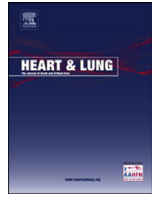




Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

Intraoperative initiation of a modified ARDSNet protocol increases survival of septic patients with severe acute respiratory distress syndrome

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ARTICLE INFO

Article history:

Received 24 March 2018

Received in revised form 12 June 2018

Accepted 14 June 2018

Available online xxx

Keywords:

Sepsis

Acute respiratory distress syndrome

Acute care anesthesiology

Emergency surgery

ARDSNet protocol

Outcome

ABSTRACT

Purpose: To assess the intraoperative initiation and feasibility of a modified NIH-NHLBI ARDS Network Mechanical Ventilation Protocol (mARDSNet protocol) in septic patients with severe ARDS.

Materials and methods: This prospective observational study included consecutive adult septic patients with severe ARDS who underwent emergency abdominal surgery prior to intensive care unit (ICU) admission. The primary outcome was survival to hospital discharge and at 90 days. Secondary outcomes were intraoperative adverse events and ICU length of stay.

Results: Seven patients were included. A statistically significant difference in lung compliance [$\epsilon=0.150$, $F(1.053, 3.158)=31.098$, $p=0.010$] and driving pressure [$\epsilon=0.263$, $F(1.844, 5.532)=7.042$, $p=0.031$] was observed with time, while plateau pressure did not change significantly during surgery [$\epsilon=0.322$, $F(2.256, 6.769)=1.920$, $p=0.219$]. Also, PEEP values were constantly increased during surgery [$\epsilon=0.252$, $F(1.766, 5.297)=9.994$, $p=0.017$], with the highest values being observed towards the end of the procedure. No intraoperative adverse events were observed. Mean (\pm SD) ICU length of stay was 10.43 (± 2.64) days, while all patients survived to hospital discharge and at 90 days.

Conclusions: The intraoperative implementation of our mARDSNet protocol is feasible and may increase the survival of septic patients with severe ARDS if initiated prior to ICU admission.

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Introduction

Acute respiratory distress syndrome (ARDS) remains a life-threatening complication characterized by diffuse lung injury.¹ The incidence of ARDS varies widely; it ranges from 1.5 cases per 100,000 to nearly 79 cases per 100,000, with European countries reporting a lower incidence than USA.² Although about 5% of mechanically ventilated patients meet the diagnostic criteria, the mortality rate also varies widely based on severity, age, and the presence of underlying medical conditions. Severe sepsis remains the most common etiology of ARDS; in these patients, ARDS develops rapidly and is associated with high mortality.³

Until now, no single treatment has been shown to modify the underlying pathological process of ARDS.¹ The majority of the patients diagnosed with ARDS present it in its moderate form, with an in-hospital mortality rate around 40%.⁴ The general rule worldwide is that patients *in extremis* are admitted to the intensive care unit (ICU) without delay for organ support and monitoring, even if the cause of ARDS necessitates surgical intervention.^{5,6} However, the delay in surgical treatment may evolve to irreversible organ injury and increase the risk of death.

Treatment of the underlying surgical condition is essential for the course of ARDS and patient outcome and therefore, emergency surgery should ideally precede ICU admission.⁷ Although intraoperative management of septic patients with ARDS is considered as extremely challenging, to the best of our knowledge there are no data and this issue warrants further investigation. The aim of this study was to assess the intraoperative initiation and feasibility of a modified NIH-NHLBI ARDS Network Mechanical Ventilation Protocol (mARDSNet protocol) in septic patients with severe ARDS.

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Material and methods

Study design and setting

This prospective study included consecutive adult patients (≥ 18 years) with septic shock complicated by severe ARDS who were admitted between November 2013 and May 2017. The study complies with the Declaration of Helsinki,⁸ while ethical approval for this study was provided by the Hospital's Ethics Committee (No 7645). Written informed consent was obtained from all subjects or a legal surrogate.

The study was undertaken in a busy urban medical center in Attica, Greece covering an area of 50.4 km² with a population of about 1,700,000 residents. In this Institution, the Department of Anesthesiology provides state-of-the art clinical care to more than 10,000 patients annually in all aspects of anesthesia and perioperative medicine.

Patients

All patients with septic shock complicated by severe ARDS who underwent emergency abdominal surgery prior to ICU admission were included in the study. Acute respiratory distress syndrome was defined according to the "Berlin definition" as an acute form of diffuse lung injury occurring in patients with a predisposing risk factor, meeting the following criteria: onset within one week of a known clinical insult or new/worsening respiratory symptoms; presence of bilateral opacities on chest X-ray, not fully explained by effusion, lobar/lung collapse, or nodules; and diagnosis of respiratory failure not fully explained by cardiac failure or fluid overload.⁹ Acute respiratory distress syndrome was classified as mild ($200 < \text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg), moderate ($100 < \text{PaO}_2/\text{FiO}_2 \leq 200$ mmHg) or severe ($\text{PaO}_2/\text{FiO}_2 \leq 100$ mmHg).¹⁰

Anesthetic management

The acute care anesthesiology team was alerted at the time of diagnosis, about 30 min prior to the surgery. Preoperative management began in the Emergency Department or the Ward and aimed at improving the physiology of patients and determining when the patient is optimized for surgery.

All patients were intubated in the operating room using a rapid sequence induction protocol. Pre-oxygenation was achieved with the placement of a nasal cannula together with a non-rebreather face mask, both at 15 L/min, five minutes prior to induction. Induction and paralysis were achieved with a combination of midazolam, fentanyl, ketamine, propofol, and succinylcholine. When paralysis ensued, the non-rebreather face mask was removed and laryngoscopy was performed with the nasal cannula at its place to facilitate apneic oxygenation. Laryngoscopy and intubation proceeded in standard fashion, while the position of the endotracheal tube was confirmed by auscultation and capnography/capnometry. Maintenance of anesthesia and muscle relaxation was achieved using the standard doses of intravenous propofol, fentanyl, remifentanyl, and cis-atracurium modified in patients with organ insufficiency.

Initial ventilator settings were volume control ventilation, constant flow, fraction of inspired oxygen (FiO_2) 1.0, tidal volume 6 ml/kg predicted bodyweight, PEEP 5 cmH₂O, and inspiration to expiration ratio 1:2. Ideal body weight was computed in men as $50 + (0.91 \times [\text{height in centimeters} - 152.4])$ and in women as $45.5 + (0.91 \times [\text{height in centimeters} - 152.4])$.¹¹ Respiratory rate was adjusted according to the last known arterial blood gas analysis to maintain end-tidal carbon dioxide 3–5 mmHg lower than the partial pressure of carbon dioxide (PaCO_2) in order to prevent abrupt hemodynamic changes. At 10 min of mechanical ventilation, severe ARDS

was confirmed using a specific threshold of the arterial partial pressure of oxygen (PaO_2)/ FiO_2 ratio measured with a minimum requirement of PEEP 5 cm H₂O.⁹ Then, tidal volume was increased to 8 ml/kg and all ventilation parameters were eventually adjusted according to the NIH-NHLBI ARDS Network Mechanical Ventilation Protocol.¹¹ Optimal levels of PEEP were identified using a test of two or three PEEP levels 15 min apart after hemodynamic stabilization, without concomitant changes in oxygenation fraction or hemodynamic treatment.¹⁰ The respiratory rate was adjusted to maintain acceptable minute ventilation and carbon dioxide removal. In order to recruit the lung during surgery, we used sustained inflation and a static increase in airway pressure (40–45 cmH₂O) applied for 20–40 sec when necessary.¹²

An arterial and a central venous catheter were inserted in all patients and respiratory and hemodynamic parameters, including cardiac output (CO), stroke volume variation (SVV), and central venous pressure (CVP), were monitored using a Datex Ohmeda S/5 Anesthesia Monitor (Datex-Ohmeda Inc, WI, USA) and a Vigileo-Flo-Trac third-generation system (Edwards Lifesciences, Unterschleißheim, Germany). Arterial blood samples were analyzed immediately using an analysis machine (Radiometer ABL800 Flex Blood Gas Analyzer, Radiometer Medical A/S, Brønshøj, Denmark). After the end of the surgical procedure, the patients were transferred to the ICU with their abdomen closed.

Data collection

Data analysis was based on predefined data points on a prospective data collection form. An independent Data and Safety Monitoring research staff monitored safety, ethical, and scientific aspects of the study. Surviving patients or their next-of-kin were contacted by telephone at 90 days after hospital discharge. For patients who were unable to be contacted by telephone, attempts were made to contact relatives who may have contact with the patient.

Study endpoints

The primary outcome was survival to hospital discharge and at 90 days. Secondary outcomes were intraoperative adverse events and ICU length of stay.

Statistical analysis

Study variables were analyzed using the Statistical Package for Social Sciences (IBM SPSS; version 24.0 for Windows IBM Corp.). The assumption of Normal distribution of the collected data was tested using the Kolmogorov–Smirnov test and presented as mean \pm SD (SE). The inter time points differences were tested by repeated measures ANOVA. In case of significant differences, the use of Bonferroni post hoc test allowed us to discover which specific means differed. Significance was accepted at $p < 0.05$.

Results

Of the 18 septic patients with severe ARDS, 7 (39%) underwent emergency abdominal surgery and were ventilated using the mARDS-Net protocol until ICU admission (Figure 1, Table 1). The remaining patients or their surrogates refused any surgical intervention and were directly admitted to the ICU for standard ARDS management and care. The source of sepsis and the Charlson Age-Comorbidity Index of our patients are presented in Table 2.

A repeated measures ANOVA with a Greenhouse–Geisser correction ($\epsilon = 0.291$) determined that FiO_2 values did not differ statistically significantly during the surgery [$F(2.040, 6.119) = 3.000, p = 0.123$]. A statistically significant difference in lung compliance

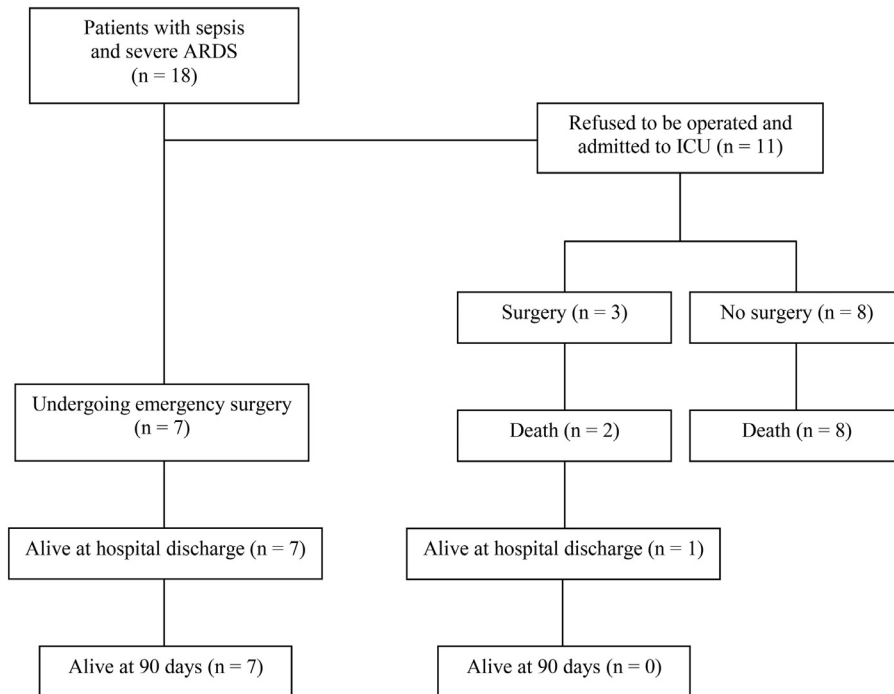


Fig. 1. Flow chart of the study. ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

$[\varepsilon=0.150, F(1.053, 3.158)=31.098, p=0.010]$ and driving pressure $[\varepsilon=0.263, F(1.844, 5.532)=7.042, p=0.031]$ was observed with time, while plateau pressure values did not change significantly during surgery $[\varepsilon=0.322, F(2.256, 6.769)=1.920, p=0.219]$. In our study, PEEP values were constantly increased with time $[\varepsilon=0.252, F(1.766, 5.297)=9.994, p=0.017]$, with the highest values being observed towards to the end of the procedure (Supplementary data file).

The hemodynamics parameters of the study are depicted in Table 3. A repeated measures ANOVA with a Greenhouse-Geisser correction ($\varepsilon=0.259$) determined that intraoperative mean arterial pressure (MAP) values did not change statistically with time $[F(1.814, 5.441)=4.881, p=0.063]$. Cardiac output decreased during surgery but remained within normal values $[\varepsilon=0.246, F(1.720, 5.160)=53.106, p<0.0005]$. Central venous pressure values were also decreased during surgery $[\varepsilon=0.158, F(1.105, 3.315)=25.793, p<0.011]$, while intraoperative fluid administration was averaged at 82 ml/h (lactated Ringer's), with most of the total volume being given within the first hour $[\varepsilon=1.000, F(1.000, 3.000)=27.349, p=0.014]$. Urine output was constantly increased with time but did not reach statistical

significance $[\varepsilon=0.374, F(2.616, 15.698)=0.320, p=0.785]$. Similarly, SVV values did not differ statistically significantly during surgery $[\varepsilon=0.200, F(1.397, 4.192)=4.255, p=0.102]$.

In our study, we did not observe any intraoperative adverse event or cardiac arrest and all patients were transported to the ICU after the end of the surgery. Mean (\pm SD) ICU length of stay was 10.43 (\pm 2.64) days, while all patients survived to hospital discharge and at 90 days. Of the 11 patients who were initially refused surgery, 3 (27%) were operated at 48 h post-ICU admission after obtaining consent from their next-of-kin. Of them, only 1 (33%) survived to hospital discharge (ICU length of stay: 21 days), but not at 90 days.

Discussion

In this study, we report for the first time the feasibility of an intraoperative mARDSNet protocol and the 100% survival rate in patients with septic shock complicated by severe ARDS who underwent emergency abdominal surgery prior to ICU admission.

Our patients required progressively increased levels of PEEP in order to improve their oxygenation, but this did not significantly reduce the need for high FiO₂. Selection of PEEP was based on gas exchange and hemodynamics and was adjusted by one of the ARDS-Net PEEP/FiO₂ tables.^{11–14} Although this protocolized approach has

Table 1
Patient characteristics

Characteristics	Value
N (%)	7 (100)
Male, n (%)	5 (71.4)
Age, y (mean \pm SD)	59.43 \pm 10.06
APACHE II (mean \pm SD)	26.39 \pm 4.14
SOFA (mean \pm SD)	31.14 \pm 4.10
Active Smoker, n (%)	4 (57.1)
Diabetes mellitus, n (%)	1 (14.3)
Hypertension, n (%)	3 (42.9)
Kidney disease, n (%)	1 (14.3)
CAD, n (%)	2 (28.6)
Heart failure, n (%)	1 (14.3)
Asthma/COPD, n (%)	2 (28.6)
ICU length, d (mean \pm SD)	10.43 \pm 2.64
Survival to hospital discharge, n (%)	7 (100)
Survival 90 days, n (%)	7 (100)

Table 2
Source of infection and severity of disease

Source of sepsis, n (%)	Number of patients (%)	CACI (Estimated related risk of death)	APACHE II	SOFA
Abdominal abscesses	1 (14%)	8 (19.37)	25	9
Peritonitis	1 (14%)	8 (19.37)	29	11
Pancreatic necrosis	1 (14%)	10 (19.37)	29	11
Peritonitis	1 (14%)	8 (19.37)	33	14
Abdominal wall necrotizing fasciitis	1 (14%)	10 (19.37)	30	13
Mesenteric ischemia	1 (14%)	9 (19.37)	35	15
Pyosalpinx	1 (14%)	11 (19.37)	37	17

CAI, Charlson Age-Comorbidity Index.

Table 3
Hemodynamic and metabolic parameters of the patients after intubation

	30 min	60 min	90 min	120 min	150 min	180 min	210 min	240 min	p value
FiO ₂ (SE)	0.79±0.27 (0.10)	0.69±0.16 (0.06)	0.67±0.14 (0.05)	0.69±0.13 (0.05)	0.7±0.15 (0.06)	0.69±0.13 (0.05)	0.73±0.1 (0.05)	0.75±0.13 (0.06)	0.123
Respiratory Rate (SE), min ⁻¹	19±4.76 (1.8)	20.14±4.6 (1.74)	20.43±3.36 (1.27)	21±3.27 (1.23)	22.57±2.14 (0.81)	22.14±1.68 (0.63)	23.75±0.5 (0.25)	24±0.82 (0.41)	0.075
PEEP (SE), cmH ₂ O Min-max	14.86±5.76 (2.18) 8.00–22.00	15.14±5.4 (2.04) 8.00–22.00	15.71±4.96 (1.87) 8.00–22.00	16±4.16 (1.57) 10.00–22.00	18.43±3.46 (1.30) 12.00–22.00	18.29±3.15 (1.19) 14.00–22.00	19.5±1.91 (0.96) 18.00–22.00	21±2 (1.00) 20.00–24.00	0.017
Plateau pressure (SE), cmH ₂ O Min-max	28.29±0.76 (0.29) 27.00–29.00	28±0.58 (0.22) 27.00–29.00	27±1.53 (0.58) 24.00–28.00	27.57±1.81 (0.69) 24.00–29.00	28.43±0.79 (0.30) 27.00–29.00	27.71±0.49 (0.18) 27.00–28.00	28.25±0.5 (0.25) 28.00–29.00	28.75±0.5 (0.25) 28.00–29.00	0.219
Lung compliance (SE), cmH ₂ O Min-max	28.29±4.15 (1.57) 23.00–34.00	30±4.51 (1.70) 24.00–36.00	33±4.76 (1.80) 26.00–40.00	36.29±3.4 (1.29) 32.00–42.00	39±3.16 (1.20) 34.00–43.00	43±2.16 (0.82) 40.00–46.00	43.75±2.22 (1.11) 41.00–46.00	47.25±5.97 (2.98) 43.00–56.00	0.010
Driving pressure* (SE), cmH ₂ O	13.43±5.44 (2.06)	12.85±5.3 (2.00)	11±4.2 (1.59)	11.29±3.77 (1.43)	10±3.27 (1.23)	9.43±2.82 (1.07)	8.75±1.5 (0.75)	7.75±1.89 (0.95)	0.031
Heart rate (SE), beats/min	107.9±14.5 (5.50)	102.1±5.7 (2.15)	100.6±4.16 (1.57)	98.29±3.64 (1.38)	97.43±5.68 (2.15)	96.29±5.31 (2.00)	94.25±2.5 (1.25)	94±0.82 (0.41)	0.064
Systolic arterial pressure (SE), mmHg	96.71±11.1 (4.18)	108.6±9.18 (3.47)	116.6±7.72 (2.92)	123.14±8.6 (3.25)	120.1±7.15 (2.70)	121.43±4.5 (1.70)	119.75±3.6 (1.78)	119.50±7.6 (3.80)	0.065
Diastolic arterial pressure (SE), mmHg	59.43±6.55 (2.48)	67.57±4.08 (1.54)	70.57±5.19 (1.96)	72.86±5.7 (2.15)	68.86±7.95 (3.00)	72.71±5.79 (2.19)	69.5±4.65 (2.33)	69±5.89 (2.94)	0.087
Mean arterial pressure (SE), mmHg	71.81±7.94 (3.00)	81.21±5.36 (2.03)	85.87±5.45 (2.06)	89.57±6.34 (2.40)	85.93±7.12 (2.69)	88.93±5.16 (1.95)	86.23±3.6 (1.80)	85.8±6.25 (3.12)	0.063
Central venous pressure (SE), mmHg	14.57±6.27 (2.37)	13.43±5.41 (2.05)	11.14±5.24 (1.98)	9.42±4.86 (1.84)	8.29±4.39 (1.66)	7.14±3.76 (1.42)	5.5±4.12 (2.06)	4.75±3.86 (0.24)	<0.0005
Cardiac output (SE), L/min	6.49±0.5 (1.19)	6.09±0.47 (0.18)	5.7±0.39 (0.15)	5.37±0.63 (0.24)	5.39±0.35 (0.13)	5.16±0.31 (0.12)	5.03±0.43 (0.21)	4.88±0.47 (0.24)	<0.0005
Stroke volume variation (SE), %	10.29±1.6 (0.61)	10.42±1.27 (0.48)	11±0.58 (0.22)	11.43±1.51 (0.57)	12.14±0.69 (0.26)	13±1.15 (0.43)	13±0.00 (0.00)	12.5±0.58 (0.29)	0.102
ETCO ₂ (SE), mmHg	39.71±4.15 (1.57)	40.14±4.3 (1.62)	41.29±3.55 (1.34)	41.86±3.02 (1.14)	40.86±3.8 (1.44)	40.43±2.51 (0.95)	40.75±0.5 (0.25)	40±0.82 (0.41)	0.433
Urine output (SE), mL	50.3±17.64 (6.67)	53.6±13.14 (4.97)	52.86±9.51 (3.60)	55±7.07 (2.67)	52.86±8.09 (3.06)	53.57±7.48 (2.83)	57.14±12.2 (4.61)	54.28±7.88 (2.97)	0.785
pH (SE)	7.27±0.09 (0.03)	NA	NA	7.29±0.05 (0.02)	NA	7.31±0.04 (0.02)	NA	7.33±0.01 (0.00)	0.790
PaO ₂ (SE), mmHg	60.93±4.99 (1.89)	NA	NA	102.5±25.9 (9.78)	NA	134.1±33.22 (12.56)	NA	159±28.7 (14.32)	0.003
PaCO ₂ (SE), mmHg	41.77±3.03 (1.14)	NA	NA	43.63±3.14 (1.19)	NA	42.89±0.87 (0.33)	NA	42.75±0.96 (0.48)	0.467
SaO ₂ (SE), %	88.11±2.95 (1.12)	NA	NA	92.94±4.91 (1.85)	NA	96.13±3.71 (1.40)	NA	96.85±2.56 (1.28)	0.020
PaO ₂ :FiO ₂ (SE), mmHg	88.1±36.5 (13.80)	NA	NA	156±57.9 (21.87)	NA	207.2±85.66 (32.37)	NA	218±59 (29.49)	0.006
Lactate (SE), mmol/L	4.38±2.43 (0.92)	NA	NA	4.39±2.37 (0.89)	NA	4.30±1.95 (0.74)	NA	5.08±1.44 (0.72)	0.199
Base deficit (SE), mEq/L	-8.30±3.85 (1.42)	NA	NA	-6.48±2.82 (1.07)	NA	-7.08±1.27 (0.48)	NA	-6.78±2.23 (1.11)	0.359
HCO ₃ (SE), mmol/L	13.85±4.54 (1.71)	NA	NA	16.7±2.56 (0.97)	NA	16.61±0.59 (0.23)	NA	17.08±0.31 (0.15)	0.272
Hb (SE), mg/dL	10.63±1.52 (0.57)	NA	NA	10±1.13 (0.43)	NA	9.59±0.98 (0.37)	NA	8.9±0.36 (0.18)	0.246

FiO₂, inspired oxygen fraction; SE, standard error; PEEP, positive end-expiratory pressure; ETCO₂, end-tidal carbon dioxide; NA, non-available; PaO₂, arterial partial pressure of oxygen; PaCO₂, arterial partial pressure of carbon dioxide; SaO₂, oxygen saturation; PaO₂/FiO₂, ratio of arterial oxygen partial pressure to fractional inspired oxygen; HCO₃, bicarbonate; Hb, hemoglobin.

* Plateau pressure – PEEP.

been associated with inadequate venous return and barotrauma, a trend towards improved mortality using the high-PEEP table has been reported.^{15,16} However, other studies demonstrated no benefit or an association with further lung injury.^{7,17–19} Of note, even in high PEEP values, the driving pressure seems to be the factor most associated with mortality.^{20,21} In our study, the progressive increase of PEEP was accompanied by a constant plateau pressure, which decreased driving pressure with time and kept the lung recruited.^{7,10,20,21}

Despite the potent deleterious effects of hyperoxia,^{10,22} we decided to maintain the relatively increased PaO₂ levels due to the possible intraoperative complications that could have been suddenly occurred. In such a case, e.g. bleeding, hypoxemia would have aggravated cardiovascular stress, limiting oxygen delivery to the tissues. In addition, the manual recruitment maneuvers may have resulted in consistent effects in terms of recruitability and gas exchange, further increasing PaO₂.^{23,24} Nevertheless, our patients were not hyperoxemic for more than 10 h, as PEEP/FiO₂ levels started to decrease within a few hours after ICU admission. Moreover, as the safety of permissive hypercapnia appears questionable and a PaCO₂ greater than 50 mm Hg has been independently associated with increased mortality,²⁵ we chose to keep a physiological PaCO₂ resulting in a pH of >7.30.²⁶

Although judicious fluid administration targeting a CVP of 6–9 mmHg (8–12 cmH₂O) is a commonly used strategy during the initial resuscitation of septic patients, our patients had a high initial CVP, possibly due to prehospital liberal fluid resuscitation. In addition, they were ventilated using very high values of PEEP, which may aggravate hemodynamics by increasing both right ventricular intracavitary pressure and afterload.²⁶ Considering that vasodilation was the main pathophysiological disturbance of shock in our patients, MAP was individually optimized using norepinephrine infusion (0.01–3 mcg/kg/min). Furthermore, all patients were actively de-resuscitated using furosemide infusion (0.1 mg/kg/h), targeting a lower CVP (~2 mmHg) in order to optimize mean circulatory filling pressure and enhance venous return. Several studies have indicated that minimizing fluid administration and administering diuretics to create a negative fluid balance are advantageous in the first few days when treating ARDS.²⁷ Our results indicate that this may be feasible even in the demanding environment of the operating room. A conservative approach and increased alveolar fluid clearance have been associated with an increase in ventilator-free days, no increased risk of organ failure, and decreased ICU length of stay.^{26–29}

In addition, we used changes in dynamic markers (CO and SVV) to monitor volume changes and responsiveness and to guide volume therapy during the surgery. Research has shown that SVV is influenced by various factors, such as tidal volume, intra-abdominal pressure, position, and vasoactive drugs, limiting its use in patients with sepsis and/or ARDS.³⁰ In our study, however, CO and SVV were progressively decreased and increased with time, respectively, while SVV was transiently decreased after a fluid bolus in four patients at 60 min and one patient at 180 min post-intubation. Our results indicate that SVV corresponded to the changes in intravascular volume, which is in agreement with increasing evidence suggesting that a change in SVV may represent a change in intravascular volume status irrespectively of the presence of influencing factors.^{31–34} Nevertheless, further research is necessary to evaluate SVV as a relative pre-load responsiveness indicator in this fragile population.

We believe that the open abdomen was one of the most significant factors that contributed to the improvement of respiratory function by facilitating mechanical ventilation and (at a lesser extent) fluid removal via evaporation from the surgical wound.³⁵ The open abdomen may increase chest wall compliance and possibly functional residual capacity and plateau pressure, shifting the lower inflection point on the pressure-volume curve to the left and decreasing alveolar opening pressure.³⁶ The resulting reduction in gas flow to the

dependent areas of the lung was possibly offset by the increased PEEP in our patients.³⁷ Of note, the open abdomen could be the reason for the well-tolerated intraoperative progressive increase in PEEP. Also, considering that the increase in pulmonary interstitial fluid often occurs because of poor lymphatic drainage due to the PEEP-induced increase in intrathoracic pressure, the open abdomen may have improved lymphatic fluid draining from the pulmonary interstitial space.³⁶

In our study, we did not observe any intraoperative adverse event, while mean (±SD) ICU length of stay in mARDSNet patients was 10.43 (±2.64) days, which is significantly decreased compared to the literature.^{4,7,14,38} Moreover, all mARDSNet patients survived to hospital discharge and at 90 days. In the future, the open abdomen may prove a promising treatment strategy in both surgical and non-surgical patients with severe ARDS and refractory hypoxemia. Our study may serve as an excellent starting point for further research in a field where survival rates still need to improve. However, although the management of patients with open abdomen can be safely achieved in the ICU,³⁹ the procedure is associated with several complications.⁴⁰ Consequently, high quality randomized trials are required prior to the implementation of the open abdomen in daily practice.

This study has several limitations. First, the sample size is small and a larger sample size may have revealed additional findings or different survival rates. However, we included consecutive patients admitted within a period of 4 years. Of the 3 ICU patients who were operated at 48 h post-admission, only one survived to hospital discharge. Therefore, it was impossible to include a comparison group. Despite the aforementioned limitations, this is the first study reporting 100% survival in patients with septic shock complicated by severe ARDS who underwent emergency abdominal surgery.

Conclusion

The intraoperative implementation of our mARDSNet protocol is feasible and may increase the survival of septic patients with severe ARDS if initiated prior to ICU admission. The open abdomen may prove a promising treatment strategy in both surgical and non-surgical patients with severe ARDS due to its potent advantages in respiratory function.

Acknowledgments

Nothing to acknowledge.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: None

Supplementary data

Supplementary data related to this article can be found, in the online version, at [doi:10.1016/j.hrtlung.2018.06.011](https://doi.org/10.1016/j.hrtlung.2018.06.011).

References

- Fuller BM, Mohr NM, Hotchkiss RS, Kollef MH. Reducing the burden of acute respiratory distress syndrome: the case for early intervention and the potential role of the emergency department. *Shock*. 2014;41:378–387.
- Confalonieri M, Salton F, Fabiano F. Acute respiratory distress syndrome. *Eur Respir Rev*. 2017;26 160116.
- Mikkelsen ME, Shah CV, Meyer NJ, Gaijeski DF, Lyon S, Miltiades AN, et al. The epidemiology of acute respiratory distress syndrome in patients presenting to the emergency department with severe sepsis. *Shock*. 2013;40:375–381.
- Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. LUNG SAFE Investigators, ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315:788–800.

5. Brienza N, Giglio MT, Marucci M, Fiore T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit Care Med.* 2009;37:2079–2090.
6. Ranucci M, Ballotta A, Castelvécchio S, Baryshnikova E, Brozzi S, Boncilli A. Surgical and Clinical Outcome Research (SCORE) Group. Intensive care unit admission parameters improve the accuracy of operative mortality predictive models in cardiac surgery. *PLoS One.* 2010;5:e13551.
7. Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. *N Engl J Med.* 2017;377:562–572.
8. van Belle G, Mentzelopoulos SD, Aufderheide T, May S, Nichol G. International variation in policies and practices related to informed consent in acute cardiovascular research: results from a 44 country survey. *Resuscitation.* 2015;91:76–83.
9. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. ARDS Definition Task Force. *Acute respiratory distress syndrome: The berlin definition.* *JAMA.* 2012;307:2526–2533.
10. Chiumello D, Brochard L, Marini JJ, Slutsky AS, Mancebo J, Ranieri VM, et al. Respiratory support in patients with acute respiratory distress syndrome: an expert opinion. *Crit Care.* 2017;21:240.
11. NIH-NHLBI ARDS Network, <http://www.ardsnet.org/> [accessed: 12 December 2017].
12. Umbrello M, Formenti P, Bolgiagli L, Chiumello D. Current Concepts of ARDS: A Narrative Review. *Int J Mol Sci.* 2016;18:64.
13. Treschan TA, Malbouisson LM, Beiderlinden M. Intraoperative mechanical ventilation strategies to prevent postoperative pulmonary complications in patients with pulmonary and extrapulmonary comorbidities. *Best Pract Res Clin Anaesthesiol.* 2015;29:341–355.
14. Weiss CH, McSparron JJ, Chatterjee RS, Herman D, Fan E, Wilson KC, et al. Summary for Clinicians: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome Clinical Practice Guideline. *Ann Am Thorac Soc.* 2017;14:1235–1238.
15. Cannon JW, Gutsche JT, Brodie D. Optimal Strategies for Severe Acute Respiratory Distress Syndrome. *Crit Care Clin.* 2017;33:259–275.
16. Putensen C, Theuerkauf N, Zinserling J, Wrigge H, Pelosi P. Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. *Ann Intern Med.* 2009;151:566–576.
17. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al. Lung Open Ventilation Study Investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA.* 2008;299:637–645.
18. Al Mercat, JC Richard, Vielle B, Jaber S, Osman D, Diehl JL, et al. Expiratory Pressure (Express) Study Group. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 2008;299:646–655.
19. Cavalcanti AB, EA Suzumura, Laranjeira LN, Paisani DM, Damiani LP, Guimarães HP, et al. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs. Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA.* 2017;318:1335–1345.
20. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med.* 2015;372:747–755.
21. Neto AS, Hemmes SN, Barbas CS, Beiderlinden M, Fernandez-Bustamante A, Futier E, et al. PROVE Network Investigators. Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data. *Lancet Respir Med.* 2016;4:272–280.
22. Radermacher P, Maggiore SM, Mercat A. Fifty Years of Research in ARDS. Gas Exchange in Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med.* 2017;196:964–984.
23. Borges JB, Okamoto VN, Matos GF, Caramez MP, Arantes PR, Barros F, et al. Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2006;174:268–278.
24. Borges JB, Carvalho CR, Amato MB. Lung recruitment in patients with ARDS. *N Engl J Med.* 2006;355:319–320.
25. Nin N, Muriel A, Peñuelas O, Brochard L, Lorente JA, Ferguson ND, et al. VENTILA Group. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. *Intensive Care Med.* 2017;43:200–208.
26. Vieillard-Baron A, Matthay M, Teboul JL, Bein T, Schultz M, Magder S, et al. Experts' opinion on management of hemodynamics in ARDS patients: focus on the effects of mechanical ventilation. *Intensive Care Med.* 2016;42:739–749.
27. Cutts S, Talboys R, Paspula C, Prempeh EM, Fanous R, Ail D. Adult respiratory distress syndrome. *Ann R Coll Surg Engl.* 2017;99:12–16.
28. Silversides JA, Major E, Ferguson AJ, Mann EE, McAuley DF, Marshall JC, et al. Conservative fluid management or dereuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. *Intensive Care Med.* 2017;43:155–170.
29. Grissom CK, Hirshberg EL, Dickerson JB, Brown SM, Lanspa MJ, Liu KD, et al. National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network. Fluid management with a simplified conservative protocol for the acute respiratory distress syndrome. *Crit Care Med.* 2015;43:288–295.
30. Kong R, Liu Y, Mi W, Fu Q. Influences of different vasopressors on stroke volume variation and pulse pressure variation. *J Clin Monit Comput.* 2016;30:81–86.
31. Fu Q, Duan M, Zhao F, Mi W. Evaluation of stroke volume variation and pulse pressure variation as predictors of fluid responsiveness in patients undergoing protective one-lung ventilation. *Drug Discov Ther.* 2015;9:296–302.
32. De Broca B, Garnier J, Fischer MO, Archange T, Marc J, Abou-Arab O, et al. Stroke volume changes induced by a recruitment maneuver predict fluid responsiveness in patients with protective ventilation in the operating theater. *Medicine (Baltimore).* 2016;95:e4259.
33. Teboul JL, Monnet X. Pulse pressure variation and ARDS. *Minerva Anesthesiol.* 2013;79:398–407.
34. Huang CC, Fu JY, Hu HC, Kao KC, Chen NH, Hsieh MJ, et al. Prediction of fluid responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and high positive end-expiratory pressure. *Crit Care Med.* 2008;36:2810–2816.
35. Voldby AW, Brandstrup B. Fluid therapy in the perioperative setting—a clinical review. *J Intensive Care.* 2016;4:27.
36. Christensen M, Craft J. The cardio-respiratory effects of intra-abdominal hypertension: Considerations for critical care nursing practice. *Intensive Crit Care Nurs.* 2018;44:53–58.
37. Pelosi P, Quintel M, Malbrain ML. Effect of intra-abdominal pressure on respiratory mechanics. *Acta Clin Belg.* 2007;62(Suppl 1):78–88.
38. Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. *N Engl J Med.* 2017;377:562–572.
39. Fitzpatrick ER. Open Abdomen in Trauma and Critical Care. *Crit Care Nurse.* 2017;37:22–45.
40. Sartelli M, Abu-Zidan FM, Ansaloni L, Bala M, Beltrán MA, Biffi W, et al. The role of the open abdomen procedure in managing severe abdominal sepsis: WSES position paper. *World J Emerg Surg.* 2015;10:35.