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Long-term outcomes in survivors of acute respiratory distress syndrome ventilated in supine or prone position

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Abstract *Purpose:* The aim of this study is to examine long-term pulmonary function and quality of life in survivors of acute respiratory distress syndrome (ARDS) previously enrolled in a randomized multicenter trial testing prone compared with supine positioning (PSII study) at five Italian centers. *Design:* Observational prospective study. *Subjects and measurements:* Pulmonary function [spirometric test, gas exchange, carbon monoxide diffusion capacity (DLCO)], high-resolution computed tomography (CT) scan, and health-related quality of life [Short Form-36 (SF-36) and St. George's Respiratory Questionnaire] were evaluated at 12 months. *Results:* Twenty-six patients (13 in each group, mean age 54.1 ± 2.8 years, body mass index 24.5 ± 1.4 kg/m^2, PaO$_2$/FiO$_2$ 117 ± 49 mmHg) were evaluated. There were no significant differences in demographic data, illness severity, or outcome between the prone and supine groups. The overall survival rate was 40%. Pulmonary function was in the normal range without any differences between the two groups. Quantitative lung CT scan analysis showed similar amounts for not aerated (8.1 ± 3.2% versus 7.3 ± 3.4%), poorly aerated (15.3 ± 3.6% versus 17.1 ± 4.9%), and well-aerated (64.0% ± 8.4 versus 70.2 ± 8.4%) lung regions, while overaerated lung region was slightly higher in the prone compared with the supine group (12.5 ± 6.5% versus 5.3 ± 5.5%). Health-related quality of life was similar to in healthy population. However, these patients showed reduction in daily activity specifically due to pulmonary disease as measured by the St. George's Respiratory Questionnaire. *Conclusions:* No differences in pulmonary function or quality of life were observed in this small group of ARDS survivor patients treated in prone versus supine position.

Keywords ARDS · Prone positioning · Health-related quality of life · Pulmonary function · Outcome

Introduction

Acute respiratory failure (ARF), caused by acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), is a rapidly progressive clinical condition characterized by impairment of gas exchange which requires mechanical ventilation [1]. Mechanical ventilation may also cause several types of lung damage called ventilator-

induced lung injury [2]. Despite a trend toward better outcome over the years, the mortality rate in ARDS remains above 40% [3], with elevated morbidity [4, 5] and social costs [6]. Moreover, it was previously found that surviving ARDS patients may present persistent functional limitation [4, 7–10] and reduction in health-related quality of life (HRQL) [5, 10–13].

Prone position has been suggested to improve gas exchange and reduce ventilator-induced lung injury [14] by inducing a more homogeneous distribution of lung stress and strain [15–18]. Although these studies showed that, in the whole population of ALI/ARDS patients, prone position did not show any benefit in outcome [19–22], in the more hypoxemic patients a significant reduction of mortality of about 10% compared with supine position has been noted [19, 21–23].

In conjunction with a randomized multicenter trial that evaluated long-term use of prone compared with supine position in a population of ARDS patients [22], we aimed to investigate in surviving patients whether prone positioning presents any advantage in terms of pulmonary function and quality of life compared with supine positioning.

Subjects and methods

This report details long-term outcomes of ARDS patients enrolled in a randomized multicenter trial (PSII study) [22] investigating possible outcome benefits of prone positioning. There were no significant differences in mortality rate between prone versus supine patients at 28 days, at intensive care discharge, or at 6 months [22]. Patients enrolled in the PSII study fulfilled the diagnostic criteria of ARDS, i.e., PaO_2/FiO_2 ratio ≤ 200 mmHg, assessed by blood gas analysis performed with positive end-expiratory pressure (PEEP) maintained between 5 and 10 cmH_2O.

ARDS survivors enrolled from five Italian intensive care units within 40 km of Milan were evaluated at 12 months. The follow-up trial consisted of physical examination, arterial blood gas analysis, high-resolution computed tomography (HRCT) of the lungs, pulmonary function test, standardized 6-min walking test evaluated with continuous oximetry [24], and assessment of health-related quality of life measured with the medical outcomes study 36-item form general health survey (SF-36) [25] and with the St. George's Respiratory Questionnaire (SGRQ) [26]. Patients were invited to participate in the follow-up trial by telephone. Each patient was interviewed and examined in a single day at Ospedale Maggiore Policlinico. If the patient missed the follow-up trial, the patient could request another trial.

The study was approved by the institutional review board of the hospital. Written consent for the follow-up study was obtained directly from the patient at the time of the visit. Simplified Acute Physiology Score II [27] and Sequential Organ Failure Assessment (SOFA) [28] were recorded at study enrollment. Other patient characteristics are reported in Table 1. Assessors were blinded to treatment group.

Table 1 Baseline characteristics

	Prone position (13)	Supine position (13)	p
Age (years)[a]	56.1 ± 15.2	52.1 ± 18.5	0.55
BMI (kg/m²)[a]	23.5 ± 3.5	25.5 ± 3.8	0.17
Female sex, no. (%)	5 (38.5)	3 (23.1)	0.39
SAPS II score[b]	33.7 ± 13.0	35.1 ± 14.6	0.80
SOFA score	7.2 ± 3.7	7.8 ± 3.3	0.71
PaO_2/FiO_2 (mmHg)[b]	121 ± 36	114 ± 40	0.62
PEEP (cmH_2O)[b]	10.5 ± 2.5	10.1 ± 2.8	0.76
Cause of ARDS, no. (%)[b]			
Pneumonia (%)	8 (61.5)	8 (61.5)	1.00
Other (%)	5 (38.5)	5 (38.5)	

Data expressed as mean ± standard deviation

BMI body mass index calculated as weight in kilograms divided by height in meters squared, *SAPS II* Simplified Acute Physiology Score II, *PaO_2* arterial oxygen partial pressure, *FiO_2* fraction of inspired oxygen, *PEEP* positive end-expiratory pressure

[a] At time of 12-month follow-up evaluation
[b] At time of enrollment in the PSII study

Blood gas analysis

Arterial blood samples were obtained from the radial artery while the patient was sitting and breathing room air. Blood gas analysis was performed by using an automated blood gas measurement system (GEM® Premier™ 4000; Instrumentation Laboratory, Bedford, USA).

Pulmonary function studies

Pulmonary function tests were carried out as standard examination at a pulmonary function laboratory. Diffusion capacity was measured by the single-breath carbon-monoxide technique. All pulmonary function measurements were performed using a DLCO Spirometer (GANSHORN Medizin Electronic GmbH, Germany). Predicted values were generated according to CECA's prediction equation [29].

Walking test data were analyzed using VISION SpO_2 data management software.

Health-related quality of life

The SF-36 questionnaire consists of 36 validated items, covering eight general health aspects concerning physical

functioning, role physical, role emotional, vitality, general health, bodily pain, social functioning, and mental health [25]. The eight health aspects are defined as follows: physical functioning, the extent to which health limits physical activity; physical role, the extent to which physical health interferes with work or limits activity; pain, the intensity of pain and the effect of pain on patient's ability to work; general health, patient's own evaluation of his or her health outlook; vitality, the degree of energy the patient has; social functioning, the extent to which health or emotional problems interfere with work or activities; and mental health, general health. From these items, summary scores for physical and mental health are calculated. Scores ranging from 0 to 100 were computed for the eight dimensions. Higher scores indicate better health-related quality of life [25]. A 5-point change in SF-36 has been determined to be a clinically meaningful difference [30].

The SGRQ is a pulmonary disease-specific health-related quality of life questionnaire covering three domain: symptoms, activity, and impact on daily life [26]. The symptoms domain relates to respiratory symptoms and their frequency and severity; the activity domain relates to activities that cause or are limited by breathlessness; the impact domain covers a range of aspects concerned with social functioning and psychological disturbances resulting from airway disease. Scores range from 0 to 100, and lower scores indicate better pulmonary-specific health-related quality of life [26].

Quantitative lung CT scan analysis

High-resolution CT scan (HRCT) of the lungs was performed in all patients in supine position with the following parameters: 1 mm sections at 15 mm intervals, 140 kV, 240 mA from the lung apices to the bases. Images were reconstructed with a high-spatial-resolution algorithm for parenchymal analysis. The outline of the lungs was manually drawn in each image, and cross-sectional lung images were processed and analyzed using a custom-designed software package, as previously discussed [31]. The volume of lung regions with different degree of aeration, classified as not aerated (density between $+100$ and -100 Hounsfield units), poorly aerated (-101 and -500 H units), normally aerated (density between -501 and -900 H units), and overinflated (density between -901 and $-1,000$ H units), were computed and expressed as percentages of total lung weight [32].

Statistical analysis

Patient characteristics, pulmonary function, and health-related quality of life data are reported as median, mean ± standard deviation (SD), and interquartile range (25th and 75th percentiles). Wilcoxon rank-sum test and unpaired Student's t test were used for continuous variables and Fisher's exact test for categorical variables. Differences were considered significant for $p < 0.05$. All statistical tests were performed with SAS(c) version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

At the follow-up, 26 patients were evaluated. Median follow-up times were 12.8 (11–13) and 12.6 (11–13) months for the prone and supine group, respectively. The overall mortality rate at the follow-up was 60% (113 patients), of which 12% (14 patients) took place from 6 to 12 months. Mortality of the patients screened at 12 months was not different between the prone and supine group (9/38 versus 5/43, respectively, $p = 0.24$; Fig. 1).

Reasons for exclusion are outlined in Fig. 1. The patients evaluated did not have any baseline clinical differences compared with those not evaluated or compared with the total number of patients enrolled in the PSII study.

The descriptive baseline and hospital data for the evaluated patients are presented in Table 1. There were no significant differences in age, sex, initial illness severity (SAPS II score), or SOFA score between patients ventilated in supine versus prone position. There were no statistically differences in gas exchange or mechanical
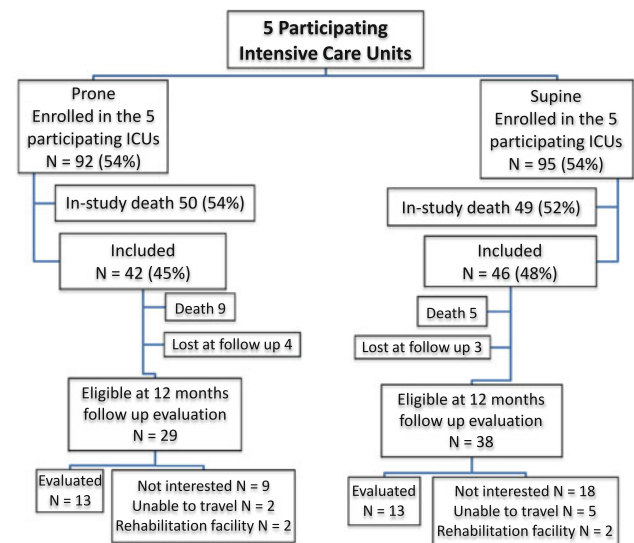

Fig. 1 Flowcharts of ARDS patients from enrollment to 12-month follow-up evaluation. Patients not interested in the study adduced as reasons general health and resumption of normal daily activities without difficulties or having moved to other cities

Table 2 Values for pulmonary function and arterial blood gases at 12-month follow-up evaluation

	Prone position (13)	Supine position (13)	p
FVC (% predicted)			
Median (interquartile range)	89.5 (80–103)	81.0 (77–90)	0.18
FEV$_1$ (% predicted)			
Median (interquartile range)	93.5 (81–104)	81.0 (70–93)	0.13
FEV$_1$/FVC (% predicted)			
Median (interquartile range)	101.5 (96–112)	101.2 (94–106)	0.40
TLC (% predicted)			
Median (interquartile range)	89.1 (77–99)	83.0 (78–90)	0.43
RV (% predicted)			
Median (interquartile range)	88.5 (79–115)	86.0 (75–91)	0.51
PaO$_2$ (mmHg)			
Mean ± SD	86.0 ± 8.5	93.6 ± 6.2	0.03
PaCO$_2$ (mmHg)			
Mean ± SD	37.2 ± 2.6	37.6 ± 3.8	0.75
pH			
Mean ± SD	7.40 ± 0.03	7.41 ± 0.02	0.54
Carbon monoxide diffusion (% predicted)			
Median (interquartile range)	99.5 (86–105)	103.5 (94–114)	0.56

FVC forced vital capacity, *FEV$_1$* forced expiratory volume in 1 s, *TLC* total lung capacity *RV* residual volume, *PaO$_2$* arterial oxygen partial pressure, *PaCO$_2$* arterial carbon dioxide partial pressure, *SD* standard deviation

ventilation during the first week of treatment between the groups.

Days of mechanical ventilation and length of intensive care stay in the prone and supine group were similar at 13 (8–28) versus 16 (10–23) days and 29 (16–45) versus 16 (10–23) days ($p = 0.22$ and $p = 0.15$), respectively.

At the follow-up, the mortality rate was not different between the prone versus supine group (64.1% versus 56.8%, respectively). However, from inclusion to follow-up, there was a trend for higher mortality in the prone compared with the supine group. Regarding pulmonary function, lung volumes were normal since the median values were always higher than 80% of predicted values, at similar levels in both groups (Table 2).

Arterial oxygenation was slightly higher in the supine compared with the prone group (Table 2); however, arterial oxygenation corrected for patient age [33] was similar between the two groups (90.2 ± 5.0 versus 88.4 ± 4.2 mmHg). None of the patients were receiving supplementary oxygen. There was not any difference in

arterial carbon dioxide or carbon monoxide diffusion capacity.

Distance walked in 6 min was similar between the two groups (Table 3), and in only one patient did arterial oxygenation fall below 90% during the 6-min walking test.

Table 3 shows the extension of parenchymal changes seen on HRCT. The mean amounts of not aerated, poorly aerated, and well-aerated lung regions were 8%, 16%, and 76% of total lung weight, being similar between the prone and supine group. The prone group had a higher amount of overaerated lung regions compared with the supine group. There was not any difference in the distribution of not or poorly aerated lung regions according to the sternal vertebral gradient.

Health-related quality of life is summarized in Table 4. The scores for all domains of SF-36 were similar to those of an age- and sex-matched control population. There were no significant differences between the prone and supine group in any of the SF-36 categories.

Table 3 Ability to exercise and CT patterns at 12-month follow-up evaluation

	Prone position (13)	Supine position (13)	p
Distance walked in 6 min (m)			
Median (interquartile range)	375 (335–445)	400 (350–450)	0.30
Percentage of predicted value (%)	71	73	0.58
Not aerated lung tissue (% of total lung weight)			
Mean ± SD	8.1 ± 3.1	7.3 ± 3.4	0.453
Poorly aerated lung tissue (% of total lung weight)			
Mean ± SD	15.3 ± 3.6	17.1 ± 4.9	0.518
Well-aerated lung tissue (% of total lung weight)			
Mean ± SD	64.0 ± 8.4	70.2 ± 8.4	0.052
Overaerated lung tissue (% of total lung weight)			
Mean ± SD	12.5 ± 6.5	5.3 ± 5.5	0.008

SD standard deviation

Table 4 Short Form-36 Questionnaire and St. George's Respiratory Questionnaire at 12-month follow-up evaluation

	Whole population ($n = 26$)			Treatment effect		
	Normal expected value[a]	Measured value	p-Value	Prone group ($n = 13$)	Supine group ($n = 13$)	p-Value
Short Form-36[b]						
Physical functioning	84 [72–91]	75 [40–90]	0.01	75 [50–90] (74.8)	80 [40–90] (83.8)	0.95
Role physical	73 [66–85]	75 [25–100]	0.08	75 [50–100] (72.6)	75 [25–100] (72.5)	0.75
Bodily pain	74 [68–82]	72 [42–100]	0.34	72 [42–100] (74.8)	61 [42–84] (73.6)	0.57
General health	62 [55–69]	70 [40–87]	0.89	72 [40–87] (58.6)	67 [42–77] (61.7)	0.89
Vitality	63 [59–65]	73 [55–85]	0.08	65 [45–85] (59.3)	75 [55–80] (63.9)	0.98
Social functioning	76 [75–78]	75 [63–88]	0.83	75 [50–88] (75.8)	75 [75–87.5] (78.3)	0.79
Role emotional	74 [66–78]	100 [33–100]	0.42	100 [33–100] (73.5)	100 [33–100] (73.5)	0.95
Mental health	65 [63–69]	72 [56–88]	0.41	72 [64–76] (64.7)	68 [56–88] (69.4)	0.83
St. George's Respiratory Questionnaire[c]						
Symptoms	12	15.4 [10.4–24.5]	N/A	15.1 [10.3–26.9] (12)	15.6 [10.8–21.4] (12)	0.83
Activity	9	35.7 [0.0–54.2]	N/A	30.3 [10.3–26.9] (9)	41.2 [0.0–56.3] (9)	1.00
Impacts	2	16.3 [4.0–32.9]	N/A	6.7 [4.0–32.7] (2)	22.2 [14.4–32.9] (2)	0.42
Total	6	25.3 [7.7–41.0]	N/A	13.3 [7.7–39.5] (6)	25.4 [10.3–42.7] (6)	0.72

Values expressed as mean [interquartile range] (normal value)
Standard deviations are not available
[a] The Italian normal values for Short Form-36 are from Apolone et al. [53]
[b] Higher score denotes better quality of life

[c] Lower score denotes better health-related quality of life. The normal St. George's Respiratory Questionnaire values are means derived from Davidson et al. [11]

Unlike in the SF-36, in both groups the SGRQ showed a slight, but significant, impairment of quality of life and a reduction in the level of activity due to respiratory disease compared with the control population. However, there were no significant differences between the prone and supine group concerning SGRQ score.

Discussion

The current study showed that (1) at follow-up in evaluated ARDS patients, pulmonary function, gas exchange, and lung CT scan analysis were within normal values; (2) SF-36 score was similar to that of healthy subjects, while SGRQ showed impairment of daily activity due to pulmonary disease; (3) there were no differences in any of the tested variables (except for overinflated tissue) between patients treated in prone or supine position.

Mortality rate and pulmonary function

As regards mechanical management of ALI/ARDS patients, only application of a low-tidal-volume strategy has been shown to significantly decrease the mortality rate [34]. However, based on the available data, also prone position has been advocated as a rescue maneuver to improve patient outcome [20–22], especially in the most severe ARDS patients [19, 21–23], due to its capability to reduce overall stress–strain [15–18] and ventilator-induced lung injury [14].

The intensive care mortality rate in ALI/ARDS patients can range between 31% and 65% [3, 35], depending on the severity of lung injury, the number of failed nonpulmonary organs, and the patient's underlying condition [36]. Moreover, ALI/ARDS patients can continue to present a higher mortality rate after intensive care discharge compared with non-ARDS mechanically ventilated patients [37, 38]. Angus et al. reported that mortality increased from 31% at 1 month to 45% at 6 months [5], while Herridge et al. showed an 11% mortality rate from discharge up to 1 year [4]. Similarly, in the present study, the mortality rate was 50% at 6 months and increased to 60% at 12 months. Unfortunately we do not know the causes of death during follow-up, thus we cannot explain whether this high mortality rate was primarily due to respiratory function impairment after acute respiratory failure or to nonpulmonary organ failure.

It was reported that impairment of pulmonary function, evaluated by spirometric test, can be a relatively common finding in surviving ARDS patients, being present in up to 70% of patients at 1 month [7, 39]. However, within the first year, pulmonary function, originally abnormal, can improve, but at 12 months, 20–50% of surviving ARDS patients can still present significant impairment in pulmonary function [4, 7–10] that usually does not ameliorate thereafter [39].

Contrary to these data, in our patients, pulmonary function was minimally impaired; median values of all spirometric tests were always higher than 80% of predicted values in the two groups.

Few studies have analyzed possible iatrogenic causes of persistence of abnormal lung function. Klein et al.

[40], in a group of patients with ARDS due to trauma, did not find any association between duration of mechanical ventilation and impairment of lung function. Ghio et al. [7] found a relationship between increase in pulmonary artery pressures and impairment in pulmonary function. Our patients received mechanical ventilation following the recommendation, which may have prevented ventilator-induced lung injury [41, 42], while mean duration of mechanical ventilation was similar to in previous studies [4, 7].

In addition to impairment on spirometric testing, reduction in DLCO has been found in surviving ARDS patients, with frequency between 40% and 80% [4, 7, 9, 10, 39, 43]. This persistent impairment in gas transfer is probably due to injury at capillary level, which promotes thickening in alveolar capillary interfaces, pulmonary fibrosis, and pulmonary vascular remodeling. Similarly to the spirometric data, DLCO and gas exchange were within the normal range values and without any difference between the two groups.

Evaluation of ability to walk for a distance is an inexpensive measure of physical function and is reduced in several diseases such as heart failure, obstructive lung disease, and neuromuscular disease [44, 45]. We found that the distance walked in the 6-min walking test was 10% lower than the predicted value. These data are similar to those previously reported by Herridge et al. [4] in ARDS survivors. Unfortunately we do not know whether this reduction could be due to dyspnea or to muscle weakness.

High-resolution CT scan

It was reported in surviving ARDS patients evaluated for lung morphology by lung CT scan after a period of 6–20 months that the reticular pattern was present in up to 80% of these patients [9, 46–48]. However, the mean extension of this injury was less than 10–15% of total lung volume [9, 46–48]. This reticular pattern is usually found in nondependent lung regions, reflecting the highly traumatizing effect of mechanical ventilation, i.e., higher overdistension–overstress, compared with dependent lung regions, in which consolidated/collapsed areas [9, 46, 48] may protect the lung from injury by mechanical ventilation. The relationship between development of lung fibrosis after ARDS and any possible risk factor is not straightforward. Some studies have found significant correlation between CT scan impairment and duration of mechanical ventilation, level of PEEP, and oxygen fraction [49, 50]. However, these data may only reflect greater severity of ARDS, which can be responsible per se for lung fibrosis [46].

Compared with previous studies in which only morphological visual analysis was done, we performed quantitative lung analysis of CT scan images to quantify lung alterations. In this analysis, four lung compartments are usually defined: normally aerated, poorly aerated (which is equivalent to ground-glass and reticular pattern), not aerated (which corresponds to collapsed and/or consolidated areas), and hyperinflated (which reflects overfilled lung regions) [32]. Poorly aerated lung regions accounted for a mean of 15% of total lung weight, without any difference between prone and supine group or between vertebral–dorsal distribution. Conversely, overaerated lung regions were significantly more present in the prone group, although this difference was not associated with any functional effect.

Health-related quality of life

Despite a consensus statement in 1994 suggesting that future outcome evaluation in intensive care should incorporate assessment of quality of life [38], it was reported that less than 2% of all critical care studies evaluated HRQL [51]. The most commonly used scale for evaluating the HRQL is the Short Form-36 (SF-36) general health survey. SF-36 is a generic questionnaire which assesses eight items from physical functioning to mental health [52]. It was previously shown that surviving ARDS patients presented significantly lower SF-36 scores at 1 year compared with comparably ill or injured patients without ARDS [4, 5, 8–11]. This reduction in HRQL was related to alteration in pulmonary function [10], impairment in muscle function [4], and duration of mechanical ventilation [13]. However, some authors suggested assessing severity of illness in surviving ARDS patients by means of St. George's Respiratory Questionnaire (SGRQ) [26]. A difference in total SGRQ score of about 4 points would indicate a clinically significant difference between populations [26]. SGRQ is a specific pulmonary disease questionnaire validated in airway disease [26]. Although the SGRQ has never been validated in ARDS patients, in whom dyspnea may also be related to extrapulmonary diseases and the relationship between laboratory measurements and symptoms might be very complex, significant alteration in all SGRQ domains in surviving ARDS patients has been reported to different extents [8, 9, 37], with older patients presenting significantly greater impairments [9]. In this study, SF-36 scores were within the normal range while SGRQ reported significant reduction in domain scores that evaluated activity (extent to which symptoms limit daily activity) and impact of the disease on patients' social and emotional lives [53]. Thus, although our patients presented normal pulmonary function and SF-36 scores, they reported pulmonary symptoms that reduced daily activities, suggesting that the patients' subjective perception of symptoms is not only related to physiological measurements [54, 55].

Limitations

Possible limitations of the current study are the small number of patients enrolled (39%, 26/67) compared with the eligible patients and the absence of any data regarding the number of patients who received rehabilitation before the follow-up. Although the evaluated patients did not have any baseline clinical differences compared with the nonevaluated patients (i.e., those lost to follow-up) or compared with the total sample of enrolled patients in the prone–supine study (PSII), we cannot exclude the possibility of substantial selection bias.

Conclusions

The present study showed that the mortality rate at 1 year after ARDS was high. However, in this small group of ARDS survivors, lung CT scan and pulmonary function were not different in patients treated in prone versus supine position.

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