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RESEARCH ARTICLE

Determinants of the esophageal-pleural pressure relationship in humans

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Pasticci I, Cadringher P, Giosa L, Umbrello M, Formenti P, Macri MM, Busana M, Bonifazi M, Romitti F, Vassalli F, Cressoni M, Quintel M, Chiumello D, Gattinoni L. Determinants of the esophageal-pleural pressure relationship in humans. *J Appl Physiol* 128: 78–86, 2020. First published November 27, 2019; doi:10.1152/japplphysiol.00587.2019.—Esophageal pressure has been suggested as adequate surrogate of the pleural pressure. We investigate after lung surgery the determinants of the esophageal and intrathoracic pressures and their differences. The esophageal pressure (through esophageal balloon) and the intrathoracic/pleural pressure (through the chest tube on the surgery side) were measured after surgery in 28 patients immediately after lobectomy or wedge resection. Measurements were made in the nondependent lateral position (without or with ventilation of the operated lung) and in the supine position. In the lateral position with the nondependent lung, collapsed or ventilated, the differences between esophageal and pleural pressure amounted to 4.4 ± 1.6 and 5.1 ± 1.7 cmH_2O. In the supine position, the difference amounted to 7.3 ± 2.8 cmH_2O. In the supine position, the estimated compressive forces on the mediastinum were 10.5 ± 3.1 cmH_2O and on the iso-gravitational pleural plane 3.2 ± 1.8 cmH_2O. A simple model describing the roles of chest, lung, and pneumothorax volume matching on the pleural pressure genesis was developed; modeled pleural pressure = 1.0057 × measured pleural pressure + 0.6592 ($r^2 = 0.8$). Whatever the position and the ventilator settings, the esophageal pressure changed in a 1:1 ratio with the changes in pleural pressure. Consequently, chest wall elastance (E_{cw}) measured by intrathoracic ($E_{cw} = \Delta Ppl/tidal\ volume$) or esophageal pressure ($E_{cw} = \Delta Pes/tidal\ volume$) was identical in all the positions we tested. We conclude that esophageal and pleural pressures may be largely different depending on body position (gravitational forces) and lung-chest wall volume matching. Their changes, however, are identical.

NEW & NOTEWORTHY Esophageal and pleural pressure changes occur at a 1:1 ratio, fully justifying the use of esophageal pressure to compute the chest wall elastance and the changes in pleural pressure and in lung stress. The absolute value of esophageal and pleural pressures may be largely different, depending on the body position (gravitational forces) and the lung-chest wall volume matching. Therefore, the absolute value of esophageal pressure should not be used as a surrogate of pleural pressure.

acute respiratory distress syndrome; esophageal pressure; lung volume; mechanical ventilation; pleural pressure

INTRODUCTION

In recent years, there has been increasing attention to and interest in the assessment of transpulmonary pressure (1, 14). It is indeed widely accepted that transpulmonary pressure, and not airway pressure, is the distending force of the lungs (16). Therefore, its determination may avoid either the underexpansion or overdistension of the lung. Indeed, an altered chest wall elastance with the consequent decrease in transpulmonary pressure may lead to lung collapse, as observed in acute respiratory distress syndrome (ARDS) patients (11) Conversely, a high transpulmonary pressure causes nonphysiological stress and strain, which, together with respiratory rate, are the main determinants of ventilator-induced lung injury (VILI) (8). Transpulmonary pressure is the difference between airway and pleural pressures. Although airway pressure measurements are easily performed, the most accepted clinically available method to estimate pleural pressure is by measuring esophageal pressure. However, the extent to which esophageal pressure reflects pleural pressure is still under debate (9, 13). Although it has been known since the first determinations of esophageal and pleural pressure that changes in pleural pressure are reflected by changes in esophageal pressure (4), the meaning of the absolute esophageal pressure is still undecided (5, 21). This issue is not only theoretical but is also of some clinical importance, since the absolute esophageal pressure values have been proposed (5) and actually used (3) for setting the level of positive end-expiratory pressure (PEEP). In this study, we aimed to define the relationship between the absolute values of esophageal and pleural pressure and their variation under different positions and ventilator settings in subjects requiring pulmonary lobectomy or wedge pulmonary resection (i.e., decreased tissue volume) in otherwise normal lungs. To further elucidate beyond the gravitational forces the role of chest and lung volume matching on pleural pressure, we developed a model to quantitate this effect, and we compared the model-derived and the measured pleural pressure. Together with the hydrostatic pressure, the chest wall and lung volume matching may account for the differences between pleural and esophageal pressure and may be of particular relevance in all of

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the conditions in which chest and lung volumes are differently altered.

METHODS

Patients

The study included 28 consecutive patients (17 men, 11 women) undergoing thoracic surgery. The project was approved by the local Institutional Review Board (no. 42960/2016; Comitato Etico Interaziendale Milano Area A, Milan, Italy; chairperson: Prof. A. M. Di Giulio). Informed consent was obtained according to Italian regulations. Anesthesia was maintained with sevofluorane and continuous infusion of remifentanil. Muscle paralysis was maintained with cisatracurium. At the end of surgery, a 28-Ch, 50-cm, five-hole chest tube (MedicoPlast International GmbH, Illingen, Germany) was positioned on the lateral thoracic wall along the mid-axillary line with the distal end in the apex of the thoracic cavity (Supplemental Fig. S1; all Supplemental material for this article can be found at https://doi.org/10.6084/m9.figshare.9981482). The correct placement of the catheter was checked with a chest X-ray.

Ventilation

The trachea was intubated with a left-sided double lumen endobronchial tube (DLT; Rusch, Teleflex Medical, Seattle, WA) of the appropriate size (37 to 41 F). Bronchoscopy was used to identify the correct position of the DLT both with the patient supine and in the lateral position. Subsequently, both the endobronchial and tracheal cuffs were inflated, and possible air leaks were excluded with an inspiratory pause. Before the one-lung ventilation, the opening of the left or right lumen of the endotracheal tube was used to passively deflate the lung. No active suction was needed. All patients were ventilated in volume control mode, with a tidal volume between 5 and 8 mL/kg of predicted body weight. A constant inspiratory flow with an inspiration to expiration (I/E) ratio of 1:2 was used. The respiratory rate was adjusted to give an end-tidal carbon dioxide concentration of 35–40 mmHg. A PEEP of 8 cmH_2O was applied, and the oxygen fraction was adjusted to maintain an arterial saturation between 96 and 99%. At the end of the surgery, after the first set of measurements (lateral without ventilation), the collapsed lung was actively re-expanded by the connection to the ventilator. A detailed description of the anesthesia conduction is available in the Supplemental Material.

Measurements

Esophageal pressure. Esophageal pressure (Pes) was measured using a standard balloon catheter (Smart Cath; Viasys, Palm Springs, CA), introduced transorally into the esophagus, and inflated with 1.5 mL of air. The correct position of the balloon was checked by the occlusion test (Baydur test) before the surgery.

Pleural pressure. A short, sterile T-connector (Medline Industries, Inc, Mundelein, IL), was inserted between the chest tube and the drain system to permit the direct measurement of pleural pressure. The tube was then connected to a one-way escape valve using a standard underwater seal. No suction was applied to the drainage system. Pleural pressure (Ppl) was measured in direct proximity to the nondependent lung by connecting the T-connector of the chest tube to a pressure transducer. It was occluded distally to the transducer to confirm that the pressure in the lumen was the same as the intrathoracic pressure (Supplemental Fig. S2).

Measurements were performed through two separated and dedicated pressure transducers at the following times: *1*) patient in the lateral position with no ventilation after closing the chest at the end of the lung resection, *2*) patient in the lateral position with ventilation of both lungs after re-expansion of the nondependent lung, and *3*) patient in the supine position with both lungs ventilated (see Fig. 1).

Respiratory Mechanics

The static airway, esophageal, and pleural pressures were measured during end-inspiratory and expiratory pauses. Mechanics were derived as follows:

$$\text{Respiratory system elastance } (E_{TOT}) = \frac{\text{Paw plateau} - \text{PEEP}}{\text{Tidal Volume}},$$

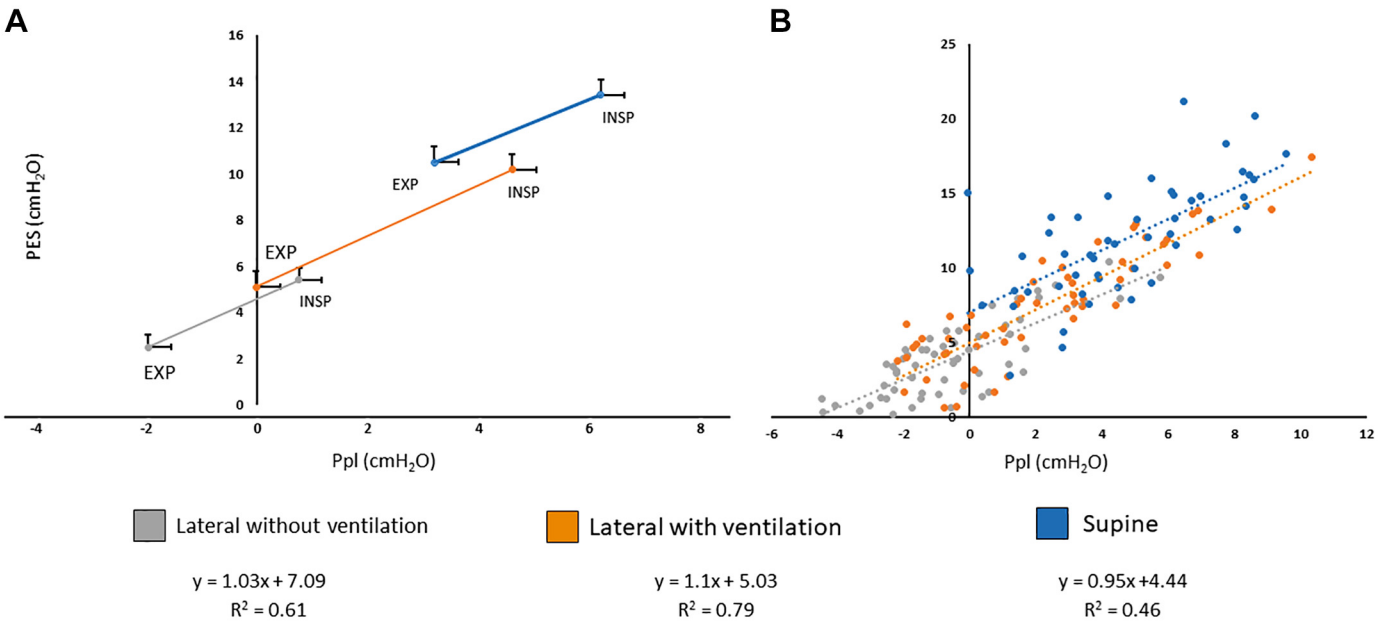

Fig. 1. Relationship between pleural (*x*-axis) and esophageal (*y*-axis) pressure in the lateral position without ventilation (gray), the lateral position with ventilation (orange), and the supine position (blue). *A*: we report end-inspiratory and end-expiratory pleural and esophageal pressure measured in the 3 positions (means ± SE). *B*: scatterplot of the individual data points. The linear regressions relative to the 3 positions are reported. Data from 3 patients in the supine position are missing. EXP, during expiratory hold; INSP, during inspiratory hold; Pes, esophageal pressure; Ppl, pleural pressure.

$$\text{Chest wall elastance } (E_{CW} = \text{Ppl derived}) = \frac{\Delta Ppl}{\text{Tidal Volume}},$$

$$\text{Chest wall elastance } (E_{CW} = \text{Pes derived}) = \frac{\Delta Pes}{\text{Tidal Volume}},$$

and

$$\text{Lung elastance } (E_{TOT} = \text{Ppl derived}) = \frac{(\text{Paw plateau} - \text{PEEP}) - (\Delta Ppl)}{\text{Tidal Volume}},$$

where Paw is the airways pressure, PEEP is the positive end-expiratory pressure, E_{cw} is the chest wall elastance, and E_{tot} is the elastance of the respiratory system.

Estimate of the Pneumothorax Volume and its Effect

Pneumothorax volume in patients with double lung ventilation (supine and lateral). In the patients in which the pneumothorax was not detectable (20 patients) at the postero-anterior X-Ray, we estimated its volume as 50 mL by default. In the patients in which the pneumothorax was visible (8 patients, only 1 with a clinically significant PNX), we estimated the volumes using the method proposed by Rhea et al. (19) and adapted by Choi et al. (6) to antero-posterior X-rays. Briefly, the average intrapleural distance was determined as the average distance between the parietal and visceral pleura as *1*) vertically, as the distance between the lung apex and the superior border of the collapsed lung lobe; *2*) horizontally, as the distance between the lateral border of the collapsed lung (divided into halves) and the inner border of the thoracic cage; and *3*) horizontally, as the distance between the border of the lower half of the collapsed lung and the inner border of the thoracic cage.

The average interpleural distance was computed as (A + B + C)/3, and the percentage of pneumothorax in the hemithorax was computed as

$$V_{PNX} = (\%\text{ of hemithorax}) = 8.73 + 10.03 \cdot \frac{(A + B + C)}{3};$$

(see Supplemental Fig. S1*B*).

Pneumothorax Volume in Patients in Lateral Position Without Ventilation

Because chest X-ray was not available in this condition, the pneumothorax volume was arbitrarily estimated from the expected difference between the chest wall and the lung volumes at the end of the surgery, after the chest wall closure and before the lung expansion. See below for the procedure.

To roughly estimate the possible effects of a close pneumothorax on the pleural pressure, we developed the following model composed by two concentric spheres with their own volume and elastance, where the outer sphere represents the volume of thoracic cage and the inner sphere the volume of the lung and the volume between the two spheres represents the pneumothorax (See Supplemental Fig. S2). If taken alone, thoracic cage, lung, and pneumothorax do have their own "resting position;" the isolated lung tends to collapse, and the thoracic cage tends to expand (see Supplemental Fig. S2). When the lung sphere is placed inside the thoracic sphere, its volume must increase:

$$V_L = V_{LR} + \frac{P_{AW} - P_{PL}}{E_L}, \quad (1)$$

where V_L is the lung volume, V_{LR} is the resting lung volume, P_{AW} is the airway pressure, P_{PL} is the pleural pressure, and E_L is the lung elastance. Note that the term $\frac{P_{AW} - P_{PL}}{E_L}$ represents the lung volume increase due to the transpulmonary pressure. As an example, at end expiration at atmospheric pressure, if the pleural pressure is −2 cmH2O, the transpulmonary pressure will be equal to 2 cmH_2O, and the volume added to the resting lung volume will be 0.4 L if the lung elastance is 5 cmH_2O/L. On the other hand, the chest wall volume will be:

$$V_C = V_{CR} + \frac{P_{PL} - P_{musc}}{E_C}, \quad (2)$$

where V_C is the chest wall volume, V_{CR} is the resting chest wall volume, P_{PL} is the pleural pressure, E_C is the chest wall elastance, and P_{musc} is the pressure exerted by the respiratory muscle (zero in our experimental condition of anesthesia and paralysis). Note that the term $\frac{P_{PL}}{E_C}$ represents the chest wall volume decrease due to the transthoracic pressure. As in the example above, the volume subtracted from the resting volume will be −0.4 L if the chest wall elastance is 5 cmH_2O/L and the pleural pressure −2 cmH_2O.

In addition,

$$V_{PNX} = V_{PNXR} - \frac{P_{PL}}{E_{PNX}}, \quad (3)$$

where V_{PNX} is the pneumothorax volume, in which we included the volume of the measurement apparatus, V_{PNXR} is the resting pneumothorax volume, P_{PL} is the pleural pressure, and E_{PNX} is the pneumothorax elastance. E_{PNX} was computed as $\frac{1033}{V_{PNX}}$. Given that

$$V_{PNX} = V_C - V_L \quad (4)$$

It follows that, substituting the variables in *Eq. 4* with *Eqs. 1*, *2*, and *3* and solving for P_{PL}, the final equation results in the following:

$$Ppl = \frac{E_{cw}E_l(V_{pnx} + V_l - V_{cw}) + E_{cw}P_{aw} + E_lP_{musc}}{E_{cw+}E_l + \frac{E_{cw}E_l}{E_{pnx}}}.$$

Model Application

To apply the above model in our population, we computed for each patient the expected lung volume and thoracic volume at atmospheric pressure (functional residual capacity FRC) according to Ibañez and Raurich (12) (for the sake of clarity, we did not consider the tissue volume, which, however, is of paramount importance when dealing with diseased and edematous lung). In these patients, we assumed that at FRC the average pleural pressure was equal to −2 cmH_2O. Using the *Eqs. 1* and *2*, we computed the lung resting volume and chest wall resting volume, and the elastances we used in the equations were the ones measured in supine position using the measured pleural pressure. To account for the lung volume reduction due to the surgery, the resting lung volume was decreased by 20% in patients undergoing lobectomy and 10% in patients undergoing wedge resection. The measuring apparatus volume (60 mL) was added to the pneumothorax volume. The pneumothorax volume introduced in the model was the one estimated from postoperative X-ray in case of lateral or supine double ventilation, whereas it was estimated based on several assumptions in lateral position without ventilation. Indeed, regarding lateral position without ventilation, this condition was tested immediately after the chest wall closure with the operated lung collapsed. On the operated side, the lung and the thoracic volumes should tend toward their resting position (i.e., the lung more collapsed and the chest wall more expanded). We arbitrarily estimated the pneumothorax volume in this condition as

$$V_{PNX} = \frac{2}{3}\left(\frac{V_{CR} - V_{LR}}{2}\right).$$

Table 1. *Patient anthropometric, clinical, and spirometric characteristics before surgery*

Patient anthropometric characteristics (n = 28)	Value
Age, yr	69 ± 11
Male sex	17 (60.7)
Actual body weight, kg	72.5 ± 13.5
Ideal body weight, kg	63.5 ± 6.5
Body mass index, kg/m^2	24.9 ± 4.6
Underlying conditions	
Hypertension	17 (60.7)
Coronary artery disease	1 (3.6)
Diabetes	4 (14.3)
Active smoker	8 (28.6)
Pulmonary function tests (%predicted)	
FVC	100.3 ± 17.8
FEV1	93.5 ± 15.1
FEV1/FVC	96.4 ± 12.7
Carbon monoxide diffusion capacity	72.9 ± 16.8
Previous lung conditions	
Obstructive	4 (14.3)
Restrictive	1 (3.6)
Previous lung surgery	4 (14.3)
Type of lung surgery	
Wedge resection	12 (42.9)
Lobectomy	16 (57.1)
Decubitus	
Left side dependent	18 (64.3)
Right side dependent	10 (35.7)
Surgery length, min	141 ± 39
One-lung ventilation length, min	133 ± 38

Values are means ± SD; values in parentheses are in percentage. Surgical procedure. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

The division by 2 accounts for the hemithorax. The fraction 2/3 was applied empirically after the radioscopy performed in some of the patients was observed (see Supplemental Fig. S1*A*).

Lateral position with ventilation. The pneumothorax volumes used in the model were the ones computed from the chest X-ray.

Supine position. The pneumothorax volumes used in the model were the ones computed from the chest X-ray. However, to account for the gravitation forces, we added to the computed value the pleural pressure and the difference between the supine and lateral position. Indeed, we assumed that the change in pleural pressure between lateral and supine was due only to the lung weight (Fig. 5).

Statistical Analysis

Results are reported as means ± SD. Data are missing for three patients in the supine position. To compare values of esophageal and pleural pressure between right- and left-sided surgery, we used an independent-samples *t*-test since the variables were normally distributed (Shapiro-Wilk test adjusted by the Holm method). We performed linear regressions to compare esophageal and pleural pressure and measured and modeled pleural pressure. To compare the change of several continuous variables with different positions, we performed a univariate linear mixed model (fixed effect: position; random effect: patient) with multiple comparisons (Tukey's method). To compare measured and modeled pleural pressure, we performed a linear mixed model (fixed effects: measured vs modeled, position; random effect: patient) with multiple comparisons. $P < 0.05$ was considered statistically significant. The data were analyzed using R software.

RESULTS

Patients Population

In Table 1, we report the main anthropometric characteristics of the 28 patients enrolled in the study, their lung history, and their surgical procedure. As shown, most of the patients had lung function tests within the normal range, regardless of their comorbidities. The gas exchange and respiratory and hemodynamic variables measured during lateral position without ventilation and with ventilation and supine position are summarized in Table 2. As shown, the gas exchange and the hemodynamic variables were within normal limits and similar during the three positions. The minute ventilation was also similar, as the significantly lower tidal volume during the one-lung ventilation was associated with a significant increase in respiratory rate. Because the mechanical data we measured in the patients who underwent right or left lung surgery were indistinguishable, from now on we considered the patients as a unique cohort (see Supplemental Table S2).

Pleural Pressure and Esophageal Pressure

In Table 3, we present all the pressures we measured in the three positions both at end-inspiration and end-expiration (airway, esophageal, pleural pressures). As shown, both the end-expiratory and end-inspiratory pleural pressures were lower in lateral position without ventilation and progressively increased in lateral position with ventilation and reached their maximal values in supine position. A similar pattern was observed with esophageal pressures. However, one should note that despite similar behavior the differences between the esophageal and pleural pressures increased from the lateral position without ventilation, to the lateral position with ventilation, and to

Table 2. *Hemodynamics and ventilatory variables measured in the 3 positions*

Variables	Lateral Position Without Ventilation	Lateral Position With Double Lung Ventilation	Supine	*P* Value
Heart rate, beats/min	64 ± 11	62 ± 10	62 ± 12	0.53
Systolic blood pressure, mmHg	99 ± 20	99 ± 20	105 ± 25	0.49
Diastolic blood pressure, mmHg	52 ± 15	51 ± 12	57 ± 12	0.21
Mean blood pressure, mmHg	68 ± 15	67 ± 12	72 ± 16	0.25
Arterial oxygen saturation, %	96.7 ± 1.8	96.7 ± 7.8	96.7 ± 1.9	1
Tidal volume, ml	344 ± 44	461 ± 57*	467 ± 49*	<0.001
Tidal volume/body weight, ml/kg	5.4 ± 0.6	7.3 ± 0.8*	7.4 ± 0.7*	<0.001
Respiratory rate, beats/min	18.5 ± 2.3	14.6 ± 2.7*	14.7 ± 2.8*	<0.001
Minute ventilation, L/min	6.7 ± 1.4	7 ± 1.5	7.1 ± 1.4	0.33
Fraction of inspired oxygen	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.44
Partial pressure of oxygen, mmHg	85 ± 10.5	85 ± 10.5	85 ± 10.9	1
Partial pressure of CO_2, mmHg	36.4 ± 3.2	36.4 ± 3.2	36.4 ± 3.3	1

Values are means ± SE. Data are missing from 3 patients in the supine position. The *P* value refers to the linear mixed model (fixed factor: position; random factor: patient). We report multiple comparisons as follows: *$P < 0.05$ vs. lateral position without ventilation.

Table 3. *Airway, pleural, and esophageal pressure measured in the 3 positions*

Variables, cmH_2O	Lateral Position Without Ventilation	Lateral Position With Ventilation	Supine	*P* Value
Plateau airway pressure	18.8 ± 3	17.7 ± 2.2*	16.3 ± 3.9*$	<0.001
PEEP	7.6 ± 0.2	7.5 ± 0.3*	7.6 ± 0.3	0.005
Pes end-inspiratory	5.3 ± 2.5	10.1 ± 3.5*	13.4 ± 4*$	<0.001
Ppl end-inspiratory	0.7 ± 2	4.6 ± 2.3*	6.2 ± 2.2*$	<0.001
Pes end-expiratory	2.5 ± 1.7	5.1 ± 2.2*	10.5 ± 3.1*$	<0.001
Ppl end-expiratory	−1.9 ± 1.2	0 ± 1.6*	3.2 ± 1.8*$	<0.001
ΔPes	2.9 ± 1.6	5 ± 1.8*	3 ± 1.6$	<0.001
ΔPpl	2.7 ± 1.5	4.6 ± 1.5*	3 ± 1.5$	<0.001

Values are means ± SE. PEEP, positive end-expiratory pressure; Pes, esophageal pressure; Ppl, pleural pressure; ΔPes, Pes end-inspiratory − Pes end-expiratory; ΔPpl, Ppl end-inspiratory − Ppl end-expiratory. Data are missing from 3 patients in the supine position. *P* value refers to the linear mixed model (fixed factor: position; random factor: patient). We report multiple comparisons as follows: *$P < 0.05$ vs. lateral position without ventilation; $$P < 0.05$$ vs. lateral position with ventilation.

supine position (4.4 ± 1.6, 5.1 ± 1.7, and 7.3 ± 2.84 cmH_2O, respectively, $P < 0{,}001$).

Figure 1*A* shows the average esophageal pressure as a function of average pleural pressure (inspiratory and expiratory) for each position, whereas Fig. 1*B* shows a scatterplot of the single data. As shown, the slopes of the pleural-esophageal pressure regression lines were close to the unity regardless of the position (1.03, 1.10, and 0.95) in the lateral without ventilation, lateral with ventilation, and supine, respectively. This indicates that, regardless of the absolute values of pleural and esophageal pressure at end-expiration, their changes during inflation occur in a 1:1 ratio (see Supplemental Fig. S3 for details).

Chest Wall and Lung Elastances

In Table 4, we present the elastances we calculated in the three positions. The chest wall elastance and the lung elastances were measured directly using the pleural pressure (E_{cw} = ΔPpl/Tidal Volume) and indirectly using the esophageal pressure (E_{cw} = ΔPes/Tidal Volume) (10). As shown in Fig. 2, the plot of the chest wall elastances computed either directly or indirectly followed the identity line. In Fig. 3, we present the elastances measured in the three different positions. As shown, the total respiratory system elastance was greater in the lateral position without ventilation than in the lateral position with ventilation or in the supine position. Lung elastance was significantly greater in the lateral position without ventilation than in the two other positions ($P < 0.01$), whereas chest wall elastance was significantly greater in the lateral position with double lung ventilation.

Measured and Model-Derived Pleural Pressures

In the lateral position without ventilation, the estimated pneumothorax averaged 0.28 ± 0.12 L, whereas the lateral position with ventilation and the supine position averaged 0.1 ± 0.09 L. These values were used in the model to compute the pleural pressure. In Table 5, we present the pleural pressure values we computed, applying the model to our population in the three positions. As shown, the computed pleural pressure was similar to the measured pleural pressure in the lateral position with and without ventilation, but it was ~1.6 cmH_2O higher in the supine position. The scatterplot of the data is presented in Fig. 4, where we show the pleural pressure obtained with the model as a function of the pleural pressure measured. The relationship is described by the following equation: modeled P_{pl} = 1.00 measured P_{pl} + 0.66 cmH_2O ($r^2 = 0.8$).

DISCUSSION

Major Findings

The major findings of this study are that *1*) esophageal and pleural pressures were lower in the lateral than in the supine position, *2*) their difference was significantly greater in the supine than in the lateral position, and *3*) every change in pleural pressure induced an identical change in esophageal pressure. Consequently, the relationships between the elastances measured directly using pleural pressure or indirectly using esophageal pressure followed the identity line.

End-Inspiratory Pleural and Esophageal Pressures

Although the absolute pleural and esophageal pressures differed in the supine and in both lateral positions, any change of ventilation leading to an increase in pleural pressure led to a change in esophageal pressure at a 1:1 ratio. This is clearly shown in Fig. 2. These results were expected, as the equivalence between change of esophageal pressure and changes in pleural pressure were already observed since the first experi-

Table 4. *Total, lung, and chest wall elastances measured by pleural and esophageal pressures in the 3 positions*

Variables, cmH_2O/l	Lateral Position Without Ventilation	Lateral Position With Ventilation	Supine	*P* Value
Total elastance	32.7 ± 7.1	22.1 ± 4.6*	18.8 ± 7.6*$	<0.001
Lung elastance Ppl	24.8 ± 6.7	11.9 ± 5*	12.3 ± 6.3*	<0.001
Lung elastance Pes	24.4 ± 6.4	11.1 ± 5.7*	12.4 ± 6.4*	<0.001
Chest wall elastance Ppl	7.8 ± 4.1	10.2 ± 3.6*	6.5 ± 3.3$	<0.001
Chest wall elastance Pes	8.3 ± 4.3	11 ± 4.2*	6.4 ± 3.5$	<0.001

Values are means ± SE. Pes, esophageal pressure-derived; Ppl, pleural pressure-derived. Data are missing from 3 patients in the supine position. *P* value refers to the linear mixed model (fixed factor: position, random factor: patient). *$P < 0.05$ vs lateral position without ventilation; $$P < 0.05$$ vs lateral position with ventilation.

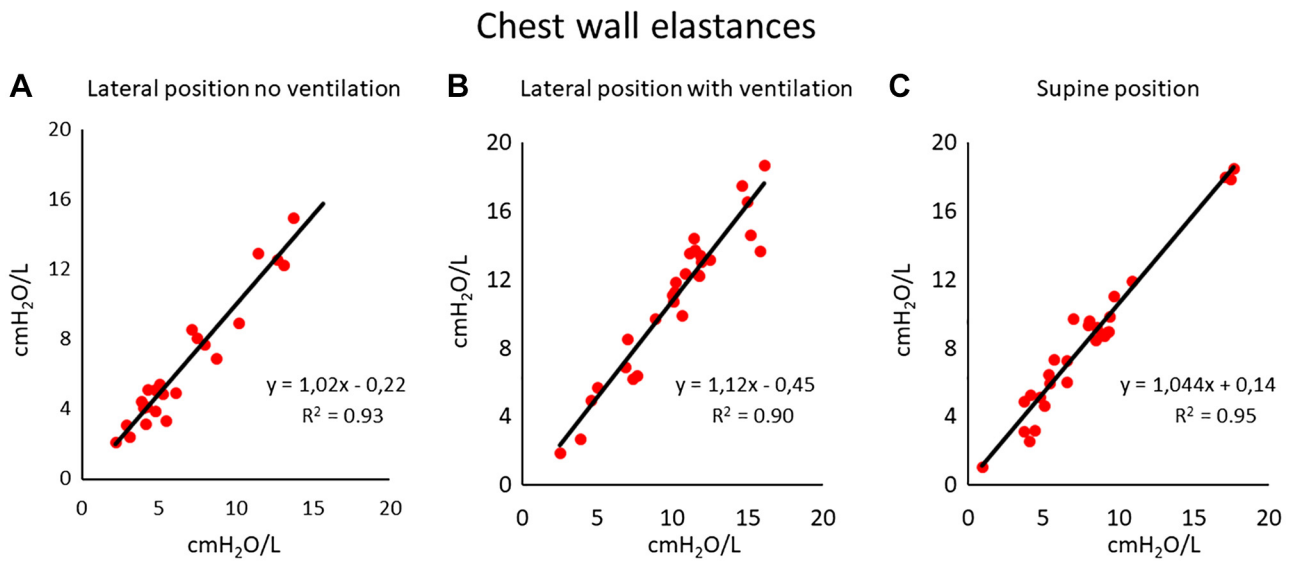

Fig. 2. Relationship between chest wall elastance as computed using Δpleural pressure (*x*-axis) and Δesophageal pressure (*y*-axis). The linear regressions relative to the 3 positions are displayed. Data from 3 patients in the supine position are missing. *A*: lateral position with no ventilation. *B*: lateral position with ventilation. *C*: supine position.

ments with esophageal manometry (4, 7, 15) and are the basis for its use in partitioning lung mechanics. The equivalence between changes in pleural and esophageal pressures, however, was also observed in the lateral position when the lung was collapsed and not ventilated. Indeed, in our study, the 2.7 ± 1.5 increase in pleural pressure during the inspiratory phase of the nondependent lung may be attributed to both the upward movement of the mediastinum and the thoracic cage interdependence. The possible effect of gas compression on the pneumothorax is negligible. Indeed, according to the general gas equation (PV = nRT), the volume of the uncompressed air is reduced by 1/1,033 of its volume for every cmH_2O of pressure applied, with 1,033 being the atmospheric pressure expressed in cmH_2O.

End-Expiratory Pleural and Esophageal Pressures

The lowest values of pleural and esophageal pressures were measured when the upper nondependent lung was unventilated and collapsed, a condition occurring immediately after the lobar resection and the closure of the chest wall. This phenomenon could not be explained only by the gravitational forces acting in the thorax. The pressure in the thoracic cavity during surgery is atmospheric. At this pressure, the volume of the thoracic cage should increase toward its resting volume, and the lung volume should decrease toward its resting volume as well (lung collapse). Therefore, after closure of the chest (when the measurements were taken), the greatest volume difference between the expanded thorax and the smaller volume of the collapsed lung resulted in the more negative pleural pressure due to the mismatch between the two structures (−1.9 ± 1.2 cmH_2O; Fig. 5*A*). In the lateral position with ventilation, pleural pressure averaged 0 ± 1.6 cmH_2O. This value likely results from the release of the lung hydrostatic pressure occurring in this position. The esophageal pressure, on the other hand, averaged 5.1 ± 2.2 cmH_2O. This value likely results from the sum of lung hydrostatic pressures superimposed to the

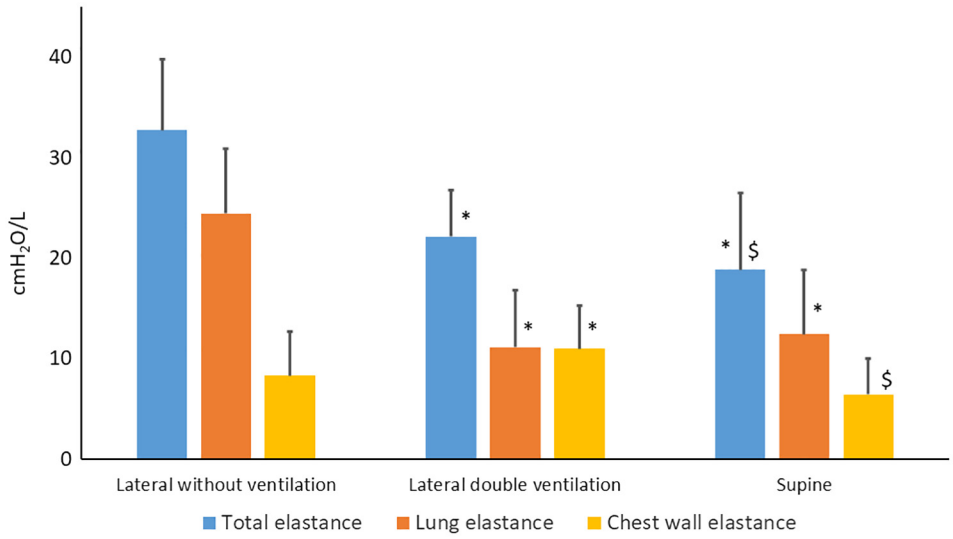

Fig. 3. Total (blue), lung (orange), and chest wall (yellow) elastances in the 3 positions (means ± SD). Data from 3 patients in the supine position are missing. *$P < 0.05$ vs. lateral position without ventilation; $$P < 0.05$ vs. lateral position with ventilation.

Table 5. *Pleural pressures (cmH_2O) measured and computed by the model in the 3 positions*

	Expiration			Inspiration		
	Measured	Modeled	*P* value	Measured	Modeled	*P* value
Lateral no ventilation	−1.9 ± 1.1	−1.4 ± 0.8	0.8	0.9 ± 1.9	1.4 ± 1.8	0.9
Lateral double ventilation	0.0 ± 1.6	0.0 ± 1.8	1	4.6 ± 2.3	4.6 ± 2.7	1
Supine	3.2 ± 1.8	4.9 ± 2.2	<0.01*	6.2 ± 2.2	7.8 ± 2.7	0.01*

Values are means ± SE. We excluded from analysis the 3 patients in the supine position. We report the *P* value of multiple comparisons (Tukey) in a linear mixed model (fixed effects: measured vs. modeled, position; random effect: patient). *Means statistically significant.

mediastinum in this position (the order of magnitude circa 2 cmH_2O) and the residual pressure exerted by the mediastinum structures (Fig. 5*B*).

The pleural-esophageal pressure differences between the supine and lateral positions are best explained by the different forces acting on the esophagus and on the pleural surface in the different positions. Because the average distance between sternum and esophagus in the supine position is ~10 cm, and assuming a mediastinal density of 1 g/mL, the compressing force acting on the esophagus would be ca. 10 cmH_2O (Fig. 5*C*). Actually, we found that the pressure on the esophageal pressure averaged 10.5 ± 3.1 cmH_2O. In contrast, the force applied on the pleural pressure at the same vertical distance from the sternum (10 cm; the superimposed pressure) should be 2.6 cmH_2O (superimposed pressure = 0.178 × vertical height + 0.008 × Vertical Height^2; see Ref. 17). Actually, the average pleural pressure we measured was 3.2 ± 1.8 cmH_2O. Therefore, a simple explanation for the difference between esophageal and pleural pressures in normal, sedated, and paralyzed subjects in the supine position (7.3 ± 2.8 cmH_2O) is that different unopposed forces act on the two structures.

Pleural Pressure Measurement

We used a 50-cm thoracic catheter with five holes in the intrathoracic section (Supplemental Fig. S1). The measurements were obtained at a constant temperature in a closed system that included the gas volume of the residual pneumothorax and that of the measuring apparatus, through which the pressure is transduced (no water column is involved). This measurement condition is more likely to reflect an "average pleural pressure" and cannot detect the regional pressure gradient (primarily due to gravitational forces) differently from other measurement techniques.

To investigate to which extent the pneumothorax may alter the pleural pressure, we modeled the chest wall and the lung as one outer and one inner sphere between which the pneumothorax volume is interposed. Despite the important limitations of the model, the computed pleural pressure fitted reasonably well with the "average pleural pressure" found experimentally (Table 5 and Fig. 4). Interestingly, we found that the pleural pressure computed by the model in the supine position was significantly higher than the measured one (~1.6 cmH_2O), whereas it was similar in the other two positions. It is tempting to speculate that this discrepancy is due to an overestimation of the gravitational forces that we assumed to be equal to the difference between lateral and supine position. If so, only 70% of difference between supine and lateral position pressure should be attributed to the gravitational forces. Our model, anyway, allows us to appreciate the quantitative effect of the pneumothorax. As an example, hypothetically doubling the pneumothorax volumes in our patient cohort, the end-expiratory pleural pressure would increase by ~1 cmH_2O, from

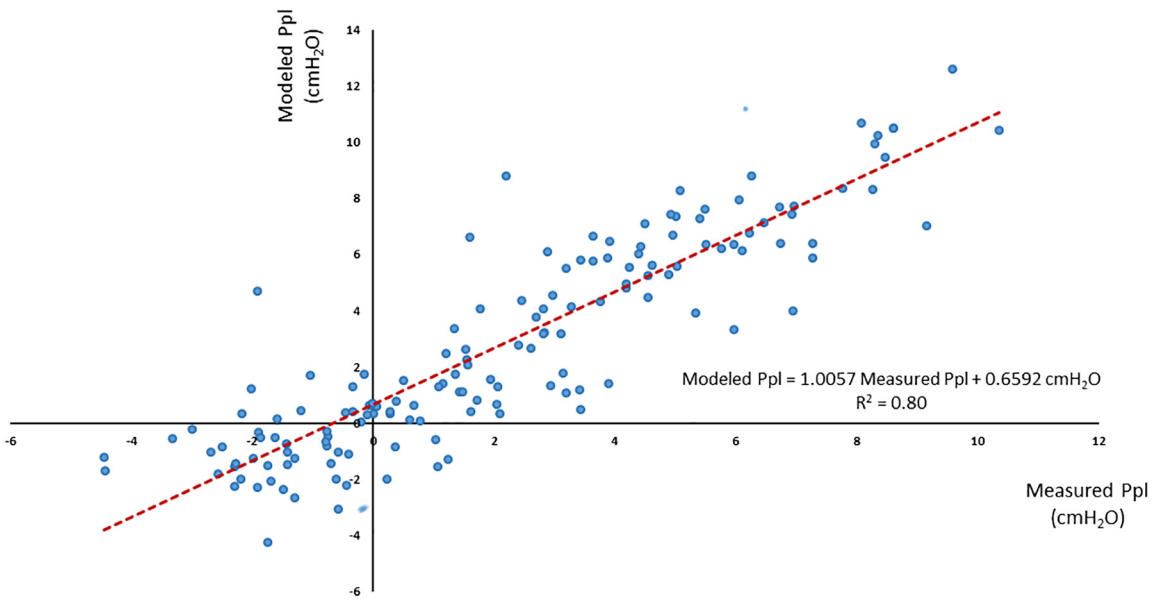

Fig. 4. Pleural pressure (Ppl) computed by the model as a function of the Ppl measured. Data are shown lumping the 3 positions together. The linear regression is shown. Data from 3 patients in the supine position are missing.

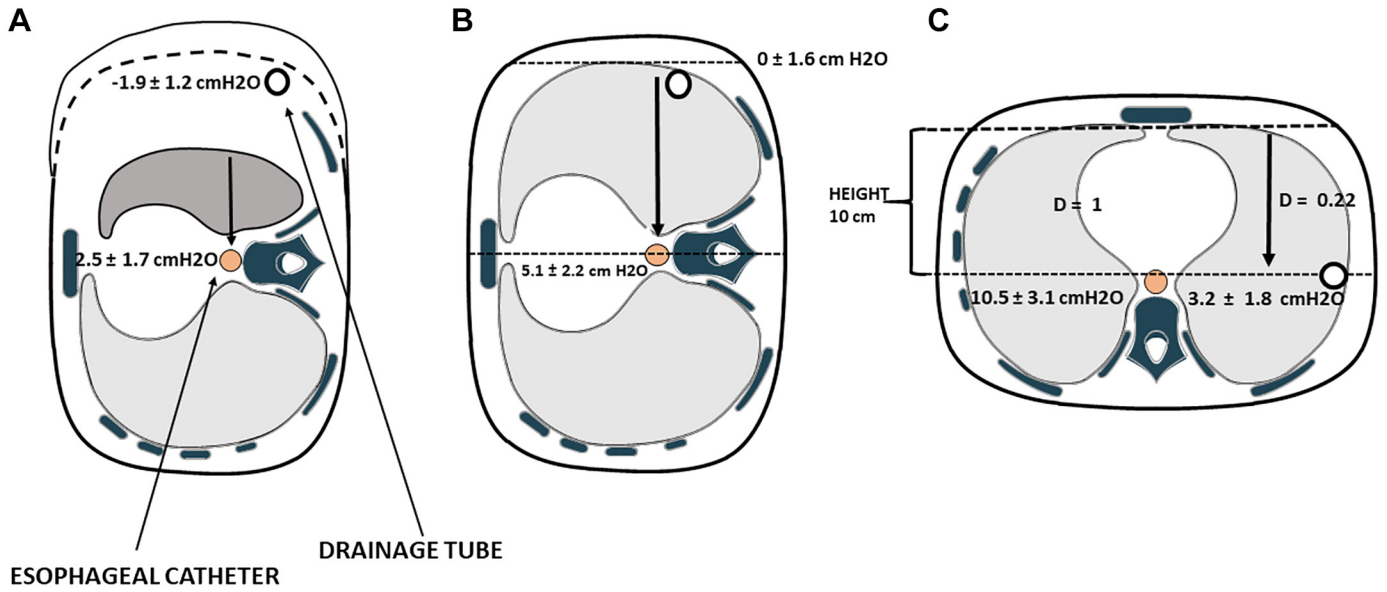

Fig. 5. Forces operating on pleural surface end esophagus in the lateral position with no ventilation (*A*), the lateral position with ventilation (*B*), and the supine position (*C*). See text for explanation.

-1.4 ± 0.8 to 0.2 ± 0.6 cmH_2O in lateral position without ventilation, from 0.0 ± 1.8 to 1.0 ± 2.2 cmH_2O in lateral position with ventilation, and from 4.9 ± 2.2 to 5.5 ± 2.2 cmH_2O in the supine position. In general, it may be shown that if the gas volume lost because of lung collapse is replaced by an equivalent volume of pneumothorax, the pleural pressure will not change, as in the closed system with the chest tube clamped, the pneumothorax behaves similarly to the lung. Indeed, the pleural pressure is unmodified if the chest wall and lung volume matching remains unmodified. In contrast, the pleural pressure will become more negative if the pneumothorax volume is lower than the lung volume reduction, and it will become more positive if the pneumothorax volume exceeds the lung volume loss. This underlines the importance of the volume matching in the genesis of pleural pressure.

Speculations on Esophageal and Pleural Pressure Relationship in the Diseased Lung

We may wonder to what extent the primary determinants of pleural pressure (compression forces, lung/chest volume relationship) are altered in ARDS and how these alterations may affect esophageal pressure. In the ARDS lung, the hydrostatic lung pressures acting on the pleural are two to three times greater than the normal due to edema (17). Therefore, in a heavy lung, the pleural pressure should be more similar to the esophageal pressure, as both the structures are subjected to a more similar superimposed pressure. Indeed, data obtained in dogs (18) and piglets with lavage-induced ARDS consistently showed the similarity of the absolute value of esophageal pressure and the pleural pressure at the middle-lung level, i.e., at the iso-gravitational level. Accordingly, Yoshida et al. (22) found that the esophageal pressure was higher than pleural pressure in the nondependent regions and lower than pleural pressure measured in the most dependent regions, as also described recently.

The phenomena described above are gravity dependent. However, the pleural pressure, regardless of the gravitational forces, depends on the match between lung and thoracic cage shape/volume. If so, we may speculate on what would happen in a purely lobar atelectasis. In this case, the decrease in lung volume relative to the chest equilibrium volume leads to a decrease in pleural pressure. This decrease may be so relevant that we may observe a shift of the mediastinum and the contralateral lung toward the atelectasis side (20). On the other hand, if one or more lobes are severely edematous with an increased lung volume, pleural pressure would increase. We may then speculate on the combined effects of gravity and lung-thorax matching. A possible model is represented in Supplemental Fig. S5. In patients with ARDS, we observed a large variability of absolute pleural pressure that may reflect the different matching between lung and chest volume. Therefore, a range of pleural-esophageal pressures relationship may be expected in the diseased lung from a more negative esophageal pressure when the prevalent phenomenon is lung collapse to a more positive pressure when edema expand the lung to a level greater than its volume equilibrium. If this were the case, it would be easy to understand why the titration of PEEP based on absolute esophageal manometry is questionable.

Limitations

The limitations of this study are straightforward; we measured pleural pressure with an unconventional method that does not account for pleural pressure gradient, just reflecting (as in clinical behavior) an "average" pleural pressure. Moreover, data were obtained in a healthy postoperative lung, and their translation to a patient with a severely diseased lung must be proved, as at the moment it is merely speculative.

The model we presented uniquely focuses on the possible mechanism of pleural pressure generation from the interaction of two structures with different resting volumes and elastance in the presence or absence of an interposed volume of air. It is an obvious oversimplification, particularly because as it ignores the gravitational effects, it assumes a linear elastance in the considered pressure interval and a normal average pleural

pressure of -2 cmH_2O. Applying this model required a lot of assumptions, beyond the Ibanez formula for functional residual capacity computation. In particular, our estimate of the pneumothorax volume in lateral position was fully arbitrary. Despite these severe limitations, the model-derived pleural pressure and the measured pleural pressure were reasonably well related in lateral position. In contrast, in the supine position the computed pressure was significantly higher (circa 1.6 cmH_2O) compared with the measured one. It is tempting to speculate that this discrepancy is due to an overestimation of the gravitational forces that we assumed to be equal to the difference between the lateral and supine position. If so, only 70% of difference between supine and lateral position pressure should be attributed to the gravitational forces.

Conclusions

The main determinants of pleural and esophageal pressure are the gravitational compressive forces and the lung-thorax volume match. Whatever change in pleural pressure was transmitted to the esophageal pressure at 1:1 ratio. Our findings fully justify the use of esophageal pressure to measure the chest wall elastance in a normal lung and, consequently, the use of the E_{cw}/E_{tot} to compute the changes in pleural pressure ($\Delta Ppl = E_{cw}/E_{tot} \times \Delta Paw$) and changes in lung stress ($\Delta PL = (E_{tot} - E_{cw}/E_{tot}) \times \Delta Paw$). Obviously, these formulas, to be meaningful, require that E_{cw} is constant in the range of the pressures studied and that lung and chest wall can expand.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

I.P., M.U., P.F., and L. Gattinoni conceived and designed research; M.U. and P.F. performed experiments; I.P., P.C., L. Giosa, M.M.M., M. Busana, M. Bonifazi, F.R., F.V., M.C., and L. Gattinoni analyzed data; I.P., P.C., L. Giosa, M.M.M., M. Busana, M. Bonifazi, F.R., F.V., M.C., M.Q., D.C., and L. Gattinoni interpreted results of experiments; I.P., M.C., and L. Gattinoni prepared figures; I.P., P.C., M.Q., D.C., and L. Gattinoni drafted manuscript; I.P., M.C., M.Q., D.C., and L. Gattinoni edited and revised manuscript; I.P., P.C., L. Giosa, M.U., P.F., M.M.M., M. Busana, M. Bonifazi, F.R., F.V., M.C., M.Q., D.C., and L. Gattinoni approved final version of manuscript.

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