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ORIGINAL WORK

Tidal Volume Lowering by Instrumental Dead Space Reduction in Brain-Injured ARDS Patients: Effects on Respiratory Mechanics, Gas Exchange, and Cerebral Hemodynamics

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Abstract

Background: Limiting tidal volume (V_T), plateau pressure, and driving pressure is essential during the acute respiratory distress syndrome (ARDS), but may be challenging when brain injury coexists due to the risk of hypercapnia. Because lowering dead space enhances CO_2 clearance, we conducted a study to determine whether and to what extent replacing heat and moisture exchangers (HME) with heated humidifiers (HH) facilitate safe V_T lowering in brain-injured patients with ARDS.

Methods: Brain-injured patients (head trauma or spontaneous cerebral hemorrhage with Glasgow Coma Scale at admission < 9) with mild and moderate ARDS received three ventilatory strategies in a sequential order during continuous paralysis: (1) HME with V_T to obtain a $PaCO_2$ within 30–35 mmHg (HME1); (2) HH with V_T titrated to obtain the same $PaCO_2$ (HH); and (3) HME1 settings resumed (HME2). Arterial blood gases, static and quasi-static respiratory mechanics, alveolar recruitment by multiple pressure–volume curves, intracranial pressure, cerebral perfusion pressure, mean arterial pressure, and mean flow velocity in the middle cerebral artery by transcranial Doppler were recorded. Dead space was measured and partitioned by volumetric capnography.

Results: Eighteen brain-injured patients were studied: 7 (39%) had mild and 11 (61%) had moderate ARDS. At inclusion, median [interquartile range] PaO_2/FiO_2 was 173 [146–213] and median PEEP was 8 cmH_2O [5–9]. HH allowed to reduce V_T by 120 ml [95% CI: 98–144], V_T/kg predicted body weight by 1.8 ml/kg [95% CI: 1.5–2.1], plateau pressure and driving pressure by 3.7 cmH_2O [2.9–4.3], without affecting $PaCO_2$, alveolar recruitment, and oxygenation. This was permitted by lower airway (− 84 ml [95% CI: − 79 to − 89]) and total dead space (− 86 ml [95% CI: − 73 to − 98]). Sixteen patients (89%) showed driving pressure equal or lower than 14 cmH_2O while on HH, as compared to 7 (39%) and 8 (44%) during HME1 and HME2 ($p < 0.001$). No changes in mean arterial pressure, cerebral perfusion pressure, intracranial pressure, and middle cerebral artery mean flow velocity were documented during HH.

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Conclusion: The dead space reduction provided by HH allows to safely reduce V_T without modifying $PaCO_2$ nor cerebral perfusion. This permits to provide a wider proportion of brain-injured ARDS patients with less injurious ventilation.

Keywords: ARDS, Brain injury, Mechanical ventilation, Protective ventilation, Ventilator-induced lung injury, Dead space

Background

Acute respiratory distress syndrome (ARDS) affects up to 30% of critically ill patients with acute brain injury [1–5], representing an independent predictor of worse clinical outcome [6].

The use of low tidal volume (V_T) to limit plateau pressure and driving pressure (i.e., plateau pressure–positive end-expiratory pressure, ΔP) reduces ventilator-induced lung injury (VILI) and improves survival in ARDS patients [7–9]. Nonetheless, lower V_T yield increased risk of hypercapnia, which is deleterious [10], especially in patients with brain injury: In this particular subset of patients, tight control of arterial partial pressure of carbon dioxide ($PaCO_2$) is needed to prevent any secondary brain injury due to increases in cerebral blood flow and intracranial pressure [11].

Consequently, in brain-injured patients with ARDS, two competing priorities arise: use of low V_T for lung protection and tight $PaCO_2$ control to maintain proper cerebral blood flow and prevent undue intracranial pressure increases. The optimal balance between brain and lung protection during mechanical ventilation is not well established, and no recommendation exists on ventilatory management of these patients. In clinical practice, patients with acute brain injury and ARDS often receive V_T exceeding 6 ml/kg of predicted body weight (PBW) [12–16].

Heat and moisture exchangers (HME) and heated humidifiers (HH) are used for gas conditioning during invasive mechanical ventilation. Although they are simpler to use, HMEs carry relevant instrumental dead space and decrease the proportion of V_T contributing to alveolar ventilation. Previous authors highlighted that replacing HME with HH decreases dead space, promotes CO_2 clearance and allows V_T and plateau pressure reduction during ARDS [17–20]: however, no data clarify to what extent ΔP is reduced by this approach and whether this is safe in patients with concomitant brain injury, for whom tight control of $PaCO_2$ is mandatory and any intervention has to be evaluated also from the perspective of cerebral hemodynamics.

We conducted a physiological study to elucidate to what extent V_T reduction with HH allows to limit ΔP and whether this is safe in terms of cerebral hemodynamics.

Methods

The study was conducted in the general intensive care unit (ICU) of a university hospital in Rome, Italy, according to the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the local institutional ethics committee. Written informed consent was obtained according to committee recommendation.

Patients

Acute brain-injured patients with ARDS were screened for enrollment. Acute brain injury was defined as a traumatic brain injury or a non-traumatic cerebral hemorrhage with a Glasgow Coma Scale at admission < 9. Diagnosis of ARDS was based on the criteria established by Berlin definition [21]. Patients were eligible for inclusion if they had acute brain injury, developed ARDS, and were monitored with invasive intracranial pressure for clinical purposes, with stable pressure values < 20 mmHg.

For safety reasons, because lowering V_T may cause alveolar derecruitment and hypoxemia, patients with severe ARDS (PaO_2/FiO_2 < 100 mmHg) were not considered for inclusion in the study. Other non-inclusion criteria were: age < 18, pregnancy, severe hemodynamic instability, contraindication to muscular paralysis, leaking chest tube, and decompressive craniotomy.

All patients were lying in the semi-seated position, intubated, sedated, paralyzed (cisatracurium 0.1 mg/kg), and mechanically ventilated in volume-controlled mode with an I-to-E ratio set at 1:2. A standard bitube circuit with Y-piece and HME filter (Hygrobac; DAR: dead space 84 ml, resistance 1.0 cmH_2O/L/s) was used in the stabilization phase. Ventilatory parameters were set by the attending physician, who was not involved in the study, but was specifically asked to optimize the ventilator settings to obtain a $PaCO_2$ between 30 and 35 mmHg and PaO_2 > 70 mmHg or a $SpO_2 \geq 98\%$, as per standard of care in brain-injured patients.

Study Protocol

Two humidification devices were used: HME (Hygrobac; DAR: dead space 84 ml, resistance 1.0 cmH2)/L/s) and HH (MR850, Fisher & Paykel, Auckland, New Zealand).

This crossover study was organized into three phases. In phase I (HME1), a HME placed distally to the Y-piece of the circuit, as in the stabilization phase. Mechanical

ventilation, as prescribed by the attending physician, was maintained for 30 min without any changes in the settings: Afterward, all relevant data were collected. In phase II (HH), the HME was removed and a HH was placed in the inspiratory limb of the circuit and V_T was titrated (20–30 ml decrease every 10 min) to obtain $PaCO_2$ equal to the one detected at the end of HME1; study data were collected 30 min after reaching the target $PaCO_2$ level. In phase III (HME2), an HME was placed again distally to the Y-piece of the circuit and all baseline settings were resumed.

All patients received cisatracurium continuous infusion, at a standard dose of 35 mg/h [22]. Patients' sedation, vasopressor dose, set PEEP, respiratory rate, FiO_2, and I-to-E ratio were kept unchanged over the entire course of the experiment.

Endotracheal suctioning was performed at study entry and was not repeated over the course of the study period, unless specifically required.

Measurements

The following parameters were continuously monitored (SC7000 Monitor, Siemens, Erlangen, Germany) during the study: heart rate, arterial blood pressure, intracranial pressure, cerebral perfusion pressure, and SpO_2.

Blood flow velocity in the middle cerebral artery was measured at the end of each study step with a 2 MHz pulsed Doppler ultrasound device (transcranial Doppler [TCD] H21—Hitachi Medical System Europe, Zug Switzerland).

The ventilator (ServoVentilator 900C, Siemens-Elema, Sweden) and a mainstream capnograph (CO_2 analyzer 930, Siemens-Elema, Sweden) were connected to a personal computer. The ventilator system transducers produced signals representing pressure in the expiratory line, ventilator flow rate, and CO_2 at airway opening. These signals were filtered to avoid aliasing and were converted from analog to digital at 50 Hz. The flow signal was calibrated under BTPS (body temperature and pressure, saturated) conditions with a 1-L syringe. Pressure was calibrated using a water manometer and CO_2 using a gas mixture with a known composition.

Tidal volume was measured as digital integration of expiratory flow signal. Tidal volume/kg of predicted body weight (PBW) was computed, with PBW calculated as described elsewhere [7].

Total PEEP ($PEEP_{TOT}$) was measured during end-expiratory occlusions, while airway plateau pressure (P_{PLAT}) was measured during a 2-second end-inspiratory occlusion. Driving pressure (ΔP) was computed as the difference between P_{PLAT} and $PEEP_{TOT}$. Static respiratory system compliance (C_{RS}) was calculated as $V_T/\Delta P$. Total, airway, and alveolar dead space was computed using volumetric capnography, according to a method validated elsewhere [23, 24]. Respiratory system mechanics, gas exchange, physiological dead space, and hemodynamics were measured in each phase of the protocol.

Elastic pressure–volume curves at set and zero PEEP were recorded in each phase of the study during low sinusoidal flow inflation, according to a method previously described in detail [25–29]. The linear C_{RS} was calculated as the steeper segment between the lower inflection point and upper inflection point of the curve at zero PEEP. The derecruited volume from set PEEP to zero PEEP was measured (Rec) and consisted in the volume difference between the pressure–volume curves recorded at set PEEP and zero PEEP that were graphically superimposed and compared at an elastic pressure of 20 cmH_2O [30, 31]. Rec was also normalized to the applied level of set PEEP: $Rec/PEEP_{TOT}$ was computed as the ratio between Rec and $PEEP_{TOT}$, and patients were classified as having a highly recruitable profile when $Rec/PEEP_{TOT} > 14.5$ ml/cmH_2O [32].

Endpoints

Primary endpoint of this physiological study was to assess during isocapnic conditions the gain provided by HH in terms of V_T, P_{PLAT}, and, ΔP reduction, as compared to HME.

Safety endpoints were the effects of a low V_T strategy on cerebral perfusion, as defined by cerebral perfusion pressure and blood flow velocity in the middle cerebral artery, and on respiratory mechanics and lung recruitment, as defined by lower and upper inflection points, linear and static C_{RS}, Rec, and $Rec/PEEP_{TOT}$.

Sample Size Calculation

Given the physiological design of the study, we did not perform a formal sample size calculation. Based on other investigations on the topic [17, 18, 20], we planned to enroll 15–18 patients that appear an adequate sample to draw conclusions on the specific endpoints addressed in the present investigation.

Statistical Analysis

Categorical data are showed as number of events (%). Continuous data are presented as median [interquartile range] and were analyzed using Friedman test for repeated measures. Post hoc paired comparisons were performed with Wilcoxon sum-rank test. Mean differences (95% CI) are displayed for most significant results. Distribution of categorical variables in the three study steps was compared with the Cochrane Q test: Paired comparisons were performed with the McNamar test.

Two-sided p value ≤ 0.05 was considered statistically significant. Analysis was performed using SPSS (version 20.0).

Results

Eighteen patients met inclusion criteria and were enrolled in the study. Demographics and clinical characteristics are shown in Table 1.

Consistently with the design of the protocol, no changes in $PaCO_2$, respiratory rate, set, and total PEEP were found among the three study steps (all $p > 0.05$; Table 2, Fig. 1).

Tidal volume, plateau pressure, driving pressure, total dead space, airway dead space, and alveolar tidal volume were significantly lower during HH as compared to HME1 (all $p < 0.05$; Table 2, Figs. 2, 3).

Consistent with these findings, static Crs was higher during HH and lower tidal volume ventilation than during HME1 ($p = 0.008$; Table 1). No significant effects on PaO_2/FiO_2 ratio, linear C_{RS}, alveolar dead space, lower and upper inflection point, Rec, $Rec/PEEP_{TOT}$, and the proportion of patients with $Rec/PEEP_{TOT} > 14.5$ ml/cmH_2O (all $p > 0.05$; Table 2) have been detected.

Heart rate, arterial pressure, intracranial and cerebral perfusion pressure, and flow velocity in the middle cerebral artery were similar in the three study steps (Table 2; Fig. 1; all $p > 0.10$).

The use of HHs, as compared to HMEs, decreased total dead space (−86 [95% CI: −73 to −98] ml, $p < 0.001$) due to significantly lower airway dead space (−84 [95% CI: −79 to −89] ml, $p < 0.001$), without affecting alveolar dead space (Table 2, Fig. 3).

The application of HH allowed an average V_T reduction of 120 [95% CI: 98–144] ml ($p < 0.001$) along with a decrease in V_T/kg PBW of 1.8 [95% CI: 1.5–2.1] ml/kg ($p < 0.001$) (Fig. 2). The use of lower tidal volume was associated with an increase in 2.3 ml/cmH_2O in static C_{RS} [95% CI: 0.6–4.1] ($p = 0.08$) and with lower P_{PLAT} and ΔP (both −3.7 [95% CI: −2.9 to −4.3] cmH_2O, $p < 0.001$); 16/18 (89%) of patients showed a $\Delta P \leq 14$ cmH_2O in the HH step, as compared to 7/18 (39%) and 8/18 (44%) during HME1 and HME2 ($p < 0.001$).

Discussion

Our results show that, in brain-injured patients with ARDS, the use of HHs permits to reduce tidal volume and ΔP without affecting cerebral hemodynamics and arterial CO_2 tension.

Consistently with previous investigations [17, 18, 20, 33] HHs, as compared to HMEs, significantly reduced total and airway dead space. The measured dead space reduction provided by HHs was 86 [95% CI: 73–98] ml and is consistent with the 90-ml instrumental dead space declared by HME manufacturer. In our study, this

Table 1 Demographics

		18 patients	
Age, years		54 [39–70]	
Female sex	no. (%)	6 (33)	
Ideal body weight, kg		67 [59–76]	
GCS at admission		6 [4–8]	
SAPS II		47 [35–54]	
Cause of acute brain injury	no. (%)	Trauma Subarachnoid hemorrhage Intracerebral hemorrhage	11 (61) 4 (22) 3 (17)
Length of mechanical ventilation before enrollment, days		5 [3–7]	
Cause of ARDS	no. (%)	Chest trauma Pneumonia Transfusion-related lung injury	5 (28) 12 (67) 1 (5)
ARDS severity	no. (%)	Mild Moderate	7 (39) 11 (61)
PaO_2/FiO_2 at inclusion, mmHg		173 [146–213]	
Total PEEP at inclusion, cmH_2O		8 [5–9]	
Total length of mechanical ventilation during the ICU stay, days		17 [13–23]	
Tracheostomy during ICU stay	no. (%)	13 (72)	
Length of ICU stay, days		22 [19–31]	
ICU Outcome, mortality	no. (%)	5 (28)	

Data expressed as median [interquartile range], if not otherwise specified

Table 2 Main results of the study

	HME1	HH	HME2	Sig. *p* value
Ventilator settings				
Tidal volume, ml	597 [535–646]*	471 [416–512]*°	614 [534–648]°	< 0.001
Tidal volume/PBW, ml/kg	8.7 [8.5–9.6]*	7 [6.6–7.3]*°	8.7 [8.5–9.9]°	< 0.001
Respiratory rate, breaths/min	13 [12–15]	14 [12–16]	13 [12–15]	0.06
Set PEEP, cmH_2O	7.5 [5–8.5]	7.5 [5–8.5]	7.5 [5–8.5]	1
Total PEEP, cmH_2O	8 [5–9.3]	8 [5–9.3]	8 [5–9.3]	1
Respiratory mechanics				
Peak pressure, cmH_2O	28 [25–31] *	22 [21–26] *°	27 [24–31] °	< 0.001
Plateau pressure, cmH_2O	22 [21–24] *§	18 [18–21] *°	23 [20–23] °§	< 0.001
ΔP, cmH_2O	15 [14–17] *§	11 [10–13] *°	15 [13–16] °§	< 0.001
Patients with $\Delta P \leq 14$ cmH_2O, no (%)	7 (39)*	16 (89)*°	8 (44)°	< 0.001
Respiratory system static compliance, ml/cmH_2O	39 [36–44] *§	41 [37–49] *	41 [37–46] §	0.006
Linear compliance, ml/cmH_2O	55 [47–65]	53 [47–62]	61 [46–65]	0.83
Lower inflection point, cmH_2O	7.5 [4.9–9.8]	7.7 [6.1–10.5]	7.4 [5.4–11.7]	0.03
Upper inflection point, cmH_2O	27 [21–32.2]	28 [19–31.6]	23.9 [17.5–27.5]	0.06
Alveolar recruitment				
Rec, ml	78 [37–137]	43 [22–121]	69 [39–129]	0.21
$Rec/PEEP_{TOT}$, ml/cmH_2O	9.4 [5.7–13.4]	6.8 [3.8–13.4]	8.7 [4.3–14.6]	0.21
Patients with $Rec/PEEP_{TOT} > 14.5$ ml/cmH_2O, no (%)	3 (17)	4 (22)	4 (22)	0.81
Volumetric capnography				
Total dead space, ml	270 [244–299]*	170 [165–214]*°	261 [239–295]°	< 0.001
Airway dead space, ml	186 [179–198]*	105 [92–114]*°	189 [171–200]°	< 0.001
Alveolar dead space, ml	79 [60–109]	67 [52–108]	76 [57–121]	0.68
Alveolar tidal volume, ml	406 [349–444]*	366 [316–414]*°	431 [367–461]°	0.002
Gas exchange				
PaO_2/FiO_2	199 [163–232]	185 [160–223]	198 [166–228]	0.27
pH	7.44 [7.41–7.47]*	7.43 [7.41–7.46]*	7.44 [7.41–7.46]	0.002
Arterial pCO_2, mmHg	33 [31–34]	34 [33–35]	34 [32–35]	0.57
Hemodynamics				
Heart rate, bpm	65 [60–74]	64 [58–77]	67 [59–72]	0.56
Mean arterial pressure, mmHg	90 [79–95]	88 [79–95]	88 [78–97]	0.83
Intracranial pressure, mmHg	14 [6–15]	13 [10–16]	12 [8–15]	0.31
Cerebral perfusion pressure, mmHg	77 [67–87]	75 [69–84]	76 [70–85]	0.68
Middle cerebral artery flow velocity, cm/sec	84 [58–102]	85 [54–96]	85 [51–102]	0.73

Data expressed as median [interquartile range], if not otherwise specified

*$p < 0.05$ for comparison HME1 versus HH

°$p < 0.05$ for comparison HME2 versus HH

§$p < 0.05$ for comparison HME1 versus HME2

allowed to reduce V_T/kg PBW by 1.8 [95% CI: 1.5–2.1] ml/kg and ΔP by 3.7 [95% CI: −2.9 to −4.3] cmH_2O.

Several strategies have been proposed to mitigate VILI and improve clinical outcome during ARDS: Among these, the most convincing are lower V_T, prone positioning and, possibly, mid-to-high PEEP with/without muscle paralysis in most severe patients [7, 22, 34–37]. Prone positioning may yield increases in intracranial pressure [38]; the use of high PEEP may not be safe in all brain-injured patients due to its possible detrimental effects on central venous pressure, venous return, cardiac output, and intracranial pressure [39]; thus, lowering V_T appears as the only available intervention to enhance lung protection in this context [40]. This appears of crucial importance when brain injury coexists, as these patients are burdened by high risk of respiratory complications, high tracheostomy rates, prolonged mechanical ventilation, and worse clinical outcome [2, 13, 41, 42].

The ΔP, which is V_T normalized to C_{RS} and is a surrogate of the dynamic strain [43], represents the final

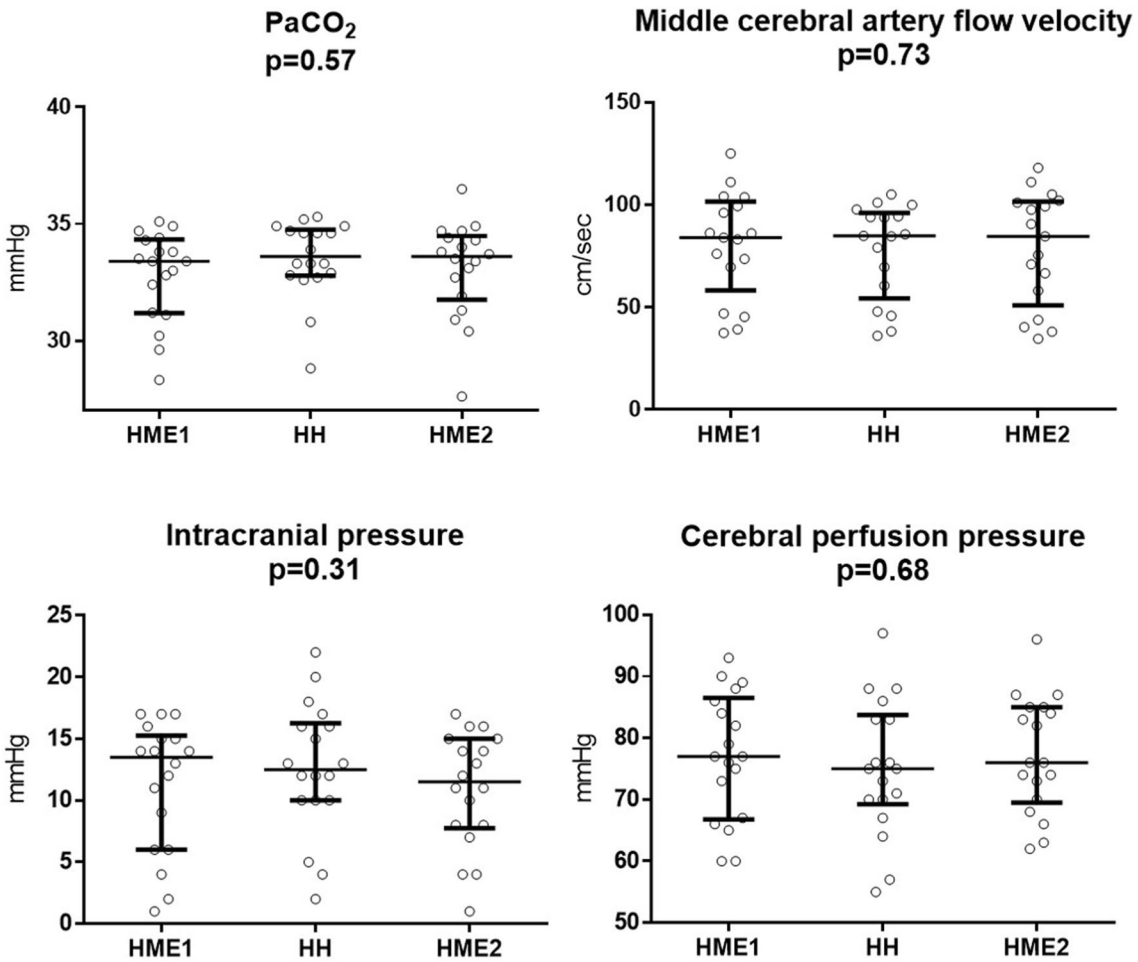

Fig. 1 $PaCO_2$, middle cerebral artery mean blood flow velocity, intracranial pressure, and cerebral perfusion pressure in the three study steps. Individual data and medians with interquartile ranges are displayed

mediator of ventilator settings effects on clinical outcome [44, 45]: Although a safe threshold for this parameter has not been identified yet, patients with $\Delta P \leq 14$ cmH_2O show improved survival [46]. Our protocol led to an increase in the proportion of patients showing $\Delta P \leq 14$ cmH_2O from 39 to 89%, thus suggesting a possible clinical benefit by this approach. Although V_T and ΔP reductions are among the most important modifiable factors capable of improving survival during ARDS [47], the use of HH was not associated with improved clinical outcome in wide unselected cohorts of mechanically ventilated patients [48]. In previous studies, however, the use of HH was not systematically accompanied by V_T reduction as it is in our protocol, so that any possible benefit could have been underestimated.

In our study, the use of low V_T leads to a significant increase in static C_{RS} without affecting the linear compliance measured between lower and upper inflection point. Lung volume, as defined by Rec, did not change nor patients' position varied among the study steps, and chest wall elastance was likely constant over the entire course of the study, thus suggesting that any observed change in respiratory mechanics reflects variations in lung mechanics: In particular, the results inhering static and quasi-static compliance indicate some degree of lung overdistention when higher V_T were used, as already suggested by other authors [20, 49, 50].

Although previous data indicate that lower V_T can favor alveolar derecruitment [7, 51, 52], we do not report significant derecruitment or oxygenation worsening during V_T reduction. Lung volume change as a response to PEEP may significantly vary among patients according to different degrees of lung recruitability [53, 54]. Accordingly, only 17–22% of our patients showed a high recruitability profile (i.e., > 14.5 ml/cmH_2O of PEEP), as compared to 50% of patients in previous ARDS cohorts

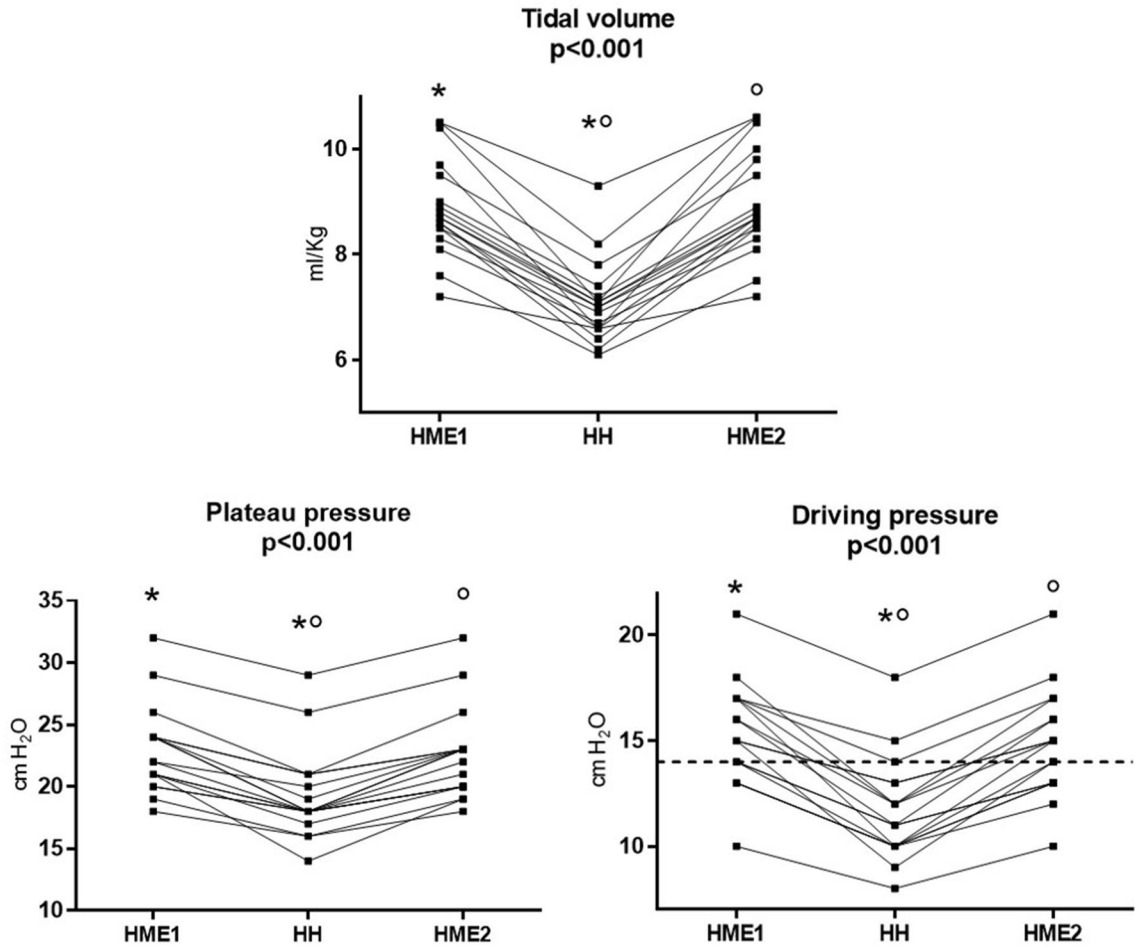

Fig. 2 Tidal volume, plateau pressure, and driving pressure, in the three study steps. Individual data are displayed. Horizontal line indicating driving pressure = 14 cmH_2O is showed: Note that 16/18 (89%) of patients have a driving pressure ≤ 14 cmH_2O in the HH step, as compared to 7/18 (39%) and 8/18 (44%) during HME1 and HME2 ($p < 0.001$). * indicates $p < 0.05$ for comparison HME1 versus HH; ° indicates $p < 0.05$ for comparison HME2 versus HH

[32], so that the scarce derecruitment effect of lower tidal volume observed in our study may be explained by this particular characteristic of the studied population. In this sense, because of the risk of further impairment in oxygenation that can be fatal in brain-injured subjects, we did not enroll patients with severe ARDS who, indeed, show the highest lung recruitability profile [54, 55]. Moreover, higher PEEP (up to 20 cmH_2O or further) may be required to achieve optimal lung recruitment [56] and such values may be difficult to apply in brain-injured patients.

Finally, and most importantly, our approach is simple, easily bedside available and showed a broad safety spectrum: No hemodynamic instability, abrupt increases in end tidal CO2 ($EtCO_2$) and intracranial pressure, decreases in SpO_2 and cerebral perfusion pressure, or any other adverse events were detected over the course of the entire study. Similarly, the use of low V_T was not associated with changes in cerebral perfusion pressure or blood flow velocity in the middle cerebral artery.

The main limitation of the present study is its sequential crossover design, since the predetermined order of interventions may have affected the outcome. However, we tried to mitigate this aspect introducing a HME2 step, when all the baseline conditions were resumed. The substantial equivalence between most of the parameters in step HME1 and HME2 suggests that the patients were not subject to changes in respiratory, hemodynamic, and cerebral conditions during any of the study period, thus contributing to the strength and reproducibility of our findings. The small differences between HME1 and HME2 can be ascribed to the limited sample and the statistical rank-based test used for the analysis. Finally, initial tidal volumes and respiratory rates reflect individual

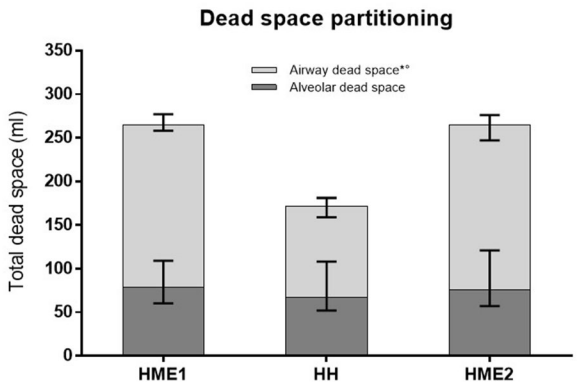

Fig. 3 Partitioning of dead space in the three study steps. Median and interquartile ranges are displayed. Total dead space was lower during HH, as compared to HME1 and HME2 ($p < 0.001$). The reduction in dead space was due to a lower airway dead space in the HH step. * indicates $p < 0.05$ for comparison HME1 versus HH; ° indicates $p < 0.05$ for comparison HME2 versus HH

clinician's attitude in the treatment of patients with brain injury, and a strictly low-tidal ventilation strategy was not applied at baseline. This is consistent with previous reports, indicating that patients with brain injury are often exposed non-protective ventilation settings [12–16]. Indeed, the aim of this study was limited to the assessment of the physiological effects of changing from an HME device to HH.

Conclusions

The use of HH in patients with brain injury and ARDS reduces instrumental dead space and allows to reduce tidal volume and driving pressure in isocapnic conditions, with no alveolar derecruitment, hypoxemia, changes in cerebral perfusion pressure nor blood flow. This increases the proportion of patients receiving mechanical ventilation within safety limits. Given its safeness and strong pathophysiological plausibility, we deem this intervention can be recommended among the first-line ventilatory management in brain-injured ARDS patients.

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Conflict of interest
DLG has received payments for travel expenses by Maquet, Air Liquide, and reports non-financial support by Dimar. MA has received payments for personal fees by Orion and Pfizer, and reports a research grant by Estor. DLG and MA disclose a research grant by General Electric Healthcare.

Ethical approval/Informed consent
The study was conducted in the general intensive care unit (ICU) of a university hospital in Rome, Italy. Written informed consent was obtained from all study participants. The study protocol was approved by the Institutional Review Board of the Catholic University of the Sacred Heart of Rome, Italy (IRB approval number 8060/13) and we have adhered to ethical considerations in the protection of all patients involved according to the principles of the Declaration of Helsinki.

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