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Bedside test for estimating stiff index in mechanically ventilated ARDS patient: a pilot study

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Abstract

Stiff index is defined as the proportion of lung tissue elasticity in relation to chest wall elasticity to pertain to its cyclic tidal volume. It is meant to reflect the risk of overloading lung pressure. Introducing the Stiff index into bedside management determines the pressure needed to keep the lung open with no risk of barotrauma.

Aim of the work The primary endpoint was to highlight the stiff index in ARDS patients as a potential surrogate for detecting the changes in lung mechanics and the assumptions underlying the estimation of relevant respiratory parameters. Secondly, we aimed to assess intrathoracic pressure ITP in view of chest wall elastance Ecw in relation to respiratory system elastance Ers within the same population.

Subjects and methods Data were collected from forty ARDS patients, diagnosed according to Berlin definition, who were admitted to ICU_S Ain Shams University hospitals during the period between December 2022 and April 2023. These populations were patients' purposive samples who underwent volume-controlled ventilation at least 2 days prior to study enrollment. Their mean age was 64.68 ± 15.01 years with males ($N=22$) to females ($N=18$) ratio 55%. Measurements of peak airway pressure, plateau pressure, and delta airway pressure change ΔPaw measured three times on end-expiratory (ee) and on end-inspiratory (ei) occlusion tests, and the higher of the three readings were reported.

Results The calculated mean Stiff index was (0.66 ± 0.159) which was correlated with Peak pressure ($r=-0.377$, $P=0.017$) and with trans-pulmonary end inspiration TPPei ($r=0.312$, $P=0.05$). The stiff index was also found to be correlated with intra-thoracic pressure ITP ($r=0.769$, P 0.001), but is not statistically significant with inspiratory tidal volume ($r=0.132$, P 0.416).

Conclusion Lung pressure loading in ARDS could be recognized by estimating an increase in stiff index. The cut point of stiff factor that limited the plateau at or below 30 cmH2o was 0.75 with 71% sensitivity and 0.63% specificity, respectively. The more the Stiff index the more was the ITP, and it had no relation to TV.

Keywords TPPei Transpulmonary pressure on end inspiration, ITP intrathoracic pressure, ARDS adult respiratory distress syndrome, Ecw elastance of chest wall

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Introduction

Stress and strain are parameters used to highlight respiratory parameters during positive pressure ventilation. In the 1960s, these terms were introduced by pulmonary physiologists to describe respiratory mechanics [1]. Strain describes the resulting change in lung volume whereas Lung stress describes the distribution of forces due to PEEP and tidal volume [2].

Elastance is the willingness of the lung to restore its resting position. This is because hysteresis is greater when breath is initiated near the residual volume and is less when at a higher lung volume. Introducing TPP, the main factor of ventilator-induced lung injury into bedside management aims to know the pressure needed to keep the lung open and to determine the influence of the chest wall on airway pressure. Eventually, esophageal pressure (P_{ES}) is essential to assess the patient's effort and the TPP generated during partial ventilatory support [3]. Measurement of TPP using an esophageal pressure balloon is not a simple technique and is less used in daily practice [4].

Stenqvist et al. [5] proposed a method to estimate TPP based non-invasively in 13 ex. vivo pigs and they demonstrated that the change in PEEP divided by lung elastance predicted the change in lung volume. When airway pressure is equilibrated with alveolar pressure, where flow is absent, the TPP corresponds to transalveolar pressure, and the airways become fully opened [6]. The need for an easy-to-use method in calculating lung elasticity has the consideration that the role of resistive forces is ruled out. Our trial was performed in combined low lungs compliance C_{lung} and chest wall C cw compliances to investigate a new term Stiff index that could be defined as the proportion of lung tissue elasticity in relation to chest wall elasticity to pertain its cyclic tidal volume.

Aim of the work

We evaluated the potential assessment of stiff factors in ARDS patients and the assumptions underlying calculating relevant respiratory parameters. Secondly, we aimed to assess ITP in view of chest wall elastance Ecw in relation to respiratory system elastance Ers in the same population during volume-controlled mechanical ventilation.

Subjects and methods

Type of study

A non-controlled, non-randomized, quasi-experimental study with purposive sampling.

Setting

ICUs of Ain Shams University between December 2022 to April 2023.

Upon approval of scientific and ethical committee research units in our chest units No. FWA000017585 the patient or his close legally responsible relevant was explained the procedure and untoward complication/s. Written informed consent or verbal (witnesses to cosign) was taken from each patient or his/her appropriate substitute decision-maker. Data were collected from 40 volume-controlled ventilated patients diagnosed with ARDS according to the Berlin definition [7, 8]. They were sedated using fentanyl and propofol.

All patients are subjected to history taking, clinical examination, and demographic data including date of birth, date of admission, clinical diagnoses, co-morbid diseases, and date of intubation. Measurements were reported as the displayed peak airway pressure, Plateau pressure, Δ Paw changes measured on occlusion expiratory and inspiratory tests, respiratory rate RR, and tidal volume TV. These were read out as three times records following a steady state of ventilatory and hemodynamic equilibrium, and the higher of three readings were reported. Measurements of lung elastance E lung, chest wall elastance Ecw, and respiratory system elastance Ers were calculated. Quasi-static compliance C sta was calculated as tidal volume divided by (plateau–$PEEP_{total}$) and the dynamic compliance C dyn was estimated by dividing tidal volume by the difference between (Peak–PEEP).

Inclusion and exclusion criteria

Inclusion criteria

Adult patients aged 18 years old or above and diagnosed as ARDS, who were connected to mechanical ventilation, for at least 2 days following admission, were enrolled. Diagnosis of ARDS was based on the Berlin definition [7] and the American-European Consensus definition [8], which removed the requirement for wedge pressure < 18 cmH20 but included acute and sudden onset of severe respiratory distress, bilateral infiltrates on frontal chest radiograph and positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) equal to or greater than or 5 cmH2o.

Exclusion criteria

Patients who had circuit leakages such as bronchopleural fistula, tracheostomy, and hemodynamic instability, e.g., shock, lung congestion, or heart failure were excluded. Patients with respiratory distress whose respiratory rate was more than 30 breaths/min, in prone position, or who had tachy-bradyarrhythmia of more than 120 beat/m or less than 60 beat/m respectively were excluded as

well. Extrapulmonary causes were not enrolled as pleural effusion, pneumothorax, post-operative abdominal surgery, intraabdominal ascites, or disturbed level of consciousness.

Statistical methods

Data were statistically described in terms of mean ± standard deviation (± SD). Numerical data were tested for the normal assumption using Kolmogorov–Smirnov test. Comparison between the study variables was done using paired *t* test. Correlation between various variables was done using Pearson moment correlation equation for linear relation of normally distributed variables and Spearman rank correlation equation for non-normal variables/non-linear monotonic relation. Accuracy was represented using the terms sensitivity, and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cutoff value for stiff-1 calculated in diagnosing plateau 30 cm H_2O or less. Two-sided p values less than 0.05 were considered statistically significant. IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows was used for all statistical analyses.

Technique

The current study used the elastance deriver method upon end-inspiratory occlusion and on end-expiratory occlusion tests [3]. Measuring of pleural pressure Ppl can be confirmed on end-expiratory pressure occlusion test during volume-controlled ventilation. This can be performed within 0.8–1.2 s [2] and is an accepted value to confirm the validity of the Ppl measure [9]. During an end-expiratory holding occlusion test, (at the beginning of inspiration) [2], the recorded negative pressure deflection from $PEEP_{total}$ to airway pressure represented pleural pressure, whereas the transpulmonary pressure remains unchanged [4].

The Intra-thoracic pleural pressure, ITP was estimated according to [1]

$$\text{ITP} = \text{Paw ei} \times (\text{E lung/Ers}) \tag{1}$$

Where E lung and Ers are elasticities of the lung and total respiratory system respectively, and Paw ei was the airway pressure record at the end of the inspiration occlusion test.

Providing airway are fully opened and Paw is atmospheric (0 = cmH2o), where no airway flow, the (0.3–0.5) second inspiratory hold pause measured the positive reflection change in airway pressure (Paw_{ei}) which surrogates pleural pressure changes at the end inspiration [3]. The P_{aw} ei and lung driving pressure ΔP were the parameters representing the corresponding pressure loads in the lung independently from the effects of the chest wall.

Transpulmonary pressure on end inspiration, TPP ei was calculated according to [3]

$$\text{TPPei} = \text{Paw ei} \times \text{Ecw/Ers} \tag{2}$$

Where E cw is the chest wall elastance.

Plateau pressure was the measurement displayed on the ventilator screen before the end-inspiratory holding maneuver. Static airway pressure (plateau pressure) does not reflect the alveolar pressure [10] and its result could be negative in its absolute value as it represented a delta difference compared to atmospheric pressure which is supposed to be zero according to elastance derived method.

Measurements of stiff index

In accordance with Umbrello M. and Chiumello D. [2018] [3] the pressure airway gradient measured on end-inspiration and end-expiration were identical with the pleural pressures measured, respectively, and the ΔP is the driving inflating force equal (P plateau -$PEEP_{total}$) [3]. These variations should be linear during tidal inflation.

$$E_{\text{Lung}} = [(P_{\text{Plateau}} - P_{\text{ES end-insp}}) - (\text{PEEP}_{\text{total}} - P_{\text{ES end-exp}})]/\text{VT} \tag{3}$$

Where ES ei and ES ee represent esophageal end inspiration and end-expiration pressures respectively, and E lung, therefore, was calculated in a negative value.

On rearrangement of the above-mentioned equation where $P_{\text{ES end- insp}}$ and $P_{\text{ES end-exp}}$ were replaced by P aw ei and Paw ex, which represent pleural pressure on end inspiration and end-expiration, respectively, it gives us

$$E_{\text{lung}} = [(\text{P}_{\text{plateau}} - \text{PEEP}_{\text{total}}) + (\text{Paw ex} - \text{P aw ei})]/\text{VT}. \tag{4}$$

Where Ppl ex and Ppl in represent ES ee and ES ei, respectively.

Given that $E_{rs} = (P_{\text{plateau}} - \text{PEEP}_{\text{total}})/\text{VT}$, with the same tidal volume, then:

$$\text{E}_{\text{lung}}/\text{Ers} = \left[(\text{P}_{\text{plat}} - \text{PEEP}_{\text{total}}) + (\text{Paw ex} - \text{P aw ei})/(\text{P}_{\text{plat}} - \text{PEEP}_{\text{total}})\right]. \tag{5}$$

Where Paw ee was the difference between the reported deflection of Paw change (on-end expiration) relative to $PEEP_{total}$, whereas P aw ei was the difference between the reported upper reflection of Paw change relative to plateau (on-end inspiration).

$$E_{\text{lung}}/\text{E rs} = 1 + [(\text{Paw ex} - \text{P aw ei})/(\text{P plateau} - \text{PEEP}_{\text{total}})]. \tag{6}$$

Since delta pleural pressure ΔPpl = (Pawex − Pawei) represents ITP, which is calculated in cmH2o and was expressed in a negative value [1]:

$$(-)\text{ITP} = \text{Paw}_{ex} \times (\text{E lung/Ers}) \quad (7)$$

Additionally, ΔP is the driving pressure of the lung which is equivalent to (P plat – PEEP_{total}).

Therefore,

$$\frac{E\ \text{lung}}{\boldsymbol{Ers}} = 1 + \frac{(-\boldsymbol{ITP})}{\Delta \boldsymbol{P}} \quad (8)$$

Because Ers = E lung + E cw, then rewriting the left side of Eq. [8]:

$$\frac{(-)\boldsymbol{E}\ \text{lung}}{(-)\boldsymbol{E}\ \text{lung} + \text{Ecw}} = 1 + \frac{(-)\boldsymbol{ITP}}{\Delta \boldsymbol{P}} \quad (9)$$

$$1 + \frac{(-)\boldsymbol{E}\ \text{lung}}{Ecw} = 1 + \frac{(-)\boldsymbol{ITP}}{\Delta \boldsymbol{P}} \quad (10)$$

Where the left side of the equation represented Stiff (e) and the right side of the equation expressed our primary endpoint which was the Stiff index.

$$\text{Stiff elastance(E)} = \left[1 + \frac{(-)\boldsymbol{E}\ \text{lung}}{\text{Ecw}}\right]. \quad (11)$$

$$\text{Stiff index} = 1 + \frac{(-)\boldsymbol{ITP}}{\Delta \boldsymbol{P}} \quad (12)$$

Consequently, the Stiff factor could be defined as the proportion of lung tissue elasticity in relation to chest wall elasticity to pertain to its cyclic tidal volume.

Measurements of chest wall elastance

Secondly, we aimed to assess ITP in view of the relative contribution of chest wall elastance Ecw to respiratory system elastance Ers. Mechanical ventilation with PEEP primarily affects cardiac function by changing lung volume and intrathoracic pressure [11]. Within this concept, we reviewed the ITP, the secondary endpoint in our study.

Results

Data of 40 volume-controlled ventilated patients diagnosed as ARDS, admitted to the ICU_S in Ain Shams University hospitals. They were collected between December 2022 to April 2023. Their mean age was 64.68 ± 15.01 years with males (n = 22) to females (n = 18) ratio 55% (Table 1). The mean ratio of PO2/Fio2 was (102.06 ± 53.91). The onset of intubation since enrollment was a mean of 7.15 ± 8.63 days. The mean of Peak, PEEP, and Plateau pressure were 32.09 ± 7.43, 6.49 ± 1.78, and 23.99 ± 7.43, respectively (Table 1).

Table 1 Demographic data of all studied populations (n = 40)

	Mean/count	SD
Age (years)	64.68	15.01
Sex (M/F)	22/18	55%/45%[a]
Onset of intubation days	7.15	8.63
PO2/FiO2 ratio	102.06	53.91
RR/ min	16.50	2.52
TV-insp ml	357.20	95.23
TV-exp ml	322.68	95.81
PEEP cmH20	6.49	1.78
PEEP total cmH20	7.54	2.46
Peak cmH20	32.09	6.97
C-dyn. ml/cmH20	14.88	5.62
C-Static ml/cmH2o	24.4	10.13
Plateau cm/H2o	23.99	7.43

Age[a] is calculated in percent (%), *TVe* tidal volume expiratory, *TV I* tidal volume inspiratory, *C dyn* dynamic compliance, *C stat* static compliance, P_{plat} pressure plateau, PEEP_{total} positive end-expiratory pressure (total)

Discussion

Stress index (SI) has been mainly evaluated to guide either PEEP alone or VT and PEEP simultaneously but not in conditions of reduced Ccw [12]. Changes in Plateau pressure and tidal ventilation surrogate the measures of lung stress and dynamic strain respectively and have been proposed to better assess the risk of hyperinflation [2]. The elastance-derived method is helpful for the measurement of changes in TPP and the changes in ITP among the inspiratory and expiratory phases respectively [3]. The age distribution is demonstrated in (Fig. 1). The privilege male-to-female contributions is demonstrated in (Fig. 2). The relative contribution of E_L /E_{rs} surrogates the pressure load on lungs within the same tidal volume (Table 2). Table 3 demonstrates the mean and SD of stiff elastance (E), index, and gradient.

Grieco DL et al. [4] demonstrated the role of TPP in patients with acute respiratory distress syndrome (ARDS) for the assessment of lung mechanics, using an elastance-derived method. The stiff factor in the current study tended to estimate the portion of ΔP that is spent to inflate the lungs relative to the portion that is required to move the chest wall (based on the relative contribution of E_{lung} to (E_{cw}/E_{rs}). In a normal situation, half of the applied PEEP would be expected to be transmitted to ITP [11] when the ratio of chest wall elastance to total respiratory system elastance is about 0.5 at functional residual capacity. This is because chest wall elastance and lung elastance are similar [12]. The elastance ratio may vary from 0.2 to 0.8 [13–15].

The same airway pressure may result in different transpulmonary pressures and pleural pressures. An increase in airway pressure might cause remarkable lung distension with an increase of TTP with a hemodynamics

Table 2 Mean and SD of respiratory measurements using elastance-derived method ($N=40$)

	Mean	SD
E cw cmH20/ml	0.068	0.024
E lung cmH20/ml	−0.022	0.018
E lung/E rs	−0.541	0.517
TPP ei cmH2o	22.67	8.38
TTP ee cmH20	3.80	1.43
ITP cmH2o	6.181	5
TPP ee cmH20	3.80	1.43
Stiff index	0.56	0.4
Delta Ppl cmH20	−8.46	5.42
Delta TPP cmH20	18.87	8.06
Palv ei cmH20	28.29	8.06

TPPei transpulmonary pressure end inspiration, *TPPee* transpulmonary pressure end expiration, *TTP* transthoracic pressure, *ITP* intrathoracic pressure, *E lung* lung elastance, *E cw* chest wall elastance, and Ers respiratory system elastance. Pressures were presented in cmH2o, Elastance in cmH2o/ml

Table 3 Demonstrating mean and SD of stiff (E), Stiff index, and Stiff gradient

	Minimum	Maximum	Mean	SD
Stiff (E)	0.27	0.97	0.66	0.195
Stiff index	-1.5	0.99	0.56	0.402
Stiff gradient	-0.86	0.90	0.47	0.349

Table 3 shows max, min, mean, and SD of all stiff components. *Stiff (E)* stiff factor (in elastance)

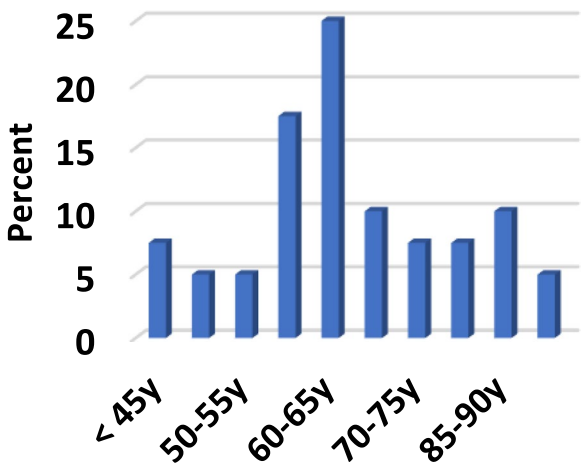

Fig. 1 Age distribution among the study sample

sequence of cardiovascular response. In ARDS patients, a combined low lung and chest wall compliances, we tested forty patients with the new lung parameter for detection of the contribution of lung elasticity (E_{lung}) relevant to chest wall elasticity (Ecw) (Figs. 1 and 2).

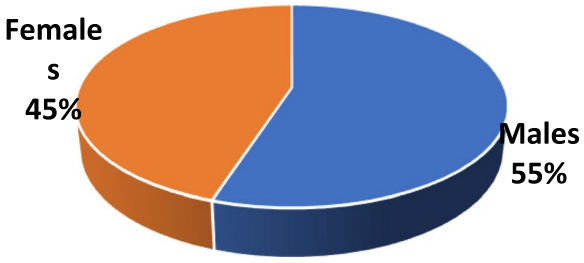

Fig. 2 Sex distribution of the study sample

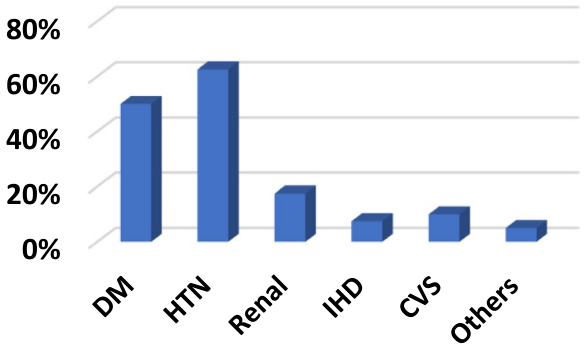

Fig. 3 Prevalence of comorbidity in population sample ($n=40$)

Table 4 Correlations between stiff index with some respiratory parameters in all patients ($n=40$)

Stiff index	*R*	*p* value
Peak cmH20	0.377	0.017*
PEEP cmH20	0.78	0.63#
C dyn ml/cmH20	−0.44	0.78#
Auto-PEEP cmH20	0.20	0.216#
TV in ml	0.132	0.416*
TV ex ml	0.275	0.086#
ITP cmH20	0.769	0.001*
Palv cmH20	0.241	0.135*
TPP ee cmH20	0.285	0.074*
Tpp ei	0.312	0.05*

Table 4 shows the correlation of the stiff index with some respiratory parameters. *P alv* alveolar pressure. Data were calculated using *Spearman's rho correlation, and #Pearson correlation

Generally, in ARDS patients there is a limit to rise in intrathoracic pressure caused by the increased pulmonary elastance. In the present study it was demonstrated that the mean of Stiff index demonstrated was (0.66 ± 0.19) (Fig. 3) and was linearly correlated with ITP ($r=0.769$, P 0.001) (Table 4), but was not correlated with PEEP ($r=0.78$, $P=0.36$) (Table 4). Although we did not evaluate the hemodynamic impact of stiff index changes,

Table 5 Correlation between some respiratory parameters ($n=40$)

	r	*P**
PEEP vs(−) ITP	0.049	0.769
E cw vs(−) ITP	0.091	0.575
TV in vs E lung	0.590	0.001
Δ Stiff Vs auto-PEEP	0.320	0.044
Peak Vs P alv	−0.098	0.003

Data were estimated using Pearson correlation, *paired sample test. Correlation was statistically positively significant between TV in vs E lung and between Δ Stiff vs auto-PEEP, and negatively between Peak Vs P alv

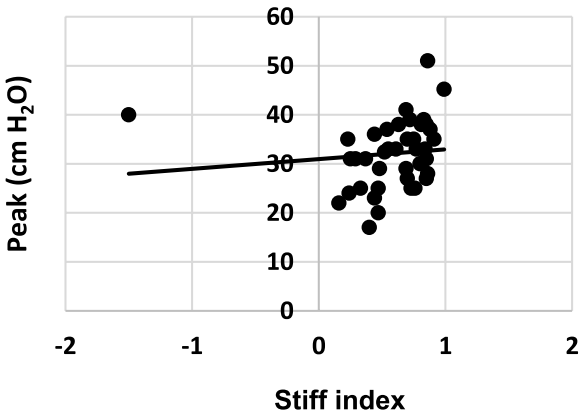

Fig. 4 Correlation between the stiff index and peak cm H_2o ($r=0.377$, $P=0.017$), the higher the Stiff index the higher is Peak pressure cmH2o

a proposed increase of the ITP with the increase of the Stiff index could improve hemodynamic response alike, regardless of the level of PEEP.

The key point is that, for a given applied pressure, the transpulmonary pressure rises when the pleural pressure decreases, regardless of chest wall elastance. This was demonstrated in our trial as ITP was not correlated with Ecw or PEEP ($r=0.19$, $P=0.595$) and (0.049, $P=0.769$), respectively (Table 5). Patients with higher lung stiffness (low lung compliance) and normal chest wall elastance have smaller increases in the rate of pressure transmission with a relatively smaller lung volume, and therefore pleural pressure changes little [16].

$$\Delta \mathrm{PCV(mmHg)} = [0.1 \pm 0.3(\mathrm{SD})] + \{[1.0 \pm 0.1(\mathrm{SD})] \times \Delta \mathrm{Ppl\ in\ mmHg}\}. \quad (14)$$

A tendency for increasing pleural pressure could be helpful in clinical practice as a greater PEEP level would cause determinist effects on the cardiovascular system [17]. The ITP is deflating negative pressure of the lung and is also called Trans-pleural pressure or intrathoracic pressure. Although it fluctuates during inspiration and expiration, intrapleural pressure remains negative throughout the breathing cycle. The calculation of ITP using a simple linear regression equation in the current study was as follows:

$$\mathrm{ITP} = -11.544 + 9.425\ (\mathrm{Stiff\ index}). \quad (13)$$

O'Quin and Marini [18] showed the fractional change of Ppl versus Paw was only slightly decreased after acute lung injury in a canine model. To capitulate, at a given applied airway pressure, the pleural pressure increases which implies a decrease in TPP and consequently the need to use a higher Peak airway pressure and the need for a higher elasticity to restore its resting volume at FRC [12]. This was confirmed in the present study as the Stiff index was found to be positively correlated with Peak pressure ($r=0.377$, $P=0.017$), (Fig. 4).

The clinical relevance of stiff index nests on the fact that when Juxta cardiac pressure increases markedly due to increased end-expiratory lung volume, it precludes over-inflation of the lung with exhaustion of its compensatory mechanism. It ultimately causes a decrease in venous return VR and cardiac output with potential hemodynamic risk [12–19]. This agreed with Jan J. Schreuder et al. (1985) who showed the relation between mean CVP and ITP in their experimental animal [20] as

Where Δ PCV is delta central venous pressure in mmHg and Δ Ppl is intra-thoracic pleural pressure in mmHg.

While the stiff index was positively correlated with peak pressure ($r=0.377$, $P=0.17$), IT was not correlated with inspiratory tidal volume ($r=0.132$, $P=0.416$) (Table 4). This contrasted with the stress index which addresses the importance of adjusting tidal volume, whereas the stiff index highlights the degree of transmitted airway pressure from the lungs to the pleura.

The Stiff index was not correlated to alveolar pressure Palv estimated on end of inspiration or the TPP on end expiration TPP ee with Spearman's rho correlation ($r=0.241$, $P=0.135$) and ($r=0.285$, $P=0.074$), respectively (Table 4). The extent of Palv transmission to the pleura is dependent on both chest wall and lung compliances. This came in agreement with Powell, F.L., et al. (2010) [16], who declared the rate of pressure transmission from alveoli to pleura as

$$\text{Rate of transmission} = C\ \text{lung}/(C\ \text{lung} + C\ \text{chest wall}) \quad (15)$$

It is in fact that ventilation-induced lung injury VILI is worse with an open chest (zero chest wall elastance)

than in the conditions in which the chest wall elastance is increased (as in experiments in which the thoracic cage was artificially constrained) [12]. This was explained in our study where ITP (mean − 6.181 ± 5) was in linear proportion to increased stiff index ($r = 0.769$, P 0.001).

One can speculate that a low-volume strategy in ARDS is recommended as a protective measure for lung parenchyma, and might also represent a protective measure for the RV afterload and pulmonary circulation [21]. Under this circumstance, the right ventricular filling pressure (defined as a gradient between CVP and pericardial pressure) does not change during changes in ITP [22]. This is because the right atrium, right ventricle, and pericardium are constrained within the thorax, and the increase of ITP, associated with an increase in Stiff index, is associated with an equal increase in both right atrial and pericardial pressures. However, overinflation of the lung or introduction of PEEP would exhaust the compensatory mechanisms and might lead to a decrease in VR [22].

For the calculation of lung stiffness, we first calculate the elasticity of the lung, chest wall, and respiratory system as follows [4]:

$$E_L = \left[\left(P_{PLAT} - P_{ES\ end-insp}\right) - \left(PEEP_{TOT} - P_{ES\ end-exp}\right)\right]/V_T \quad (16)$$

Where PES end-insp and PES end-exp represent esophageal pressures on end-inspiration and on end- expiration respectively. PES end insp can be measured from changes in Paw ei, and $P_{ES\ end-exp}$ can also be calculated from (Paw ee). Thereafter, E_L is thus calculated, in a negative value.

$$E_{RS} = (P_{PLAT} - PEEP_{TOT})/V_T \quad (17)$$

$$E\ cw = Ers - E\ lung \quad (18)$$

Gattinoni et al. (2004) [12] estimate the end-inspiratory pleural pressure Ppl as the product of Paw ei times the ratio between lung (El) and respiratory system elastance (Ers). The ITP pressure portion is required to move the chest wall to the resting position. Its estimations using elastances ratios were discussed, see Table 1.

The end-inspiratory transpulmonary pressure TPPei is estimated as Pawei times the ratio between Ecw and Ers. This method estimates the portion of Paw that is spent to inflate the lungs only [3].

$$TPPei = Paw\ ei \times Ecw/Ers \quad (19)$$

Stiff index was positively correlated with TPP ei ($r = 0.312$, $P = 0.05$) (Fig. 5).

Similarly, TPPee is computed using the following formula [3]:

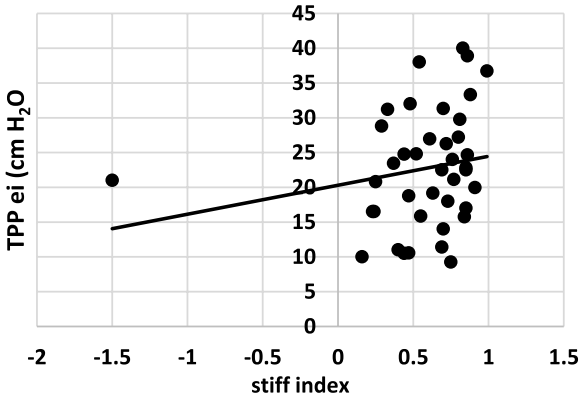

Fig. 5 Positive correlation between Stiff index and TPP ei cmH2o ($r = 0.312$, $P = 0.05$)

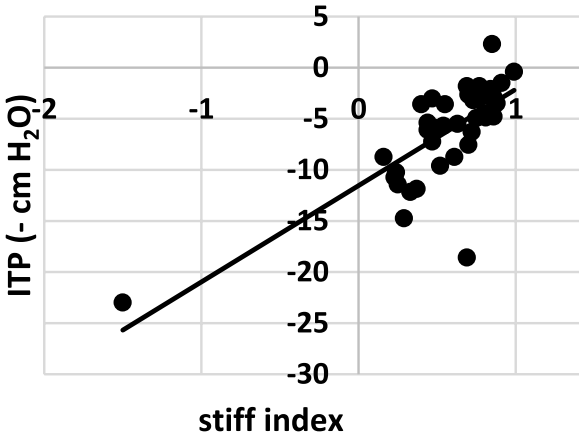

Fig. 6 Correlation between the stiff index and (−) ITP cm H_2O, where the higher the Stiff index the higher the ITP ($r = 0.769$, $P = 0.001$)

$$TPP\ ee = Paw\ ee \times Ecw/Ers \quad (20)$$

Where TPP ee and Paw ee are airway pressures measured at the end-expiratory occlusion test.

The difference of TPP between inspiration and expiration, Δ TPP was calculated as follows:

$$\Delta TPP = TPP\ ei - TPP\ ex \quad (21)$$

Where Δ TPP is the driving pressure of lung distension and is derived in a positive value.

Note, in normal lungs the Elastance derived method inquired linearity of the pressure–volume curve during inflation, where TPP ee (mean 3.8 ± 1.43) equaled approximately zero atmospheric pressure. Figure 6 demonstrates a positive correlation between Stiff index and (- ITP), $r = 0.769$.

Positive-pressure ventilation increases lung volume only by increasing Paw. In the current study, there was a positive correlation between inspiratory tidal volume TV in and E lung ($r = 0.59$, $P = 0.001$). The Stiff index was

not correlated with inspiratory VT ($r=0.132$, $P=0.41$) or expiratory TV ($r=0.275$, $P=0.08$). Apparently, it highlighted the impact of increased lung stiffness in response to increased applied peak pressure and/or TPPei rather than the influence of either TV alone or even the influence of E lung purse unless the relationship to Ecw was respectable.

The cut point of stiff factor that met the limits of the plateau at or below 30 cmH2o was 0.75 with 71% sensitivity and 0.63% specificity, respectively. The AUC was 0.859, std 0.064, *P* value 0.002 and CI 95% (0.733–0.985), (Fig. 7).

Validation signals

Striving for confirmation of stiff index validity, it was needed to apply estimations in two different situations. We proceeded to calculate ITP/Δ P on inspiratory phase for detection of Stiff index, and on the other hand, the stiff gradient which was estimated as the delta changes of plural pressure to the delta changes Transpulmonary pulmonary pressure among both the inspiratory and expiratory phases. These two types of stiff components were compared to Stiff (e) as the standard reference for means of accuracy.

Δ Ppl was calculated (in a negative value) in the current study as

$$\Delta = \text{Ppl} = (\text{Paw ee} - \text{PEEP}) - (\text{Paw ei} - \text{Plateau}). \tag{22}$$

Where Δ Ppl was, thus, calculated in negative values in cmH2o.

Whereas ITP was expressed and calculated in a negative value as

$$\text{ITP} = \text{Paw ei} \times \text{E lung/Ers} \tag{23}$$

There was no significant difference (P 0.073) between ITP (mean − 6.18 ± $P=0.073$) used in stiff index and Δ Ppl (mean − 8.46 ± 5.42), used in stiff gradient, (Table 6). Meanwhile, the lung driving pressure equating ΔP = (Pplat − PEEP total), used in calculating stiff

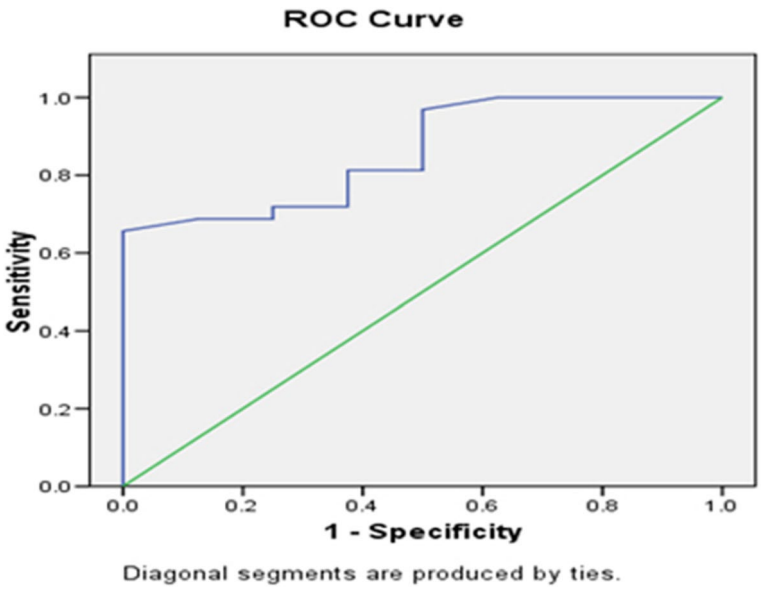

Fig. 7 ROC of stiff index pertaining Plateau at or greater than 30 cmH2o. ROC curve of stiff elastance where the best cut point to ensure plateau equal or less than 30 cmH2o was 0.75 with 71% sensitivity and 63% specificity, respectively. Area under the curve 0.859, std 0.064, and *p* value = 0.002 with CI 95% (0.733–0.985)

Table 6 Comparison of (Plateau–$PEEP_{total}$) vs ΔTPP and ITP Vs Δ Ppl in all patients ($n=40$)

Paired differences							
	Mean	**SD**	**Std error mean**	**CI Δ Stiff (Upper). (lower)**	***t***	**Δ Stiff**	***P* value**
(Plateau–PEEP total) vs ΔTPP	−2.340	6.48	1.02	(−4.41). (0.26)	−2.281	39	0.028
(−) ITP vs (−) Δ Ppl	2.27	7.82	1.237	(−0.22) (4.78)	1.8	39	0.07

The table shows a statistically significant difference between (Plateau–$PEEP_{total}$) and ΔTPP, but no statistically significant difference between (−) ITP and (−) Δ Ppl

index, showed a significant difference ($P=0.02$) with Δ TPP = (TPP ei–TPP ee), calculated in stiff gradient, (Table 6). This results in a non-statistically significant difference ($P=0.183$) between Stiff (e) (mean 0.66 ± 0.195) and Stiff index (mean 0.56 ± 0.4), (Table 7). It implied that stiff index, calculated on the inspiratory phase, was equivalent to Stiff (e).

Differently, we recognized a statistically significant difference between Stiff (E) with (mean 0.66 ± 0.195) and stiff gradient (mean 0.47 ± 0.74) with P value = 0.001, (Table 7). It implied that measurements of the Stiff gradients were inequivalent to Stiff (e), and, so far, was not reliable as accurate as the standard measurement. In clinical practice, the Stiff index should be estimated on the end-inspiratory phase, whereas stiff gradient could be implemented in the measurements performed during both inspiration and expiration.

Additionally, we found Stiff index and Stiff gradient showed a non-statistically significant difference, P 0.145. This could be useful in the explanation of the difference in respiratory mechanics pertaining to the inspiratory phase on the one hand, and the ones pertaining to both inspiratory and expiratory phases on the other hand. Consequently, the delta Stiff or Δ Stiff, measured as (stiff index-Stiff gradient), was observed to be statistically positively correlated with auto-PEEP, Pearson correlation ($r=0.320$, $P=0.044$), (Table 5). In extrapolation, the more Δ stiff the more the potential impact of inadvertent highly auto-PEEP. This assumption might hold true since the Stiff index was not correlated with auto-PEEP, Pearson correlation ($r=0.2$ $P=0.216$), (Table 4).

Clinical application of stiff index

A 'safe' airway plateau pressure between 30 and 35 cmH_2O may give widely differing transpulmonary pressures in patients with normal or increased chest wall elastance [23–25]. This concept is of important issue for patients with ventilator-induced lung injury VILI, since it emphasizes the role of alveolar pressure or the actual pressure the alveoli are exposed to.

Table 7 Comparative analysis between the mean of Stiff (E) vs stiff index vs stiff gradient

	Stiff index vs Stiff e	Stiff gradient vs Stiff (e)	Stiff-gradient vs stiff-index
Z	−1.333	−4.601	−1.459
P value	0.183	0.001	0.145

Data were based on positive ranks. There was no statistical difference between Stiff index vs Stiff e, and no statistical difference between Stiff gradient vs Stiff index, while there was a statistically significant difference between Stiff gradient vs Stiff (e)

Essentially, the sum of TPPei and Ppl mountain Palv, (mean 28.9 ± 8.06) which can be calculated in the current study as

$$\text{Palv} = \text{TPPei} - (-)\Delta\text{Ppl}. \tag{24}$$

Gattinoni L et al. (2004) [12] found pleural pressure was normal in pulmonary ARDS patients [13]. However, these values are for ordinate and cannot be generalized since most clinical situations are at odds of low lung and chest wall compliances, and still have the consideration of auto-PEEP measurement. The latter could be adversely high or low, for instance in hyperinflated lung in COPD or restricted lung volume in kyphoscoliosis, respectively.

For that reason, physicians should be aware, in acute lung injury with low chest wall compliance, of the alveolar pressure in relation to ITP. However, we failed to define a correlation of stiff index with P alv (r = 0.291, $P=0.69$) Spearman's correlation. We presumed a regression equation of Palv as it was correlated with the peak pressure, $r=0.462$, $P=0.003$, and where it was estimated in a simple linear equation, Spearman's rho correlation as

$$\text{Palv} = 11.124 + 0.534\ (\text{Peak P.}) \tag{25}$$

Obviously, for the same applied alveolar pressure (let us say 30 cmH_2O) with stiff index ratio of 0.66, the TPP would be 22.5 cmH_2o and pleural pressure would be − 7.5 cmH_2, whereas, if stiff index was increased to 0.75 the transpulmonary pressure will be increased to 24 cmH_2o but the pleural pressure will be only − 6 cmH_2o. The message is that both TPP and ITP increase with increasing Stiff index.

Wherein the loss of pulmonary reserve may become clinically important a reduced elastic recoil with consequent change in lung volume was reported in diabetic patients [26]. This population contributed approximately fifty percent of comorbidities in our study. Additionally, FRC is reduced in ARDS to 65% of its predicted in the supine position according to weight, height, and sex, and the small number of trials showing that FRC and EELV were reduced by 17% and 18% respectively in supine and prone position [21]. The validity of tidal volume correlation with stiff index lags is due to the limitations met in the current study.

In extrapolation, circumstances where unavoidable higher dead space ventilation, the stiff factor had to be reduced with a reduction of peak pressure and TPPei with a consequent of a decrease of the oscillatory volume and decreases of delta dead space VD to TV ratio. This is explained as the ratio of dead ventilation to tidal volume VD /TV is inversely proportionate to tidal volume.

Limitations of the study

Due to the diversity of types of ventilators used, some measurements were not displayed on the screen as the read-out, and manual inspiratory pause often led to erroneously low Paw_{ei} pressure readings, particularly when too long in duration. The second limitation met was inaccessible IBW in the settings of our study, which needed to be related to the patients' TV rather than its absolute value. This might explain the hardness to confirm the correlation of TV with stiff factor. One limitation of the derived elastance method is precision rather than accuracy, where If airway pressures were higher or lower than atmospheric pressure (equal zero in this method), an under or over-estimation of pleural pressure might exist respectively. Secondly, the assumption this method may lose its linearity at the extremes of the pressure–volume curve made an enormous higher recording of stiff index with such model of low lung and chest wall compliances, e.g., ARDS.

Conclusion and recommendation

Lung pressure loading in ARDS could be recognized by estimating stiff index. The role of stiff factor could be highlighted in view of the peak and ITP changes and not due to tidal volume. The more the stiff factor, the more TPP with risk of barotrauma and the more the ITP with a potential protective effect on venous return. We suggest the rational approach for assessing stiff index routinely as a bedside test in ARDS patients. It is recommended that a controlled software system programming be innovated in such that stiff index would be selected in norms of "best stiff index". This could be relevant to the lowest dead space ventilation in future research.

Abbreviations

Paw ei	Pressure airway end inspiration
Paw ee	Pressure airway end-expiration
TPPei	Transpulmonary pressure end inspiration
TPPee	Transpulmonary pressure end-expiration
ITP	Intrathoracic pressure
ΔP	Driving pressure of lung
ΔPpl	Delta pleural pressure
ΔTPP	Delta transpulmonary pressure
Ecw	Elastance of chest wall
E rs	Elastance of respiratory system
$P_{ES\ end\text{-}insp}$	Esophageal pressure end inspiration
$P_{ES\ end\text{-}exp}$	Esophageal pressure end-expiration
*P*alv	Alveolar pressure
TVe	Tidal volume expiratory
TV I	Tidal volume inspiratory
C dyn	Dynamic compliance
C stat	Static compliance
Stiff (E)	Stiff factor (elastance)
P_{plat}	Plateau pressure
$PEEP_{total}$	Positive end-expiratory pressure(total)
ΔPCV	Delta central venous pressure

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Authors' contributions

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Availability of data and materials

Associated data are available in a data repository.

Declarations

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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