○ Annals of Intensive Care

RESEARCH

External chest-wall compression in prolonged COVID-19 ARDS with low-compliance: a physiological study

Luca Bastia[1], Emanuele Rezoagli[2,3], Marcello Guarnieri[4], Doreen Engelberts[5], Clarissa Forlini[4], Francesco Marrazzo[4], Stefano Spina[4], Gabriele Bassi[4], Riccardo Giudici[4], Martin Post[5], Giacomo Bellani[2,3], Roberto Fumagalli[2,4], Laurent J. Brochard[6*†] and Thomas Langer[2,4†]

Abstract

Background: External chest-wall compression (ECC) is sometimes used in ARDS patients despite lack of evidence. It is currently unknown whether this practice has any clinical benefit in patients with COVID-19 ARDS (C-ARDS) characterized by a respiratory system compliance (C_{rs}) < 35 mL/cmH$_2$O.

Objectives: To test if an ECC with a 5 L-bag in low-compliance C-ARDS can lead to a reduction in driving pressure (DP) and improve gas exchange, and to understand the underlying mechanisms.

Methods: Eleven patients with low-compliance C-ARDS were enrolled and underwent 4 steps: baseline, ECC for 60 min, ECC discontinuation and PEEP reduction. Respiratory mechanics, gas exchange, hemodynamics and electrical impedance tomography were recorded. Four pigs with acute ARDS were studied with ECC to understand the effect of ECC on pleural pressure gradient using pleural pressure transducers in both non-dependent and dependent lung regions.

Results: Five minutes of ECC reduced DP from baseline 14.2 ± 1.3 to 12.3 ± 1.3 cmH$_2$O ($P < 0.001$), explained by an improved lung compliance. Changes in DP by ECC were strongly correlated with changes in DP obtained with PEEP reduction ($R^2 = 0.82$, $P < 0.001$). The initial benefit of ECC decreased over time (DP = 13.3 ± 1.5 cmH$_2$O at 60 min, $P = 0.03$ vs. baseline). Gas exchange and hemodynamics were unaffected by ECC. In four pigs with lung injury, ECC led to a decrease in the pleural pressure gradient at end-inspiration [2.2 (1.1–3) vs. 3.0 (2.2–4.1) cmH$_2$O, $P = 0.035$].

Conclusions: In C-ARDS patients with C_{rs} < 35 mL/cmH$_2$O, ECC acutely reduces DP. ECC does not improve oxygenation but it can be used as a simple tool to detect hyperinflation as it improves C_{rs} and reduces P_{pl} gradient. ECC benefits seem to partially fade over time. ECC produces similar changes compared to PEEP reduction.

Keywords: COVID-19, ARDS, Respiratory mechanics, Mechanical ventilation, Ventilator-induced lung injury, Chest-wall compression, Driving pressure, Gas exchange

---

*Correspondence: laurent.brochard@unityhealth.to
†Laurent J. Brochard and T. Langer share the senior authorship
6 Interdepartmental Division of Critical Care Medicine, University of Toronto, Keenan Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, 209 Victoria Street, Room 4-08, Toronto, ON M5B 1T8, Canada
Full list of author information is available at the end of the article

Background

SARS-CoV-2 can lead to severe respiratory failure (C-ARDS) with some clinical and radiological characteristics that match the presentation of acute respiratory distress syndrome (ARDS) [1–3]. The management of mechanical ventilation of C-ARDS does not differ much

Bastia *et al. Annals of Intensive Care*   (2022) 12:35

Page 2 of 10

from classic ARDS, with general aims to maintain adequate gas exchange and prevent ventilator-induced lung injury (VILI) with protective ventilation with low tidal volume (V_t), low driving pressure (DP) and by the use of prone position [4–7]. A subset of patients with C-ARDS suffers from a significant reduction in respiratory system compliance (C_{rs}); this seems to be especially represented in C-ARDS patients needing prolonged mechanically ventilation due to unresolving respiratory failure [8, 9]. Due to this decrease in C_{rs}, even low tidal volumes (i.e., below 6 mL/kg) often produce high DP values given the existing relationship between DP and C_{rs} (i.e., DP $= V_t/C_{rs}$) [4]. Recent reports also mentioned the paradoxical positive effects of different supine body positions as well as chest or abdominal compression on respiratory mechanics in such patients [10–14].

In patients with prolonged C-ARDS and low C_{rs} at higher risk of VILI, we used the application of an external chest-wall compression (ECC) [10–13]. We hypothesized that this could reduce regional hyperinflation and reduce the pleural pressure gradient. We, therefore, decided to conduct a prospective physiological study.

The primary aim of the study was to determine if the application of ECC in patients with prolonged C-ARDS and low C_{rs} leads to a decrease of the DP and would indicate the presence of regional hyperinflation. We hypothesized that ECC can reduce ventral hyperinflation improving C_{rs} and reduce DP. Secondary aims were (1) to assess the consequences of ECC on ventilation distribution, partitioned respiratory mechanics, shunt fraction and dead space, and (2) to compare the effect of ECC and PEEP reduction. Besides respiratory mechanics static measurements, esophageal pressure (P_{es}) and electrical impedance tomography (EIT) were analyzed to understand partitioned respiratory mechanics and regional distribution of ventilation during the protocol. Moreover, we performed a preclinical study in a porcine model of acute ARDS in which ECC was applied and pleural pressure (P_{pl}) catheters were employed to test the possibility that ECC decreases the P_{pl} gradient.

Materials and methods
Human study
This single center physiological study was approved by the institutional review board (Comitato etico Milano Area 3, # 179-30032021). Informed consent was obtained according to Italian regulations. Patients admitted to the COVID-19 ICU (Rossini) of the ASST Grande Ospedale Metropolitano Niguarda, Milan for C-ARDS were enrolled. The study was performed on a convenience sample of 11 patients.

Study protocol

- Inclusion criteria were the following: (1) > 18 years; (2) diagnosis of C-ARDS (laboratory confirmation of SARS-CoV-2 infection and concomitant ARDS according to Berlin definition [15]); (3) mechanically ventilated (Evita V800, Dräger, Lübeck, Germany) with sedation and myorelaxation in volume-controlled mode; (4) protective V_t (≤ 6 mL/kg) and (5) $C_{rs} \leq 35$ ml/cmH$_2$O on clinical settings.
- Exclusion criteria were: (1) Pregnancy; (2) hemodynamic instability; and (3) Contra-indication to electrical impedance tomography (EIT) positioning (e.g., trauma, burns, pace-maker, defibrillator).

The study protocol had four steps (Additional file 2: Figure E1): (1) at baseline (before the positioning of a weight on the chest wall), we ensured that hemodynamics was stable; then, during an expiratory hold maneuver, we performed a brief static chest compression with a 5-L saline bag, and recorded the change in P_{aw} determined by this compression (Additional file 2: Figure E2). (2) ECC, with a 5-L bag placed in the middle of the thorax using the sternum as a landmark, for 60 min; (3) ECC discontinuation, 10 min without compression; and (4) PEEP reduction from baseline by the same amount of static pressure developed by the saline bag (step 1).

At enrollment, clinical ventilator settings were used. No standardized protocol to set PEEP was available in the ICU; therefore, PEEP was set upon clinician's decision in a tertiary referral hospital.

During all steps, the patients were placed in supine flat position (0° trunk inclination) to standardize every measurement [16] and the ventilator settings were unchanged (except for PEEP in step 4). No recruitment maneuvers were performed.

Before the protocol was started, a 5 Fr esophageal balloon (Cooper surgical, Trunbull, CT, USA) was positioned in 9 out of 11 patients enrolled in the study to partition respiratory mechanics. The proper position of the esophageal balloon was ensured [17]. Patient hemodynamics was monitored by a central line and invasive arterial pressure.

At the end of each step, and after 5, 30 and 60 min of step 2 (ECC), we performed expiratory and inspiratory holds to obtain static measurements of airway (P_{aw}) and esophageal pressure (P_{es}). The distribution of tidal volume between ventral (non-dependent, regions of interest $1+2$) and dorsal (dependent, regions of interest $3+4$) lung areas was assessed through the analysis of

Bastia *et al. Annals of Intensive Care*   (2022) 12:35

Page 3 of 10

EIT data (PulmoVista 500, Dräger, Lübeck, Germany) to obtain a regional V_t as previously described [18, 19]. In addition, end-expiratory lung impedance (EELI, a surrogate of end-expiratory lung volume [20]) was analyzed by EIT [21]. The following variables were calculated:

- Respiratory system Driving pressure or DP = Plateau Pressure (P_{plat}) − Total PEEP (set PEEP + intrinsic PEEP).
- Respiratory system compliance or $C_{rs} = V_t$/DP.
- Regional C_{rs} = Regional V_t derived from EIT/DP.
- Transpulmonary pressure (absolute value) or $P_L = P_{aw} − P_{es}$.
- Lung compliance or $C_{lung} = V_t/(P_L$ inspiration − P_L expiration).
- Chest-wall compliance or $C_{cw} = V_t/(P_{es}$ inspiration − P_{es} expiration).

P_{aw} and P_{es} waveforms as well as EIT data were prospectively recorded and stored for offline analysis.

Arterial and central venous blood samples were obtained to assess gas exchange and to calculate shunt fraction at baseline, at the end of step 2 (60 min of ECC), at step 3 and step 4. Shunt fraction was calculated as follows: $(C_cO_2 − C_aO_2)/(C_cO_2 − C_vO_2)$, where C_cO_2 represents the O_2 content of capillary blood, C_aO_2 the arterial O_2 content and C_vO_2 the O_2 content of venous blood. Alveolar dead space was calculated as follows: $(P_aCO_2 − P_{Et}CO_2)/P_aCO_2$, where P_aCO_2 is the arterial partial pressure of carbon dioxide (CO_2) and $P_{Et}CO_2$ represents the end-tidal CO_2 value.

Our primary endpoint was the DP change after the application of an ECC. We hypothesized that ECC would produce a decrease in DP.

Secondary endpoints were: change in chest-wall compliance (C_{cw}); change in lung compliance (C_{lung}); change in regional C_{rs} (i.e., of non-dependent and dependent lung); change in gas exchange, shunt fraction and dead space after ECC.

Animal study

We performed an experimental porcine study using ECC in a two-hit lung injury model. The aim of the study was to measure directly the effect of ECC on pleural pressure. Ventral and dorsal P_{pl} were, therefore, directly measured to understand the effect of ECC on P_{pl} gradient, differentiating between non-dependent and dependent lung areas.

The experiments were conducted in the animal facility of The Hospital for Sick Children Hospital (Toronto, ON, Canada). All experimental procedures followed the guidelines of the Canadian Council on Animal Care and were approved by the Animal Care Committee, Research Institute, The Hospital for Sick Children (protocol number 46420).

Animal preparation

Four healthy Yorkshire pigs (32.6 ± 2.1 kg) were sedated and paralyzed. Pigs were intubated and mechanically ventilated in volume-controlled mode in supine position. An esophageal catheter (Nutrivent; Sidam, Mirandola, Italy) was inserted to record P_{es} and positioned as previously described [17, 18]. Pleural pressure (P_{pl}) was directly recorded in the dorsal and ventral part of the pleural space in the right lung with two balloons (Cooper surgical, Trunbull, CT, USA). To ensure a proper P_{pl} measurement, the calibration of pleural catheters was done at each PEEP level and the minimal non-stressed volume of the balloon with a stable P_{pl} measure was selected [22].

Afterwards, we established lung injury by a two-hit model: surfactant depletion with saline lavage followed by injurious ventilation, as described previously [18].

Experimental data and measurement

The mechanical ventilator (GE Carestation 620, Boston, MA, USA) was set as follows: V_t 6 mL/kg, respiratory rate 25/min, F_iO_2 1.0. Ventral and dorsal pleural pressures were measured during respiratory holds both at end-inspiration and at end-expiration for every PEEP step. Every step lasted 20 min and was done without (first 10 min) and with (second 10 min) ECC using a 2.3 kg sandbag on top of the thorax. The pleural pressure gradient was calculated as follows: P_{pl} gradient = P_{pl} dorsal − P_{pl} ventral and averaged between different PEEP steps.

Statistical analysis

Data were expressed as mean ± SD or median ± interquartile range, as appropriate. Data were compared using one-way repeated measures ANOVA followed by Newman–Keuls or Sidak–Holm post hoc tests. If both the normality and equal variance tests failed, repeated measures ANOVA on ranks was used. Difference in continuous data in the preclinical model between baseline and ECC was assessed using the Wilcoxon signed-rank test. Statistical analyses were performed using STATA/16 MP (TX, USA), GraphPad Prism 8.0.2 (La Jolla, CA, USA) and Systat software Inc. (Sigmaplot 12.0, UK). Statistical significance was set at $P < 0.05$ (two-tailed).
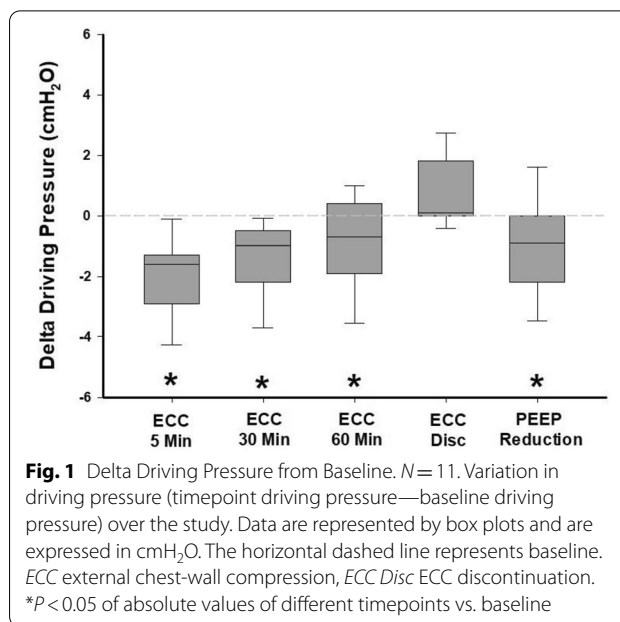
Results

Patients

Among the 11 patients, 7 were male and were studied on average 17.3 ± 8.6 days from mechanical

Bastia *et al. Annals of Intensive Care* (2022) 12:35

Page 4 of 10

Table 1 Baseline demographic and clinical characteristics

Demographic characteristics	
Male, *n* (%)	7 (64%)
Age (years)	59 ± 14
BMI (kg/m²)	29 ± 8
Clinical illness severity	
Time from disease onset to ICU admission, days	9 (6–10)
Time from ventilation initiation to enrollment, days	17.3 ± 8.6
Time from disease onset to enrollment, days	26.0 ± 8.2
Chronic APACHE	
A	6 (55%)
B	5 (45%)
C	0
D	0
Comorbidities	
Coronary artery disease, *n* (%)	1 (9%)
Hypertension, *n* (%)	4 (36%)
Diabetes, *n* (%)	2 (18%)
Neoplasia, *n* (%)	3 (27%)
Ventilatory variables at enrollment	
Tidal volume (mL)	364.5 ± 72.0
Tidal volume per predicted body weight (mL/kg of PBW)	5.38 ± 0.58
Respiratory rate (breaths per minute)	24 ± 2
Total PEEP (cmH₂O)	12.6 ± 2.9
Peak inspiratory pressure (cmH₂O)	32.2 ± 2.2
Plateau pressure (cmH₂O)	26.8 ± 2.4
Driving pressure (cmH₂O)	14.2 ± 1.2
Respiratory system compliance (mL/cmH₂O)	25.9 ± 5.9
Lung compliance (mL/cmH₂O)	28.7 ± 6.1
Chest-wall compliance (mL/cmH₂O)	152 (120.2–305.1)
Mean airway pressure (cmH₂O)	17.0 ± 2.8
Minute ventilation (L)	8.8 ± 2.3
Ventilatory ratio	2.1 ± 0.4
Inspiratory esophageal pressure (cmH₂O)	14.9 ± 3.4
Expiratory esophageal pressure (cmH₂O)	12.8 ± 3.1
Gas exchange at enrollment	
P_aO_2 (mmHg)	88.2 (77.1–127.6)
P_aCO_2 (mmHg)	55.9 ± 6.6
pH	7.371 ± 0.03
P_aO_2/F_iO_2 (mmHg)	163 (109–220)
F_iO_2 (%)	60 (50–65)
End-tidal CO₂ (mmHg)	42 (39–50)
Dead space (%)	18.6 (12.6–27.1)
Shunt fraction (%)	15.5 (7.1–27.3)

Data are expressed as *N* (%), median and interquartile range or mean ± standard deviation as appropriate

BMI body mass index, *ICU* intensive care unit, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure
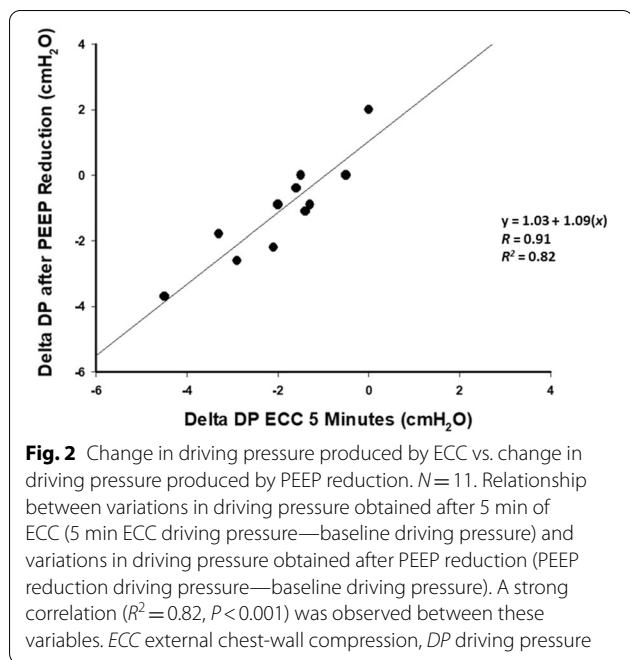

Fig. 1 Delta Driving Pressure from Baseline. *N* = 11. Variation in driving pressure (timepoint driving pressure—baseline driving pressure) over the study. Data are represented by box plots and are expressed in cmH₂O. The horizontal dashed line represents baseline. *ECC* external chest-wall compression, *ECC Disc* ECC discontinuation. *$P < 0.05$ of absolute values of different timepoints vs. baseline

ventilation initiation. C_{rs} was 25.9 ± 5.9 mL/cmH₂O, V_t was 5.4 ± 0.6 mL/kg of PBW (i.e., 365 ± 72 mL). Patients had a median P_aO_2/F_iO_2 ratio of 163 mmHg (109–220) and moderate to severe hypercapnia ($PaCO_2 = 55.9 \pm 6.6$ mmHg) with a ventilatory ratio of 2.1 ± 0.4 [23]. Table 1 summarizes baseline and physiological characteristics of the studied population.

Effect of ECC on driving pressure

As compared to baseline, the ECC caused a significant decrease in DP after 5 min (14.2 ± 1.3 vs. 12.3 ± 1.3 cmH₂O, $P < 0.001$) (Additional file 1: Table E2). After 30 and 60 min from the beginning of the ECC, the DP was still significantly lower as compared to baseline values; however, a slight increase of DP over time was observed (12.7 ± 1.4 cmH₂O at 30 min and 13.3 ± 1.5 cmH₂O at 60 min, respectively, $P < 0.001$ and $P = 0.03$ as compared to baseline). Once compression was discontinued the DP returned to baseline values (14.9 ± 1.8 vs. 14.2 ± 1.3 cmH₂O, $P = 0.3$).

Effect of PEEP reduction

According to the measurements performed in Step 1, the increase in airway pressure caused by ECC performed during an expiratory hold, PEEP was reduced
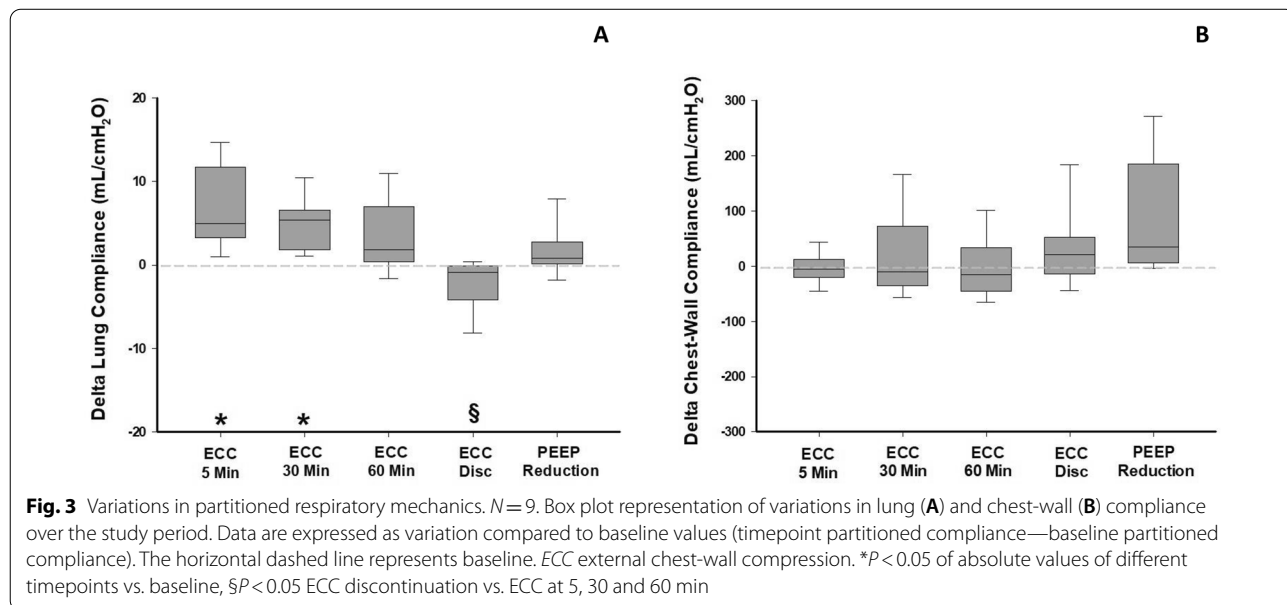
Bastia *et al. Annals of Intensive Care*   (2022) 12:35

Page 5 of 10

Fig. 2 Change in driving pressure produced by ECC vs. change in driving pressure produced by PEEP reduction. $N=11$. Relationship between variations in driving pressure obtained after 5 min of ECC (5 min ECC driving pressure—baseline driving pressure) and variations in driving pressure obtained after PEEP reduction (PEEP reduction driving pressure—baseline driving pressure). A strong correlation ($R^2=0.82$, $P<0.001$) was observed between these variables. *ECC* external chest-wall compression, *DP* driving pressure

by 3 cmH$_2$O in every patient during the last step (Additional file 2: Figure E2). After the reduction of PEEP by 3 cmH$_2$O (i.e., final step) we observed a significant reduction of DP (13.1 ± 1.3 cmH$_2$O, $P=0.01$). The difference of DP between each step and baseline are shown in Fig. 1, absolute DP values are reported in Additional file 1: Table E2. A strong linear correlation was observed between the decrease in DP recorded 5 min after initiation of ECC and the one obtained after PEEP reduction ($R^2=0.82$, $P<0.001$, Fig. 2; bias$=-$ 0.86 cmH$_2$O, upper limit of agreement$=0.40$ cmH$_2$O, lower limit of agreement$=-$ 2.13 cmH$_2$O, Additional file 2: Figure E8).

Effect of ECC on respiratory mechanics

The ECC caused a significant increase in C_{rs} after 5 and 30 min, as compared to baseline values (baseline 25.9 ± 5.9 mL/cmH$_2$O, 5 min of ECC 30.2 ± 7.8 mL/cmH$_2$O, 30 min of ECC 29.2 ± 7.7 mL/cmH$_2$O, $P<0.001$ for both). After 60 min of ECC and after its discontinuation no significant differences were observed ($P=0.06$ and $P=0.5$, respectively). Decreasing PEEP by 3 cmH$_2$O produced a significant increase in C_{rs} as compared to baseline (28.3 ± 7.8 mL/cmH$_2$O, $P=0.028$, Additional file 1: Table E2).

When partitioning respiratory mechanics, we observed that the increase in C_{rs} was attributable to an increased C_{lung} during the entire ECC period. Compared to baseline values (28.7 ± 6.1 mL/cmH$_2$O), C_{lung} increased both at 5 (35.5 ± 9.3 mL/cmH$_2$O, $P<0.001$) and 30 min (33.3 ± 8 mL/cmH$_2$O, $P=0.016$) of ECC (Fig. 3A). After 60 min of ECC, C_{lung} was still higher as compared to baseline, but the difference was not statistically significant (32.1 ± 7.9 ml/cmH$_2$O, $P=0.06$). In the last two steps (i.e., ECC discontinuation and PEEP decrease) we did not observe difference compared to baseline. When ECC was discontinued C_{lung} was significantly lower compared

Fig. 3 Variations in partitioned respiratory mechanics. $N=9$. Box plot representation of variations in lung (**A**) and chest-wall (**B**) compliance over the study period. Data are expressed as variation compared to baseline values (timepoint partitioned compliance—baseline partitioned compliance). The horizontal dashed line represents baseline. *ECC* external chest-wall compression. *$P<0.05$ of absolute values of different timepoints vs. baseline, §$P<0.05$ ECC discontinuation vs. ECC at 5, 30 and 60 min

Bastia *et al. Annals of Intensive Care*   (2022) 12:35

Page 6 of 10

to ECC at 5, 30 and 60 min (26.5 ± 6.3 vs., respectively, 35.5 ± 9.3, 33.3 ± 8.0 and 32.1 ± 7.9 mL/H$_2$O). We did not find any significant change of C_{cw} over time despite ECC (Fig. 3B).

No statistical difference regarding end-expiratory transpulmonary pressure was found between baseline and each step (Additional file 2: Figure E3, Panel A). On the other hand, the inspiratory transpulmonary pressure (Additional file 2: Figure E3, Panel B) was reduced by ECC, from 11.7 ± 4.3 cmH$_2$O (baseline) to 7.7 ± 5.0, 8.1 ± 5.2 and 9.1 ± 5.1 cmH$_2$O (respectively, after 5 [$P < 0.001$], 30 [$P < 0.001$] and 60 [$P = 0.007$] min).

Effect of ECC on gas exchange and hemodynamics

P_aO_2 and P_aO_2/F_iO_2 ratio did not change with ECC. The $P_AO_2 - P_aO_2$ gradient increased from 254.4 (162.0–327.2) at baseline to 266.4 (164.1–328.7) after 60 min of ECC ($P = 0.02$), (Additional file 1: Table E3). Moreover, there was a trend toward a decrease in CO_2 with ECC ($P = 0.06$) as underlined by a significant increase in pH ($P = 0.01$). Dead space, shunt fraction and ventilatory ratio were not affected by ECC and PEEP reduction (Additional file 1: Table E3). No statistical difference between steps was found regarding hemodynamic variables (Additional file 1: Table E4).

Effect of ECC on regional ventilation and compliance

Changes in regional redistribution of ventilation caused by ECC were assessed by EIT and used to derive regional C_{rs}. Additional file 2: Figure E4 panel A shows the V_t
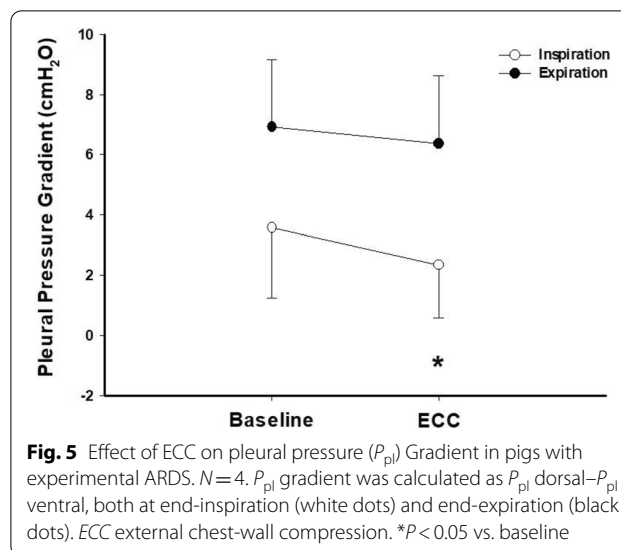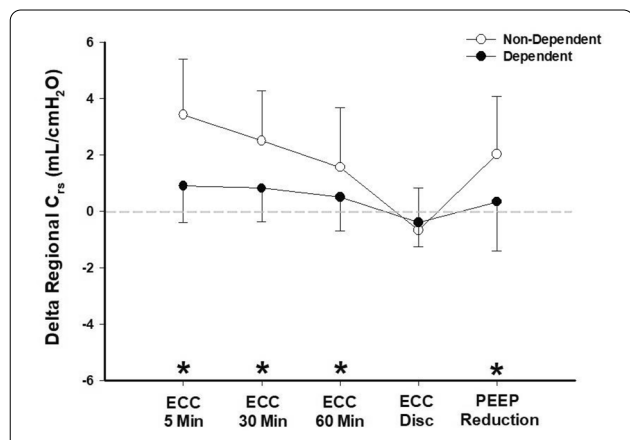

Fig. 4 Variations in regional respiratory system compliance (C_{rs}). $N = 11$. Variation in regional respiratory system compliance (expressed as timepoint regional compliance—baseline regional compliance, C_{rs}). White dots represent non-dependent lung regions (ventral), black dots represent dependent lung regions (dorsal). *ECC* external chest-wall compression. *$P < 0.05$ of absolute values of different non-dependent regional C_{rs} timepoints vs. non-dependent regional C_{rs} baseline

Fig. 5 Effect of ECC on pleural pressure (P_{pl}) Gradient in pigs with experimental ARDS. $N = 4$. P_{pl} gradient was calculated as P_{pl} dorsal–P_{pl} ventral, both at end-inspiration (white dots) and end-expiration (black dots). *ECC* external chest-wall compression. *$P < 0.05$ vs. baseline

distribution between non-dependent (ventral) and dependent (dorsal) lung regions across all steps. After 5 min of ECC a slight increase in non-dependent ventilation (62.3 ± 9.2 to $64.7 \pm 8.3\%$ ($P = 0.01$)) and a decrease in dependent ventilation (37.7 ± 9.2 to $35.3 \pm 8.3\%$ ($P = 0.01$) was observed. No difference was found after 30 and 60 min. After ECC discontinuation, V_t distribution was similar to baseline (Additional file 2: Figure E4 Panel B). PEEP reduction produced a change in V_t distribution almost identical to what was observed after 5 min of ECC (non-dependent lung, $64.7 \pm 8.3\%$; dependent lung, $35.3 \pm 8.3\%$, both $P = 0.01$ compared to baseline). A linear association between these two variables was observed ($R^2 = 0.51$, $P = 0.01$, Additional file 2: Figure E5).

The derived regional C_{rs} (i.e., regional V_t/DP) is shown in Fig. 4 and it is expressed as delta regional C_{rs} for each step compared to baseline. At baseline, the non-dependent regional C_{rs} was 16.4 ± 5.5 mL/cmH$_2$O, while it was 9.4 ± 2.2 mL/cmH$_2$O for the dependent lung regions. After 5, 30 and 60 min of ECC the non-dependent C_{rs} was 19.8 ± 6.6 ($P < 0.001$), 18.9 ± 6.7 ($P < 0.001$) and 17.9 ± 6.5 mL/cmH$_2$O ($P = 0.04$), respectively. Finally, when PEEP was decreased the non-dependent regional C_{rs} also increased to 18.4 ± 6.1 mL/cmH$_2$O ($P = 0.005$). While dependent regional C_{rs} did not change significantly with ECC, non-dependent (ventral) C_{rs} was always significantly higher during ECC as compared to baseline.

Effect of ECC on the regional distribution of EELI

Regional EELI values recorded after 5 min of ECC were compared with EELI values obtained at 30 and 60 min, and EELI variations were computed. The analysis was thus performed exclusively during the ECC application to avoid signal distortion caused by the compression of the

Bastia *et al. Annals of Intensive Care* (2022) 12:35

Page 7 of 10

belt [24]. ECC led to a progressive reduction over time of global EELI ($-$ 277.8 $\pm$ 481.7 AU after 60 min ECC, Additional file 2: Figure E6 as an example). Regional analysis showed that the EELI reduction during ECC was in the non-dependent part with an absolute value at 60 min ECC [26.3 ($-$ 55.4–71.8) AU] significantly lower compared to the one observed after 5 min of ECC [415.9 (148.5–639.1) AU, $P=0.014$] (Additional file 2: Figure E7).

Animal study: effects of ECC on pleural pressure gradient

In Fig. 5, we report the effect of ECC on P_{pl} gradient on average between different PEEP steps. The P_{pl} gradient (i.e., the difference between the dependent and non-dependent pleural pressure), was measured at end-inspiration and was significantly lower with ECC compared to baseline [2.2 (1.1–3.0) vs. 3.0 (2.2–4.1), $P=0.035$]. On the contrary the P_{pl} gradient measured at end-expiration did not change significantly with ECC ($P=0.4$).

Discussion

Our study showed that in a population of C-ARDS characterized by a C_{rs} below 35 mL/cmH$_2$O the application of an ECC led to a rapid decrease of DP and increase in C_{rs}, explained by an improvement of C_{lung}. The increase in C_{lung} was mainly driven by the non-dependent lung, suggesting a reduction of lung hyperinflation in this lung region. PEEP reduction had comparable mechanical effects. Finally, in an animal model of ARDS, the ECC lowered the P_{pl} gradient, suggesting a better parenchymal homogeneity.

Effect of ECC on respiratory mechanics

After 5 min of an ECC by a 5-L bag we demonstrated that C_{rs} increases, leading to a significant decrease in DP. This allowed to improve protective mechanical ventilation by reducing DP for a given V_t. This change in respiratory mechanics could be caused either by a recruitment of previously collapsed alveolar units (usually occurring in the dependent lung) or by a reduction of the overdistended volume, localized predominantly in the non-dependent lung. EIT analysis demonstrated that ECC for 5 min produced a significant increase in non-dependent C_{rs}. This finding, along with the rapid reversal of C_{rs} once ECC was discontinued, the negative expiratory and inspiratory values of P_L and the progressive reduction of end-expiratory lung volume [10, 12], make the hypothesis of dorsal recruitment unlikely and suggest—in contrast— a reduced hyperinflation phenomenon. Indeed, ECC reduced the respiratory system (chest-wall and lung) volume (i.e., EELI) leading to a C_{lung} improvement. The mechanism of this regional compliance change is related

to a downward shift of the respiratory system pressure (Additional file 2: Figure E13) [12, 13]. Interestingly, C_{cw} was not significantly affected by ECC. This is consistent with the effects of obesity, which imposes and extra-load on the chest but does not modify chest wall compliance [25].

The hyperinflation reduction hypothesis was also proposed by Rezoagli et al. [13]. The authors observed, after external chest compression, an EELI reduction and an increase in the non-dependent lung compliance. Other authors reported ECC to be a useful maneuver to attenuate hyperinflation in patients with asthma [26, 27]. On the other hand, a recent case report on C-ARDS supports the dorsal recruitment theory [12]. Given that these findings are based on a single case observation it is difficult to explain the differences with our findings.

Similar studies [13, 14] show that a compression applied to the abdomen either by gravitational forces (Trendelenburg position) or by external compression determines a cephalad displacement of the diaphragm and compresses the lungs, leading to a DP reduction and a better C_{rs}. Hence, chest-wall and abdominal compressions, although exerting different forces, seem to produce similar effects when applied to a hyperinflated lung.

Sustained effect of ECC on respiratory mechanics and gas exchange

Lung mechanics after 30 and 60 min showed a progressive loss of the benefit (DP reduction and C_{rs} improvement) as compared to the one observed after 5 min of ECC. These data suggest, therefore, a possible time-dependent effect of ECC on respiratory mechanics. Our findings show that ECC plays its role predominantly in the non-dependent lung. At this level, the regional C_{rs}, after an initial increase, decreases over time. On the contrary, regional C_{rs} of the dependent region was fairly stable during the 60 min of ECC. Interestingly, we found a similar behavior of EELI, where ECC seems to selectively determine an EELI loss in the non-dependent lung, resulting in a reduction of the hyperinflated volume. On the other hand, it is conceivable that a long-term ECC could favor the reduction of the non-hyperinflated volume, possibly explaining the observed loss of the benefits to C_{rs} over time.

This asymmetrical (ventral vs. dorsal) influence of ECC on respiratory system can be explained also from a pleural pressure perspective, where ECC might cause an asymmetrical change in P_{pl} (and P_L) as suggested by our preclinical results (see below).

Despite a study advocating ECC to increase oxygenation [11], we did not observe an increase in P_aO_2 or P_aO_2/F_iO_2 after 60 min of ECC. P_aCO_2 was slightly reduced by

Bastia *et al. Annals of Intensive Care*   (2022) 12:35

Page 8 of 10

ECC and can be related to the decrease non-dependent hyperinflation. However, we did not observe any difference in dead space through steps. We acknowledge that these are preliminary physiologic findings and the sample size is not powered to capture significantly differences on gas exchange.

C-ARDS or ARDS?

The patients enrolled in the study were still on mechanical ventilation despite several days. Hence, they represent a subset of prolonged, unresolving C-ARDS with different mechanical properties compared to early C-ARDS [9]. This population limits generalizability of our data regarding C-ARDS on one hand. On the other hand, our results are likely to be observed in classical ARDS considering the similarities existing between late, low-C_{rs} C-ARDS and classical ARDS, as suggested by recent literature [13].

PEEP titration: is set PEEP too high?

Our data show a robust correlation between the DP reduction after 5 min of ECC and the DP change after PEEP reduction. Therefore, it is possible that short term ECC may inform the clinician about: (1) presence of hyperinflation and (2) the expected DP resulting from a PEEP reduction. The idea of ECC as a bed-side tool has been already proposed, in theory, for abdominal compressions [14, 28]. Our results, strengthen this rationale. Similar findings were reported by Carteaux et al. [12].

Was, therefore, set PEEP too high? Probably yes. Prolonged C-ARDS parenchyma is relatively unmodified by recruitment maneuver and PEEP [9]. In this "fibrosis-like" condition, we observed hyperinflation with slightly negative end-expiratory P_L (between 0 and − 2 cmH$_2$O). Despite recent evidence showed that such P_L levels were associated with lower mortality [29], no data on outcome are available using this approach in late C-ARDS. Therefore, we might speculate that in this subset of patients PEEP favored more hyperinflation of already aerated lung than recruitment of collapsed alveoli.

Translational research insight

The porcine experimental data allowed us to measure P_{pl} directly in the ventral and dorsal pleural space. Of note, the P_{pl} gradient (P_{pl} dorsal–P_{pl} ventral) is associated to the homogeneity of lung parenchyma assessed with quantitative computed tomography [19, 30, 31]. We found that ECC reduces on average the P_{pl} gradient compared to baseline. This reduction implies that ECC increases P_{pl} in an asymmetrical way: ventral P_{pl}, close

to the site of ECC, increases more than dorsal P_{pl} leading to a greater reduction of P_L for a given P_{aw}. Once again, ventral lung seems more affected from the ECC than the dorsal one.

Clinical implications: ECC as a bedside tool to detect lung overdistension

Based on our data, we think that a brief ECC could be a valuable, quick, and simple bed-side tool to detect hyperinflation, which is a major contributor to VILI. Hence, it can possibly help the clinician adjust PEEP and/or V_t setting if permitted by the level of pH and P_aCO_2. It has been proposed that ECC could be a surrogate of prone position to be used in those patients, where prone position is not feasible [11, 28]. We did not observe an improvement in gas exchange. Moreover, the ECC did not promote recruitment and its effects were time dependent. Indeed, despite a relatively short period of time (1 h) the mechanical benefits of ECC seem to fade over time. This behavior is opposite as compared to prone positioning, where benefits are correlated with time, and therefore, longer durations are encouraged [32].

Limitations

Our study has some limitations. First, human subjects and pigs differ for amount of weight on the thorax, chest-wall shape and type of lung injury. For this reason, clinical and translational results should be interpreted with caution. Second, this study does not explore ECC with different weights. It is possible that different pressures applied to the respiratory system could yield different mechanical responses. Third, clinical ventilatory settings were used throughout the study as per clinical decision, hence PEEP was not standardized upon a specific titration approach (i.e., incremental vs. decremental PEEP trial, P_L trial) before enrollment. Fourth, steps were not randomized throughout the study. Fifth, we studied a small convenience sample. Larger studies are, therefore, warranted to confirm our results. Finally, we did not explore the long-term effects of ECC, which will need properly designed studies to be assessed.

Conclusions

In patients with late C-ARDS, with prolonged mechanical ventilation and low C_{rs}, ECC can suggest a decrease in hyperinflation in the non-dependent lung regions and leads to a sudden improvement of C_{rs}, at least transiently. The extent of C_{rs} improvement with ECC is similar to the improvement obtained with decreasing PEEP. A brief ECC could, therefore, be a simple and useful tool to detect hyperinflation at the bedside. Over time, the

Bastia *et al. Annals of Intensive Care*   (2022) 12:35

Page 9 of 10

"VILI-sparing" effect of ECC is gradually lost and thus, ECC may not be suitable for a prolonged use (i.e., > 1 h). Hemodynamics and gas exchange are not affected by 1 h of chest compression.

Abbreviations
ECC: External chest-wall compression; PEEP: Positive end-expiratory pressure; ARDS: Acute respiratory distress syndrome; Sars-CoV-2: Severe acute respiratory system coronavirus 2; C-ARDS: COVID-19 ARDS; VILI: Ventilator-induced lung injury; V_t: Tidal volume; DP: Driving pressure; C_{rs}: Respiratory system compliance; EIT: Electrical impedance tomography; P_{aw}: Airway pressure; P_{es}: Esophageal pressure; P_{pl}: Pleural pressure; P_{plat}: Plateau pressure; P_L: Transpulmonary pressure; Clung: Lung compliance; C_{cw}: Chest-wall compliance; EELV: End-expiratory lung volume; EELI: End-expiratory lung impedance.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13613-022-01008-6.

Additional file 1. Contains legends for additional figures and additional tables.

Additional file 2. Contains additional figures.

Author contributions
LB conceived and designed the study, collected human and animal data, analyzed the data, interpreted data and wrote the manuscript; ER contributed in the study design, analyze and interpreted the data, drafted and revised the manuscript; MG contributed in the study design, collected human data, analyzed data and revised the manuscript; DE collected animal data and revised the manuscript; CF collected human data and revised the manuscript; FM revised the manuscript; SS revised the manuscript; GB contributed in the study design and revised the manuscript; RG contributed in the study design and revised the manuscript; MP revised the manuscript; GB interpreted the results, contributed in data analysis and revised the manuscript; RF revised the manuscript; LJB interpreted the results, contributed in data analysis and revised the manuscript; TL contributed in the study design and in data analysis, interpreted the results, drafted and revised the manuscript. All authors read and accepted the final manuscript.

Availability of data and materials
The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All studies were approved by the national ethics committees. Human study: Comitato etico Milano Area 3, # 179-30032021. Animal study: Animal Care Committee, Research Institute, The Hospital for Sick Children (protocol number 46420).

Consent for publications
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Neurointensive Care Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy. [2]School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy. [3]Department of Emergency and Intensive Care, ASST Monza, San Gerardo Hospital, Monza, Italy. [4]Department of Anesthesia and Critical Care, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy. [5]Translational Medicine Program, Hospital for Sick Children, Toronto, ON, Canada. [6]Interdepartmental Division of Critical Care Medicine, University of Toronto, Keenan Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, 209 Victoria Street, Room 4-08, Toronto, ON M5B 1T8, Canada.

References
1. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy [published correction appears in JAMA. 2021 May 25;325(20):2120]. JAMA. 2020;323(16):1574–81. https://doi.org/10.1001/jama.2020.5394.
2. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395(10239):1763–70. https://doi.org/10.1016/S0140-6736(20)31189-2.
3. Ziehr DR, Alladina J, Petri CR, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. Am J Respir Crit Care Med. 2020;201(12):1560–4. https://doi.org/10.1164/rccm.202004-1163LE.
4. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372(8):747–55. https://doi.org/10.1056/NEJMsa1410639.
5. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2159–68. https://doi.org/10.1056/NEJMoa1214103.
6. Network ARDS. Ventilation with lower tidal volumes as compared with traditional tidal volumes for ALI and the ARDS. N Engl J Med. 2000;342:1301–8. https://doi.org/10.1056/NEJM200005043421801.
7. Langer T, Brioni M, Guzzardella A, et al. Prone position in intubated, mechanically ventilated patients with COVID-19: a multi-centric study of more than 1000 patients. Crit Care. 2021;25(1):128. https://doi.org/10.1186/s13054-021-03552-2.
8. Vandenbunder B, Ehrmann S, Piagnerelli M, et al. Static compliance of the respiratory system in COVID-19 related ARDS: an international multicenter study. Crit Care. 2021;25(1):52. https://doi.org/10.1186/s13054-020-03433-0.
9. Rossi S, Palumbo MM, Sverzellati N, et al. Mechanisms of oxygenation responses to proning and recruitment in COVID-19 pneumonia. Intensive Care Med. 2022;48(1):56–66. https://doi.org/10.1007/s00134-021-06562-4.
10. Bottino N, Panigada M, Chiumello D, Pelosi P, Gattinoni L. Effects of artificial changes in chest wall compliance on respiratory mechanics and gas exchange in patients with acute lung injury (ALI). Crit Care. 2000;4(Suppl 1):P117. https://doi.org/10.1186/cc837.
11. Samanta S, Samanta S, Soni KD. Supine chest compression: alternative to prone ventilation in acute respiratory distress syndrome. Am J Emerg Med. 2014;32(5):489. https://doi.org/10.1016/j.ajem.2013.11.014.
12. Carteaux G, Tuffet S, Mekontso DA. Potential protective effects of continuous anterior chest compression in the acute respiratory distress syndrome: physiology of an illustrative case. Crit Care. 2021;25(1):187. https://doi.org/10.1186/s13054-021-03619-0.

Bastia *et al. Annals of Intensive Care*   (2022) 12:35

Page 10 of 10

13. Rezoagli E, Bastia L, Grassi A, et al. Paradoxical effect of chest wall compression on respiratory system compliance: a multicenter case series of patients with ARDS with multimodal assessment. Chest. 2021;160(4):1335–9. https://doi.org/10.1016/j.chest.2021.05.057.

14. Kummer RL, Shapiro RS, Marini JJ, Huelster JS, Leatherman JW. Paradoxically improved respiratory compliance with abdominal compression in COVID-19 ARDS. Chest. 2021. https://doi.org/10.1016/j.chest.2021.05.012.

15. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526–33. https://doi.org/10.1001/jama.2012.5669.

16. Marrazzo F, Spina S, Forlini C, et al. Effects of trunk inclination on respiratory mechanics in patients with COVID-19 associated ARD. Am J Respir Crit Care Med. 2022. https://doi.org/10.1164/rccm.202110-2360LE.

17. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A simple method for assessing the validity of the esophageal balloon technique. Am Rev Respir Dis. 1982;126(5):788–91. https://doi.org/10.1164/arrd.1982.126.5.788.

18. Bastia L, Engelberts D, Osada K, et al. Role of positive end-expiratory pressure and regional transpulmonary pressure in asymmetrical lung injury. Am J Respir Crit Care Med. 2021;203(8):969–76. https://doi.org/10.1164/rccm.202005-1556OC.

19. Katira BH, Osada K, Engelberts D, et al. Positive end-expiratory pressure, pleural pressure, and regional compliance during pronation: an experimental study. Am J Respir Crit Care Med. 2021;203(10):1266–74. https://doi.org/10.1164/rccm.202007-2957OC.

20. Hinz J, Hahn G, Neumann P, et al. End-expiratory lung impedance change enables bedside monitoring of end-expiratory lung volume change. Intensive Care Med. 2003;29(1):37–43. https://doi.org/10.1007/s00134-002-1555-4.

21. Bronco A, Grassi A, Meroni V, et al. Clinical value of electrical impedance tomography (EIT) in the management of patients with acute respiratory failure: a single centre experience. Physiol Meas. 2021;42(7):074003. https://doi.org/10.1088/1361-6579/ac0e85.

22. Mojoli F, Chiumello D, Pozzi M, et al. Esophageal pressure measurements under different conditions of intrathoracic pressure. An in vitro study of second generation balloon catheters. Minerva Anestesiol. 2015;81(8):855–64.

23. Sinha P, Calfee CS, Beitler JR, et al. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2019;199(3):333–41. https://doi.org/10.1164/rccm.201804-0692OC.

24. Frerichs I, Pulletz S, Elke G, Gawelczyk B, Frerichs A, Weiler N. Patient examinations using electrical impedance tomography—sources of interference in the intensive care unit. Physiol Meas. 2011;32(12):L1–10. https://doi.org/10.1088/0967-3334/32/12/F01.

25. Coudroy R, Vimpere D, Aissaoui N, et al. Prevalence of complete airway closure according to body mass index in acute respiratory distress syndrome. Anesthesiology. 2020;133(4):867–78. https://doi.org/10.1097/ALN.0000000000003444.

26. Fisher MM, Bowey CJ, Ladd-Hudson K. External chest compression in acute asthma: a preliminary study. Crit Care Med. 1989;17(7):686–7. https://doi.org/10.1097/00003246-198907000-00018.

27. Watts JI. Thoracic compression for asthma. Chest. 1984;86(3):505. https://doi.org/10.1378/chest.86.3.505b.

28. Marini JJ, Gattinoni L. Improving lung compliance by external compression of the chest wall. Crit Care. 2021;25(1):264. https://doi.org/10.1186/s13054-021-03700-8.

29. Sarge T, Baedorf-Kassis E, Banner-Goodspeed V, et al. Effect of esophageal pressure-guided positive end-expiratory pressure on survival from acute respiratory distress syndrome: a risk-based and mechanistic reanalysis of the EPVent-2 Trial. Am J Respir Crit Care Med. 2021;204(10):1153–63. https://doi.org/10.1164/rccm.202009-3539OC.

30. Pelosi P, Goldner M, McKibben A, et al. Recruitment and derecruitment during acute respiratory failure: an experimental study. Am J Respir Crit Care Med. 2001;164(1):122–30. https://doi.org/10.1164/ajrccm.164.1.2007010.

31. Bryan AC. Conference on the scientific basis of respiratory therapy. Pulmonary physiotherapy in the pediatric age group. Comments of a devil's advocate. Am Rev Respir Dis. 1974;110(6 Pt 2):143–4. https://doi.org/10.1164/arrd.1974.110.6P2.143.

32. Munshi L, Del Sorbo L, Adhikari NKJ, Hodgson CL, Wunsch H, Meade MO, et al. Prone position for acute respiratory distress syndrome: a systematic review and meta-analysis. Ann Am Thorac Soc. 2017;14(Suppl_4):S280–8. https://doi.org/10.1513/AnnalsATS.201704-343OT.

Publisher's Note