0.636$, in groups A, B and C respectively).

Discussion

The present study identified no significant differences in pulmonary physiologic measurements and ventilatory settings between the three ARDS age groups studied. Older patients stayed longer in the ICU and exhibited higher, although not significant, mortality.

Aging is associated with significant changes in respiratory physiology, including structural changes in the lungs and chest wall with consequent alterations in measurable mechanical properties of respiratory system and gas exchange [18]. Development of ARDS in elderly patients may impose additional burden to severely compromised respiratory mechanics and function.

It is well known that with aging, there is a progressive increase in the rigidity of the chest wall and a decrease in the elastic recoil of the lung [3]. On the one hand the increased elastance of chest wall may aggravate ARDS associated atelectasis formation, but on the other hand, the decreased elastance of the lung with consequent small airway closure and hyperinflation might protect from such a phenomenon [19].

Therefore, the net result of these age-related alterations and ARDS related alterations in respiratory mechanics and gas exchange seems unpredictable.

In line with previous reports [20,21], our patients exhibited high values of Est , r_s but no significant differences were found between the three age groups studied. Increased Est , r_s in ARDS patients has been attributed to the decreased functional lung volume with concurrent small airways closure and atelectasis formation [22]. The decreased lung elastic recoil pressure characterizing the "senile emphysema" could have possibly ameliorated the anticipated ARDS derangements of Est , r_s and thus, a lower Est , r_s should be expected in aged patients. This was not the case in our patients. It should be noted however, that we measured static elastance of the respiratory system and not of the lungs and chest wall separately. The loss of inward elastic recoil of the lungs with age might have been counterbalanced by the concomitant reduction in chest wall compliance. Given that no esophageal pressures were measured in our patients, the exact contribution of the chest wall and the lung in the obtained Est , r_s values cannot be evaluated.

Similar to Est , r_s , R_{max} , r_s was found to be increased in our cohort but no differences between the three age groups were detected. Increased R_{max} , r_s in ARDS patients has been previously described [20,23] and attributed to decreased lung volume and time-constant inequalities [22,24]. In elderly subjects R_{max} , r_s have been described to be normal [25] or

slightly decreased [26]. Although small airways closure has been associated with the decrease in maximal expiratory flow observed in elderly patients [27,28], this phenomenon is not expected to affect R_{max} , r_s since peripheral airways make a relatively small contribution to the total resistance of the respiratory system [29].

Increasing age has been associated with decreased arterial PO_2 , due to small airway closure [30], decreased alveolar surface [25] and decreased diffusing capacity of the lungs [31]. In our cohort, oxygenation derangements, as they were assessed by PaO_2/FiO_2 ratio and $A-aDO_2$, were not found to be different between age-groups.

To our knowledge, there are no studies showing that aged ARDS patients have worst oxygenation. To the contrary, there are studies showing better oxygenation indices in older ARDS patients. In fact, Gee et al. in a small cohort of ARDS patients found that PaO_2/FiO_2 ratio was greater in the patients >60 years old as compared with the younger group [10]. Similarly, Eachempati et al. studied 343 ARDS patients in a surgical ICU and reported that the younger patients (<65 years) presented with lower initial PaO_2/FiO_2 [8]. Detailed studies on gas exchange relationships may be warranted in order to elucidate the possible effect of age on ARDS associated oxygenation derangements.

No significant differences were found in ventilatory settings between the three age groups apart from a lower $Tl/TTOT$ ratio in elderly patients resulting in longer expiratory times. Although no differences in intrinsic PEEP were identified, the increased air trapping [32] and the age-related airflow limitation that have been detected in elderly subjects [18,33] might have affected the physicians' ventilator choices. Tidal volumes used were higher than suggested by the ARDS Network [34]. As per our protocol however, we were obliged to maintain the ventilatory settings selected by patients' attending physicians, which at any event reflect common practice [35]. Previous studies identified the use of lower PEEP levels in elderly patients [10,36]. In the present cohort, the similarity of ventilator settings between the three age groups may be interpreted by the comparable physiologic measurements across the age spectrum.

Aged patients presented with significantly higher severity scores. It should be noted however, that age is accounted for these scores estimation, thus introducing a bias. In line with previous findings, older patients had a longer duration of ICU stay [9]. Although difference in ICU mortality between the three age groups did not reach statistical significance, probably due to the small size of our age-groups, our findings are consistent with previous reports in larger ARDS cohorts showing significantly higher mortality in aged ARDS patients [36,37]. Age related declines in cardiovascular function [10], increased incidence of sepsis [38] and presence of chronic underlying health problems, have been suggested, among others, as possible explanations.

Age-related alterations in respiratory mechanics and gas exchange that could partially explain poor outcome in the older patients were not identified at the early phase of ARDS

in our cohort. However, the effect of age-associated respiratory modifications in the evolution of the syndrome mechanics remains to be elucidated. Peripheral airway closure and expiratory flow limitation, commonly seen in spontaneously breathing aged subjects [28] as well as ARDS related atelectasis, can be associated with lung heterogeneity and the development of shear stresses during mechanical ventilation [39], which may lead to lung injury [40]. Furthermore, the decrease in respiratory reserve, including decreased muscle strength and ability to protect the airway [41] may explain why older patients have greater difficulty remaining extubated and being successfully discharged from the ICU [9].

Conclusion

An overt impact of age on respiratory system mechanics and gas exchange in early ARDS patients was not detected in our cohort. Nevertheless, elderly patients demonstrated a trend for higher mortality along with significantly longer hospitalization in the ICU. Further studies on lung and chest wall mechanics as well as on ventilation perfusion relationships are needed to better clarify the effect of age on respiratory function in ARDS patients and help treatment approach and ongoing research.

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