Impact of lung compliance on neurological outcome in patients with acute respiratory distress syndrome following out-of-hospital cardiac arrest

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Abstract

Background

Acute respiratory distress syndrome (ARDS) following cardiac arrest is common and associated with in-hospital mortality. We aimed to investigate whether lung compliance during targeted temperature management is associated with neurological outcome in patients with ARDS after out-of-hospital cardiac arrest (OHCA).

Methods

This observational study was conducted in the emergency intensive care unit from January 2011 to April 2019 using data from a prospective patient registry. Adult patients (age ≥18 years) who survived non-traumatic OHCA and subsequently developed ARDS based on the Berlin definition were included. Mechanical ventilator parameters such as peak inspiratory pressure, tidal volume, minute ventilation, positive end expiratory pressure, and compliance were recorded for 7 days or until death, and categorized as maximum, median, and minimum. The primary outcome was favorable neurological outcome defined as Cerebral Performance Category score 1 or 2 at hospital discharge.

Results

Of 246 OHCA survivors, 119 (48.4%) patients developed ARDS. A favorable neurologic outcome was observed in 23 (19.3%). Patients with favorable outcome had significantly higher lung compliance (38.6 cm H 2 O vs 27.5 cm H 2 O), lower inspiratory pressure (12.0 cm H 2 O vs 16.0 cm H 2 O), and lower peak inspiratory pressure (17.0 cm H 2 O vs 21.0 cm H 2 O) than those with poor neurologic outcome (all P <0.01). In time-dependent cox regression models, all maximum (hazard ratio [HR] 1.05, 95% confidence interval [CI] 1.03-1.08), minimum (HR 1.08, 95% CI 1.04 – 1.12), and median (HR 1.06, 95% CI 1.03-1.10) compliances were independently associated with good neurologic outcome. Median compliance > 31.4 mL/cm H 2 O at day 1 had the highest area under the receiver operating characteristic curve (0.732) with positive predictive value of 90%.

Conclusion

Lung compliance may be an early predictor of neurologic intact survival in patients with ARDS following cardiac arrest.
Introduction
Despite recent advances in prevention and resuscitation, the mortality and morbidity of cardiac arrest (CA) remain high [1-3]. Postcardiac arrest syndrome (PCAS), the major cause of death in CA patients, is characterized by systemic post-arrest ischemia-reperfusion injury with activation of the inflammatory response; its in-hospital mortality is > 50% [4]. PCAS can affect multiple organs. Pulmonary involvement manifests as acute respiratory distress syndrome (ARDS), which often results in poor clinical outcome [5]. The authors postulated that ARDS accelerates ischemic brain injury caused by aggravating the mismatch of supply and demand of oxygen (O$_2$) and carbon dioxide (CO$_2$).
Mechanical ventilation is the cornerstone of managing and treating ARDS. However, it can also cause parenchymal lung damage through over-distension and cyclic alveolar opening and closing [6-8]. Lung-protective ventilation utilizing lower tidal volume (V$_T$) and higher positive end-expiratory pressure (PEEP) has been shown to improve survival in numerous trials [9]. In addition, fluid restriction, use of neuromuscular blocking agents, and prone ventilation reduce mortality in severe ARDS patients [10]. Therefore, discovering accurate prognostic markers of ARDS severity is essential to facilitate risk stratification and apply novel therapeutic interventions to improve outcomes. Since lung compliance correlates with the aerated functional component of the pulmonary system [11], we hypothesized that lung compliance, an easily measured clinical variable, could be an important prognostic marker than V$_T$ or PEEP in patients with ARDS after CA.
This study aims to investigate whether lung compliance during targeted temperature management (TTM) is associated with neurological outcome in patients with ARDS after out-of-hospital cardiac arrest (OHCA).

Material And Methods
Study design and population
This retrospective study used prospectively collected data that were entered into the Asan Medical Center emergency intensive care unit OHCA patient registry from January 2011 to April 2019. Asan Medical Center is a tertiary referral academic center in Seoul, Korea with 2,700 beds and approximately 130,000 Emergency Department patient visitations annually. The study was approved...
by the institutional research ethics committee; the requirement for informed consent was waived
because the study was retrospective in nature.

The OCHA registry consists of all adults (age ≥ 18 years) admitted to the emergency intensive care
unit with non-traumatic CA. Patients with the following criteria are excluded from the registry: age <
18 years, presumed traumatic CA, “do not resuscitate” status, transfer to other hospital, and decline
proper treatment. This study enrolled patients from the registry who developed ARDS within 48 hours
after CA. We identified ARDS patients using the Berlin definition. In brief, we found those who had two
consecutive arterial blood gas analysis (ABGA) with partial pressure of arterial oxygen (PaO2)/fraction
of inspired oxygen (FiO2) (P/F) ratio < 300 in a mechanically ventilated patient with bilateral
radiographic opacities. All chest radiographs were reviewed by radiologists. We excluded patients
who received extracorporeal membrane oxygenation (ECMO) during or after cardiopulmonary
resuscitation (CPR). Moreover, we exclude the cases of cardiogenic pulmonary edema which were
defined as left ventricle ejection fractions below 30% based on transthoracic echocardiography.

**Routine post-cardiac arrest care protocol**

For all patients, CPR and post-resuscitation care, including coronary intervention and TTM, were
administered in accordance with the current Advanced Cardiac Life Support guidelines. TTM consists
of three phases: induction, maintenance, and rewarming. TTM was induced with a cooling device with
self-adhesive hydrogel coated pads (Arctic Sun Energy Transfer Pads, Medivance Corp, Louisville, CO).
The target temperature of 33–36°C was maintained for 24 hours (maintenance phase), and patients
were then rewarmed to 36.5°C at a rate of 0.25°C/hr. Temperature was monitored using an
esophageal probe and continuous intravenous propofol and opioids (morphine or remifentanil) were
administered for sedation and analgesia during TTM. ABGA was performed in all patients just after
return of spontaneous circulation (ROSC) and repeated every 2 ± 1 hours. In addition, all patients
were mechanically ventilated in pressure-controlled mode and every change of ventilator parameter,
such as V_T, PEEP, inspiratory pressure, peak inspiratory pressure (PIP), plateau pressure (P_plat),
respiratory rate (RR), and minute ventilation was recorded in the electronic medical record by
experienced intensive care unit nurses.
Definitions of variables
As part of the protocol, we performed a chest radiograph at least once in a day and obtained ABGA every hour during induction and every 2 hours during the maintenance period. Using the results of ABGA and ventilator parameters, P/F ratio and compliance (\(V_T/(P_{plat}-PEEP)\)) were calculated. In addition, we categorized the calculated measures, including \(V_T\), minute volume, and compliance as maximum, median, and minimum for 7 days or until death, whichever came first. If there were missing ABGA or ventilator variable data, the means of each variable were filled before the statistical analysis.

We extracted demographic and baseline clinical data from the registry, including age, sex, and underlying diseases. In addition, we gathered other CA data according to the Utstein Style recommendations, including location, witnessed arrest, bystander CPR, duration of CPR, initial documented rhythm, presumed arrest cause, and initial electrocardiography rhythm. The Sequential Organ Failure Assessment (SOFA) score was determined from the initial data on admission. The primary outcome of the study was the association of lung compliance with favorable neurologic outcome at discharge (defined as Cerebral Performance Category (CPC) score of 1 or 2). The CPC score is a well-validated outcome measure for comatose patients after CPR. Other ventilator parameters were compared between ARDS and non-ARDS patients as secondary outcomes.

Statistical analyses
Statistical analyses were performed using SPSS Statistics for Windows version 23 (SPSS Inc., Chicago, Illinois, United States). Continuous variables were expressed as median with interquartile range. Categorical variables were analyzed with the chi-square or Fisher’s exact tests. The normality of distribution was examined using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for comparisons between the good and poor neurologic outcome groups. To examine the association between ARDS and poor neurologic outcome, we used a Cox regression model with maximum, median, and minimum lung compliances as a time-varying covariate. The diagnostic accuracy of lung compliances was compared by using receiver operating characteristic (ROC) curves and calculating the area under the curve (AUC). In addition, sensitivity, specificity, positive predictive value, negative
predictive value, positive likelihood ratio, and negative likelihood ratio were calculated by standard statistical methods. The optimal cut-off value of compliances for neurologic outcome was determined with the Youden index (sensitivity + specificity - 1) from the ROC analysis. P < 0.05 was considered significant.

Results
During the study period, a total of 295 registry patients survived CA, and 246 were analyzed after excluding 49 who received ECMO and had cardiogenic pulmonary edema. Among these, 119 patients (48.4%) developed ARDS within 48 hours (20 mild, 48 moderate, 51 severe). Of the 119 patients with ARDS, 23 (19.3%) had a favorable neurologic outcome at discharge.

Baseline characteristics
The baseline characteristics of the study population are presented in Table 1. The median age was 66 years with male predominance (66.4%). Hypertension (47.9%) was the most frequent comorbidity followed by diabetes (37.8%). These did not differ significantly between the good and poor neurologic outcome groups. The favorable neurologic outcome group had a significantly higher proportion of patients with a shockable initial rhythm (64.3% vs 16.0%; p < 0.001), presumed cardiac cause (65.2% vs. 41.7%; p = 0.061), shorter CPR duration (11.0 vs. 31.5 minutes; p < 0.001), and shorter mechanical ventilator duration. Other comorbidities and characteristics of CA did not differ significantly between the two groups.
| Characteristics          | Total (n = 119) | Poor outcome (n = 96) | Good outcome (n = 23) | p-value |
|--------------------------|-----------------|-----------------------|-----------------------|---------|
| Age                      | 66.0 (55.0–78.0) | 67.0 (55.0–77.0)      | 66.0 (57.0–80.0)      | 0.874   |
| Male                     | 79 (66.4)       | 62 (64.6)             | 17 (73.9)             | 0.468   |
| Past history             |                 |                       |                       |         |
| Previous ACS             | 26 (21.8)       | 18 (18.8)             | 8 (34.8)              | 0.525   |
| Previous PCI             | 17 (14.3)       | 12 (12.5)             | 5 (21.7)              | 0.318   |
| Hypertension             | 57 (47.9)       | 49 (51.0)             | 8 (34.8)              | 0.173   |
| Diabetes mellitus        | 45 (37.8)       | 39 (40.6)             | 6 (26.1)              | 0.237   |
| CKD                      | 23 (19.3)       | 20 (20.8)             | 3 (13.0)              | 0.560   |
| Malignancy               | 12 (10.1)       | 10 (10.4)             | 2 (8.7)               | 1.000   |
| Characteristics of Cardiac arrest |             |                       |                       |         |
| Witnessed arrest         | 86 (72.3)       | 68 (70.8)             | 18 (78.3)             | 0.607   |
| Bystander CPR            | 75 (63.0)       | 61 (63.5)             | 14 (60.9)             | 0.814   |
| Shockable rhythm         | 22 (23.2)       | 13 (16.0)             | 9 (64.3)              | < 0.001 |
| Cardiac cause            | 55 (46.2)       | 40 (41.7)             | 15 (65.2)             | 0.061   |
| Total CPR time (min)     | 29.0 (14.0–41.0) | 31.5 (21.3–43.8)      | 11.0 (4.0–21.0)       | < 0.001 |
| SOFA at admission        | 12.0 (11.0–15.0) | 12.0 (11.0–15.0)      | 11.5 (10.5–15.0)      | 0.654   |
| MV duration (day)        | 7.0 (3.0–9.0)   | 7.0 (2.0–9.0)         | 7.0 (5.0–13.0)        | 0.050   |

Data are presented as median with interquartile ranges.

Abbreviations: ARDS = acute respiratory distress syndrome; CA = cardiac arrest; MI = myocardial infarction; ACS = acute coronary syndrome; PCI = percutaneous coronary intervention; CKD = chronic kidney disease; LC = liver cirrhosis; CPR = cardiopulmonary resuscitation; MV = mechanical ventilator.

Mechanical ventilator parameters on admission and neurologic outcome

The result of ABGA and mechanical ventilator settings on admission for each patient group are summarized in Table 2. Good neurologic outcome group showed lower PaCO\(_2\) level (46.0 mmHg vs 57.0 mmHg; p = 0.005) and higher pH (7.2 vs. 7.0, p = 0.001) than that of poor outcome group.

Regarding ventilator settings, patients with good outcome showed significantly lower requirements of inspiratory pressure (12 cm H\(_2\)O vs. 16 cm H\(_2\)O; p < 0.001), PIP (17.0 cm H\(_2\)O vs. 21.0 cm H\(_2\)O; p < 0.001), and respiratory rate (18.0/min vs. 20.0/min; p = 0.013). Moreover, compliance was significantly higher in the favorable outcome group (38.6 mL/cm H\(_2\)O vs. 27.5 mL/cm H\(_2\)O; p < 0.001).
Comparisons of ABGA and mechanical ventilator parameters on admission in the ARDS patients

| Parameters                      | Total (n = 119) | Poor outcome (n = 96) | Good outcome (n = 23) | p-value |
|---------------------------------|----------------|----------------------|-----------------------|---------|
| pH                              | 7.0 (6.9–7.2)  | 7.0 (6.8–7.2)        | 7.2 (7.0–7.3)         | 0.001   |
| PaO₂, mmHg                      | 86.0 (68.4–115.8) | 86.0 (70.4–115.8) | 77.1 (62.5–137.4) | 0.287   |
| PaCO₂, mmHg                     | 54.0 (40.0–73.0) | 57.0 (43.5–76.0) | 46.0 (32.6–60.5) | 0.005   |
| PEEP, cm H₂O                    | 5.0 (4.0–8.0)   | 5.0 (4.0–8.0)        | 5.0 (4.0–7.0)         | 0.638   |
| Inspiratory pressure, cm H₂O   | 15.0 (12.0–18.0) | 16.0 (14.0–18.0) | 12.0 (12.0–13.5) | < 0.001 |
| Pplat, cm H₂O                   | 21.0 (17.3–25.8) | 21.0 (18.0–22.0) | 17.0 (16.0–20.0) | < 0.001 |
| Respiratory rate                | 20.0 (18.0–22.0) | 20.0 (18.0–22.0) | 18.0 (15.0–20.0) | 0.013   |
| Tidal volume, ml                | 427.0 (367.0–497.0) | 420.0 (360.0–489.5) | 458.0 (395.5–545.0) | 0.053   |
| Compliance, ml/cm H₂O           | 29.7 (21.8–36.9) | 27.5 (21.6–34.0) | 38.6 (33.1–46.2) | < 0.001 |
| Minute ventilation, L/min       | 8.2 (7.6–10.4)  | 8.8 (7.7–10.3)       | 8.8 (6.5–10.7)        | 0.609   |

Abbreviations: ABGA = arterial blood gas analysis; ARDS = acute respiratory distress syndrome; PEEP = positive end expiratory pressure; Pplat = plateau pressure.

Compliance and good neurologic outcome

Table 3 shows the time-dependent regression model for predicting the neurologic outcome. All of the maximum, median, and minimum lung compliances were independent risk factors for favorable neurologic outcome at discharge. Among these variables, the minimum value was significantly associated with the neurologic outcome (adjusted hazard ratios (HR) 1.08, 95% confidence interval (CI) 1.04–1.12; p < 0.001).

Table 3

| Variables | Univariate | Multivariate |
|-----------|------------|--------------|
|           | HR         | 95% CI       | p-value | Adjusted HR | 95% CI       | p-value |
| Shockable | 3.12       | 1.21–8.03    | 0.018   | 2.06        | 0.73–5.81    | 0.170   |
| Cardiac cause | 1.54       | 0.05–4.41    | 0.418   |             |             |         |
| CPR duration | 0.95       | 0.92–0.99    | 0.012   | 0.95        | 0.90–1.00    | 0.039   |
| MV duration | 1.25       | 1.10–1.43    | < 0.001 | 1.21        | 1.11–1.33    | < 0.001 |
| Compliance Maximum | 1.05       | 1.03–1.06    | < 0.001 | 1.05        | 1.03–1.08    | < 0.001 |
| Compliance Minimum | 1.06       | 1.04–1.09    | < 0.001 | 1.08        | 1.04–1.12    | < 0.001 |
| Compliance Median  | 1.05       | 1.03–1.07    | < 0.001 | 1.06        | 1.03–1.10    | < 0.001 |

Abbreviations: HR = hazard ratio; CI = confidence interval.

Differences of day-1 compliance for neurologic outcome

Overall trends of maximum, minimum, and median compliances by neurologic outcome group over time are shown in additional file [see Additional file 1]. For all seven compliances, day 1 showed significant large differences between the good and poor outcome groups that decreased over 7 days (Fig. 1). To analyze the diagnostic value of each compliance, ROC curves were calculated (Fig. 2).

Median compliance at day 1 had the highest AUC (0.732), followed by maximum (0.702), and
minimum (0.629). After calculating the cut-off values for each compliance using the Youden index, sensitivity and specificity were calculated (Table 4). Maximum compliance above 32.5 at day 1 presented the highest specificity (72.0%), positive likelihood ratio (2.48), and positive predictive value (90.4%) than that of other compliances.

| Compliance | Sensitivity | Specificity | PLR | NLR | PPV  | NPV  |
|------------|-------------|-------------|-----|-----|------|------|
| D1 max > 32.5 | 69.5        | 72.0        | 2.48| 0.42| 90.4 | 38.3 |
| D1 min > 28.6 | 64.9        | 66.7        | 1.95| 0.53| 88.4 | 32.7 |
| D1 median > 31.4 | 59.3        | 66.7        | 1.78| 0.61| 90.0 | 24.5 |

Abbreviations: D = day; PLR = positive likelihood ratio; NLR = negative likelihood ratio; PPV = positive predictive value; NPV = negative predictive value.

Discussion

In this registry-based study, we found that 19.3% (23/119) of patients who developed ARDS after successful resuscitation from CA had a favorable neurologic outcome. Lung compliance was associated with neurologic intact survival by time-dependent regression analysis and had the highest predictive value for good neurologic outcome at day 1. Our neurologic intact survival rate of ARDS patients is lower than previous studies which reported rates ranging 29.8% – 53.2% [12–14]. This is consistent with a recent finding from Johnson et al [5], who reported 50% mortality among patients who developed ARDS compared with 32% in patients who did not. Even though the clinical impact of ARDS on PCAS patients is not fully known, the occurrence of ARDS after CA may have a negative impact on both survival and recovery of neurologic impairments [15–17]. In addition, the incidence of ARDS following CA has not been well reported; it varies from 5–65% depending on how ARDS is defined [8, 18]. However, it may be common due to the overlap between the pathophysiology of ARDS and PCAS. Lung contusion, ischemia, and exposure to high-dose oxygen during CPR and following reperfusion after CA, a profound systemic inflammatory response, ventilator-associated injuries, secondary infections, and systemic immune reactions could contribute the development of ARDS[19, 20]. Thus, early recognition of ARDS after CPR may allow for prompt initiation of treatment known to improve outcome, such as low tidal volume ventilation, prone positioning, and continuous neuromuscular blockade [21–23].

Although it is well-established to avoid hyperoxemia and hypocapnia, clinical evidence to guide
mechanical ventilation strategy in patients with PCAS is limited and inconsistent. Talmor et al. performed a retrospective study using a time-weighted average of $V_T$ and suggested that lower $V_T$ was an independent factor in achieving a good neurologic outcome [24]. To prevent ventilator-induced lung injury, low $V_T$ and optimized PEEP may also be essential in patients with PCAS. However, specific $V_T$ and PEEP settings cannot be recommended because different lung stress or strain levels can be present in patients with the same severity status of ARDS after CA [25]. Therefore, lung compliance calculation and the patient’s ARDS status could be more informative to reflect the degree of lung injury than $V_T$ and PEEP.

In the good neurologic outcome group, we found that lung compliance, whether maximum, minimum, or median, was associated with neurologic outcome at discharge. The compliance difference between groups was dramatic in the first 24 hours after admission and diminished over time. These results imply that the recovery of lung and brain injury is determined in the initial phase, and management of PCAS should focus on the first 24 hours. This study could not confirm whether ventilator settings are simply markers of disease severity or related to prognosis, however, in either case, lung compliance provides more information than $V_T$ and PEEP regarding outcome. Furthermore, strategies to optimize lung compliance may have a role in treatment.

This study had several limitations. First, because of its retrospective design, our results may not be generalized to other circumstances. Second, the diagnosis of ARDS was based on P/F ratio, chest images, and echocardiography, ARDS incidence might be overestimated because hydrostatic pulmonary edema could not be found based on these examinations. However, the Berlin definition allowed some flexibility, including combining cardiogenic pulmonary edema because it is impossible to exclude all pure cardiogenic causes, even when measuring cardiac function through echocardiography. Moreover, some post-cardiac arrest patients can have concomitant ARDS and cardiogenic pulmonary edema. Third, we excluded patients who received ECMO, had a terminal illness, or declined proper management, which may have introduced selection bias. Fourth, we did not consider other confounding factors, such as quality of initial CPR, combined infections, and use of
vasopressors that may have influenced the results. Finally, the sedative and neuromuscular blocking agent dosages for each patient and abdominal pressure were not controlled, which could have had an impact on calculated compliance.

Conclusion
Lung compliance may be an early independent predictor of neurologic intact survival in ARDS patients following CA.

List Of Abbreviations
ABGA, arterial blood gas analysis
ARDS, acute respiratory distress syndrome
AUC, area under the curve
CA, cardiac arrest
CI, confidence intervals
CPC, cerebral performance category
CPR, cardiopulmonary resuscitation
ECMO, extracorporeal membrane oxygenation
ED, Emergency Department
FiO$_2$, fraction of inspired oxygen
HR, hazard ratio
IHCA, in-hospital cardiac arrest
OHCA, out-of-hospital cardiac arrest
PaO$_2$, partial pressure of arterial oxygen
PCAS, post-cardiac arrest syndrome
PEEP, peak end-expiratory pressure
PIP, peak inspiratory pressure
P$_{\text{plat}}$, plateau pressure
ROC, receiver operating characteristic
ROSC, return of spontaneous circulation
RR, respiratory rate

SOFA, sequential organ failure assessment

TTM, target temperature management

$V_T$, tidal volume

Declarations

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None.

Authors’ contribution

J.S.K. participated in drafting, data collecting and analyzing. Y.J.K. and M.Y.K. participated in conceptualizing and data collecting. S.M.R., C.H.S. and S.A. read and revised the manuscript. W.Y.K. supervised, read, and approved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Reviewed and approved by Asan Medical Center IRB with waiver of written consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures
Figure 1

Differences of compliances on day 1 depend on neurologic outcomes
Figure 2

ROC comparisons of maximum, minimum, and median day-1 compliance

Supplementary Files

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Additional file 1.pdf