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

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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/cmH2O.

**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 cmH2O ($P < 0.001$), 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 cmH2O 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) cmH2O, $P = 0.035$].

**Conclusions:** In C-ARDS patients with $C_{rs} < 35$ mL/cmH2O, 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

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...
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 $V_t (\leq 6$ mL/kg) and (5) $C_{rs} \leq 35$ ml/cmH2O 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, Trubull, 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
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 ($P_{pl\text{, plat}}$) – Total PEEP (set PEEP + intrinsic PEEP).
- Respiratory system compliance or $C_{rs} = V_t/\text{DP}$.
- Regional $C_{rs} = \text{Regional } V_t$ derived from EIT/DP.
- Transpulmonary pressure (absolute value) or $P_L = P_{aw} – P_{es}$.
- Lung compliance or $C_{lung} = V_t/(P_L \text{ inspiration} – P_L \text{ expiration})$.
- Chest-wall compliance or $C_{cw} = V_t/(P_{es} \text{ inspiration} – P_{es} \text{ expiration})$.

$P_{aw}$ 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: $(C_{\text{O}_2} – C_{\text{O}_2})/(C_{\text{O}_2} – C_{\text{O}_2})$, where $C_{\text{O}_2}$ represents the $\text{O}_2$ content of capillary blood, $C_{\text{O}_2}$ the arterial $\text{O}_2$ content and $C_{\text{O}_2}$ the $\text{O}_2$ content of venous blood. Alveolar dead space was calculated as follows: $(P_C\text{CO}_2 – P_{es}\text{CO}_2)/P_C\text{CO}_2$ where $P_C\text{CO}_2$ is the arterial partial pressure of carbon dioxide ($\text{CO}_2$) and $P_{es}\text{CO}_2$ represents the end-tidal $\text{CO}_2$ 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, Trumbull, 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, $F\text{O}_2$ 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±inter-quartile 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. (Sigmamplot 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
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) | 32.3 ± 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 |             |         |
| P₅O₂ (mmHg)                | 88.2 (77.1–127.6) |         |
| P₅CO₂ (mmHg)               | 55.9 ± 6.6  |         |
| pH                         | 7.371 ± 0.03|         |
| P₅O₂/F₅O₂ (mmHg)           | 163 (109–220) |         |
| F₅O₂ (%)                   | 60 (50–65)  |         |
| End-tidal CO₂ (mmHg)       | 42 (39–50)  |         |
| Dead space (%)             | 18.6 (12.6–27.1) |         |
| Shunt fraction (%)          | 15.5 (7.1–27.5) |         |

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

ventilation initiation. Cᵣₛ was 25.9 ± 5.9 mL/cmH₂O, Vᵣ was 5.4 ± 0.6 mL/kg of PBW (i.e., 365 ± 72 mL). Patients had a median P₅O₂/F₅O₂ ratio of 163 mmHg (109–220) and moderate to severe hypercapnia (PaCO₂ = 55.9 ± 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...
by 3 cmH₂O in every patient during the last step (Additional file 2: Figure E2). After the reduction of PEEP by 3 cmH₂O (i.e., final step) we observed a significant reduction of DP (13.1 ± 1.3 cmH₂O, \(P = 0.01\)). 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 cmH₂O, upper limit of agreement = 0.40 cmH₂O, lower limit of agreement = −2.13 cmH₂O, 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/cmH₂O, 5 min of ECC 30.2 ± 7.8 mL/cmH₂O, 30 min of ECC 29.2 ± 7.7 mL/cmH₂O, \(P < 0.001\) 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 cmH₂O produced a significant increase in \(C_{rs}\) as compared to baseline (28.3 ± 7.8 mL/cmH₂O, \(P = 0.028\), 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/cmH₂O), \(C_{lung}\) increased both at 5 (35.5 ± 9.3 mL/cmH₂O, \(P < 0.001\) and 30 min (33.3 ± 8 mL/cmH₂O, \(P = 0.016\)) 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/cmH₂O, \(P = 0.06\)). 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 to baseline.
to ECC at 5, 30 and 60 min (26.5 ± 6.3 vs. 35.5 ± 9.3, 33.3 ± 8.0 and 32.1 ± 7.9 mL/H2O). We did not find any significant change of Ccw 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 cmH2O (baseline) to 7.7 ± 5.0, 8.1 ± 5.2 and 9.1 ± 5.1 cmH2O (respectively, after 5 [P < 0.001], 30 [P < 0.001] and 60 [P = 0.007] min).

**Effect of ECC on gas exchange and hemodynamics**

P2O2 and P2O2/F1O2 ratio did not change with ECC. The P2O2 – P1O2 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 CO2 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 Crs. Additional file 2: Figure E4 panel A shows the Vt 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 ± 8.3% (P = 0.01)) and a decrease in dependent ventilation (37.7 ± 9.2 to 35.3 ± 8.3% (P = 0.01) was observed. No difference was found after 30 and 60 min. After ECC discontinuation, Vt distribution was similar to baseline (Additional file 2: Figure E4 Panel B). PEEP reduction produced a change in Vt distribution almost identical to what was observed after 5 min of ECC (non-dependent lung, 64.7 ± 8.3%; dependent lung, 35.3 ± 8.3%, both P = 0.01 compared to baseline). A linear association between these two variables was observed (R2 = 0.51, P = 0.01, Additional file 2: Figure E5).

The derived regional Crs (i.e., regional Vt/DP) is shown in Fig. 4 and it is expressed as delta regional Crs for each step compared to baseline. At baseline, the non-dependent regional Crs was 16.4 ± 5.5 mL/cmH2O, while it was 9.4 ± 2.2 mL/cmH2O for the dependent lung regions. After 5, 30 and 60 min of ECC the non-dependent Crs was 19.8 ± 6.6 (P < 0.001), 18.9 ± 6.7 (P < 0.001) and 17.9 ± 6.5 mL/cmH2O (P = 0.04), respectively. Finally, when PEEP was decreased the non-dependent regional Crs also increased to 18.4 ± 6.1 mL/cmH2O (P = 0.005). While dependent regional Crs did not change significantly with ECC, non-dependent (ventral) Crs 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
belt [24]. ECC led to a progressive reduction over time of global EELI (−277.8 ± 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 Plat gradient on average between different PEEP steps. The Plat 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 Plat 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 Crs below 35 mL/cmH2O the application of an ECC led to a rapid decrease of DP and increase in Crs, 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 Plat 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 Crs increases, leading to a significant decrease in DP. This allowed to improve protective mechanical ventilation by reducing DP for a given VT. 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 over-distended volume, localized predominantly in the non-dependent lung. EIT analysis demonstrated that ECC for 5 min produced a significant increase in non-dependent Crs. This finding, along with the rapid reversal of Crs once ECC was discontinued, the negative expiratory and inspiratory values of Plat 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, Ccw 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 Rezogli 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 Crs. 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 Crs 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 Crs 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 Crs 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 Plat (and Plr) 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 O2 or P O2/FiO2 after 60 min of ECC. P acO2 was slightly reduced by
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, unresolved 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-Crs 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
“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, Tidal volume; DP: Driving pressure; Crs: Respiratory system compliance; EIT: Electrical impedance tomography; Pns: Airway pressure; Pp: Esophageal pressure; Ple: Pleural pressure; Pplat: Plateau pressure; Ppl: Transpulmonary pressure. Clung: Lung compliance; Ccw: Chest-wall compliance; EELV: End-expiratory lung volume; EELI: End-expiratory lung impedance.

Supplementary Information
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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, analyzed the data, revised and accepted the final manuscript; MG contributed in the study design, analyzed the 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; TF collected human data and revised the manuscript; MG contributed in the study design, collected human data, analyzed the data and revised the manuscript; DE collected animal data and revised the manuscript; MG contributed in the study design, collected human data, analyzed and interpreted the data, drafted and revised the manuscript. All authors read and accepted the final manuscript.

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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.

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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/rcrm.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. 2013;368(23):2159–68. https://doi.org/10.1056/NEJMc1305027.
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/NEJMoa1304103.
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/NEJM200003123421801.
7. Langer T, Brioni M, Gazzardella 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. Vandenkoender 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 KM, Sverzellati N, et al. Mechanisms of oxygenation responses to prone positioning 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, Chiumento 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. Curneaux 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.
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.2021.05.012.

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.2021.05.057.

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.202107-2360LE.

17. 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.

18. 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.

19. 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.

20. 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.

21. Mojoli F, Chiumentello D, Pozzi M, et al. Esophageal pressure measurements under different conditions of intrathoracic pressure. Minerva Anestesiol. 2015;81(8):855–64.

22. 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.

23. 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/ard.1974.1106P2.143.