# Analysis of Dynamic Intratidal Compliance in a Lung Collapse Model

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## ABSTRACT

**Background:** For mechanical ventilation to be lung-protective, an accepted suggestion is to place the tidal volume ($V_T$) between the lower and upper inflection point of the airway pressure-volume relation. The drawback of this approach is, however, that the pressure-volume relation is assessed under quasistatic, no-flow conditions, which the lungs never experience during ventilation. Intratidal nonlinearity must be assessed under real (*i.e.*, dynamic) conditions. With the dynamic gliding-SLICE technique that generates a high-resolution description of intratidal mechanics, the current study analyzed the profile of the compliance of the respiratory system ($C_{RS}$).

**Methods:** In 12 anesthetized piglets with lung collapse, the pressure-volume relation was acquired at different levels of positive end-expiratory pressure (PEEP: 0, 5, 10, and 15 cm $H_2O$). Lung collapse was assessed by computed tomography and the intratidal course of $C_{RS}$ using the gliding-SLICE method.

**Results:** Depending on PEEP, $C_{RS}$ showed characteristic profiles. With low PEEP, $C_{RS}$ increased up to 20% above the compliance at early inspiration, suggesting intratidal recruitment; whereas a profile of decreasing $C_{RS}$, signaling overdistension, occurred with $V_T > 5$ ml/kg and high PEEP levels. At the highest volume range, $C_{RS}$ was up to 60% less than the maximum. With PEEP 10 cm $H_2O$, $C_{RS}$ was high and did not decrease before 5 ml/kg $V_T$ was delivered.

**Conclusions:** The profile of dynamic $C_{RS}$ reflects nonlinear intratidal mechanics of the respiratory system. The SLICE analysis has the potential to detect intratidal recruitment and overdistension. This might help in finding a combination of PEEP and $V_T$ level that is protective from a lung-mechanics perspective.

### What We Already Know about This Topic

- Lung mechanics analyzed at quasistatic, no-flow conditions do not reflect the true dynamic compliance of the lungs

### What This Article Tells Us That Is New

- In anesthetized animals with stable lung collapse induced by negative pressure, intratidal compliance decreased when a tidal volume greater than 5 ml/kg was delivered and when high positive end-expiratory pressure levels were used, suggesting lung overdistension

TRADITIONALLY, lung mechanics are analyzed at quasistatic, no-flow conditions, despite the obvious fact that the lung never experiences such a condition during dynamic uninterrupted ventilation.[1,2] By their very nature, quasistatic lung mechanics wall out the exploration of intrabreath events, such as inspiratory recruitment and overdistension or any sequential pattern of such events. This hampers the discussion on ventilation-associated mechanical lung injury. The conclusion that a particular combination of positive end-expiratory pressure (PEEP) and tidal volume ($V_T$), for example, is potentially harmful is often based on indirect evidence, rather than on direct visualization of what actually happens mechanically within the breath. Knowledge of intrabreath events is, however, a prerequisite for assessing whether those events do exist, whether they induce injury and, if so, how to account for their impact.

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Repetitive inspiratory recruitment and overdistension appear as nonlinearities within the course of dynamic intratidal compliance of the respiratory system ($C_{RS}$). Here, we investigated whether those nonlinearities can be visualized and quantified by the dynamic "gliding-SLICE" method.[3] We studied lungs in which collapse had been induced by negative pressure application and confirmed by thoracic computed tomography (CT). If anything, the negative pressure-induced lung collapse model mimics the situation after tracheal suction. It generates a lung collapse with low compliance and $PaO_2$ that is stable for at least 2 h (see Supplemental Digital Content 1, http://links.lww.com/ALN/A673), and rather than about its clinical relevance, we were concerned about having a model available that would present with a stable, reproducible collapse in otherwise healthy lungs, such that intrabreath nonlinearities would be attributable to collapsed lung volume being recruited and/or overdistended by increasing levels of airway pressures. We assumed that the occurrence of cyclic end-expiratory collapse with subsequent early inspiratory recruitment would be suggested by the intratidal $C_{RS}$ profile, as determined by the gliding-SLICE technique, and that the $C_{RS}$ profile would change in a comprehensive way with PEEP. We compared the gliding-SLICE method to the stress index[4] that, conceptually, is able to detect nonlinearities as well as to the standard measurement of $C_{RS}$ at quasistatic no-flow conditions.

## Materials and Methods

### Study Protocol

The local Ethics Committee (Uppsala University, Uppsala, Sweden) approved the protocol. Twelve piglets (mean body mass, 27 kg) had their lungs mechanically ventilated at different PEEP levels (0, 5, 10, and 15 cm $H_2O$) set at random. We did not apply a zero-PEEP control condition between the different PEEP steps, because we felt that recruitment/derecruitment effects potentially varying would be taken care of by the random PEEP setting.

Lung collapse was generated by (1) induction of anesthesia with pure oxygen and (2) amplified by negative pressure application (a suction device was connected to the endotracheal tube and negative pressure was applied until $SaO_2$ dropped below 80%, usually within 2 min). The stability of the negative pressure model with respect to low compliance and $PaO_2$ had been checked in pilot animals (for respiratory parameters and CT images of exemplary animals, see Supplemental Digital Content 1, http://links.lww.com/ALN/A673), and we have obtained additional thoracic CTs in a separate study (unpublished data; those CT data were achieved in March 2007 from M. Lichtwarck-Aschoff, L.Vimlati, and R. Kawati, Uppsala, Sweden). In brief, up to one fourth of the total lung volume became atelectatic and/or extremely poorly aerated upon negative pressure application, with the collapsed areas being distributed preferentially to the dependent zones near the diaphragm, rather than being homogeneously distributed. No significant resolution of the lung collapse could be seen at 30 min in the CT; $PaO_2/FiO_2$ and quasistatic compliance remained low for more than 2 h without any improving tendency. Peak inspiratory pressures of 50 cm $H_2O$ and PEEP of 20 cm $H_2O$ were required to fully recruit the collapsed lungs after 2.5 h of controlled mechanical ventilation at PEEP 0 cm $H_2O$; even then, the recruitment effect was only transient, unless a PEEP of 10 cm $H_2O$ was applied.

Ventilation was volume-controlled throughout. Tidal volume ($V_T$) was set to 12 ml/kg at a constant inspiratory flow rate. Inspiration-to-expiration ratio was 1:1. Ventilator frequency was set to 20 $min^{-1}$ and $FIO_2$ to 1.0. Anesthesia was maintained by ketamine (20 $mg \cdot kg^{-1} \cdot h^{-1}$) and morphine (0.5 $mg \cdot kg^{-1} \cdot h^{-1}$); neuromuscular block was achieved by pancuronium bromide (0.25 $mg \cdot kg^{-1} \cdot h^{-1}$). Normal saline (10 $mg \cdot kg^{-1} \cdot h^{-1}$) was continuously infused. A bolus of 10 $mg \cdot kg^{-1}$ dextrane was given to ensure relative normovolemia at all PEEP levels.

### Monitoring

Ventilation was applied *via* an endotracheal tube (ID 9 mm; Mallinckrodt, Athlone, Ireland) using a Servo$^i$ ventilator (MAQUET Critical Care AB, Solna, Sweden). All measurements were performed after a 10-min stabilization period. Respiratory flow was measured with a Fleisch-type pneumotachograph (PNT series #37194719; Hans Rudolph, Inc., Shawnee, KS), and airway pressure was measured *via* a transducer connected to a side port. Data were recorded with AcqKnowledge software (version 3.2.7; BIOPAC Systems, Inc., Santa Barbara, CA) at a sample frequency of 500 Hz. For offline analysis and figure design, Matlab (R2007b; The Mathworks, Natick, MA) was used.

### CT Analysis

In four animals, helical chest CT scans[5,6] were taken during inspiratory hold at each PEEP step. Regions of interest (*i.e.*, lungs) were manually delineated and analyzed by dedicated software (Maluna v2.04; University of Mannheim, Mannheim, Germany). Lung collapse was defined as densities −100 to 100 HU, poor aeration ranged from −500 to −100, normal aeration from −850 to −500, and overaeration from −1,000 to −850 HU.

### Analysis of Lung Mechanics

**Quasistatic Compliance.** The quasistatic compliance of the respiratory system ($C_{qstat}$) was determined from end-inspiratory hold maneuvers of 5 s, according to Equation 1:

$$C_{qstat} = \frac{\text{end-inspiratory pause pressure} - \text{end-expiratory pause pressure}}{\text{tidal volume}}$$

**Stress Index.** The stress index was determined as described by Ranieri *et al.*[4] In brief, the exponential function $p = a \cdot t^b + c$ is fitted to the inspiratory pressure curve. With $t$ representing

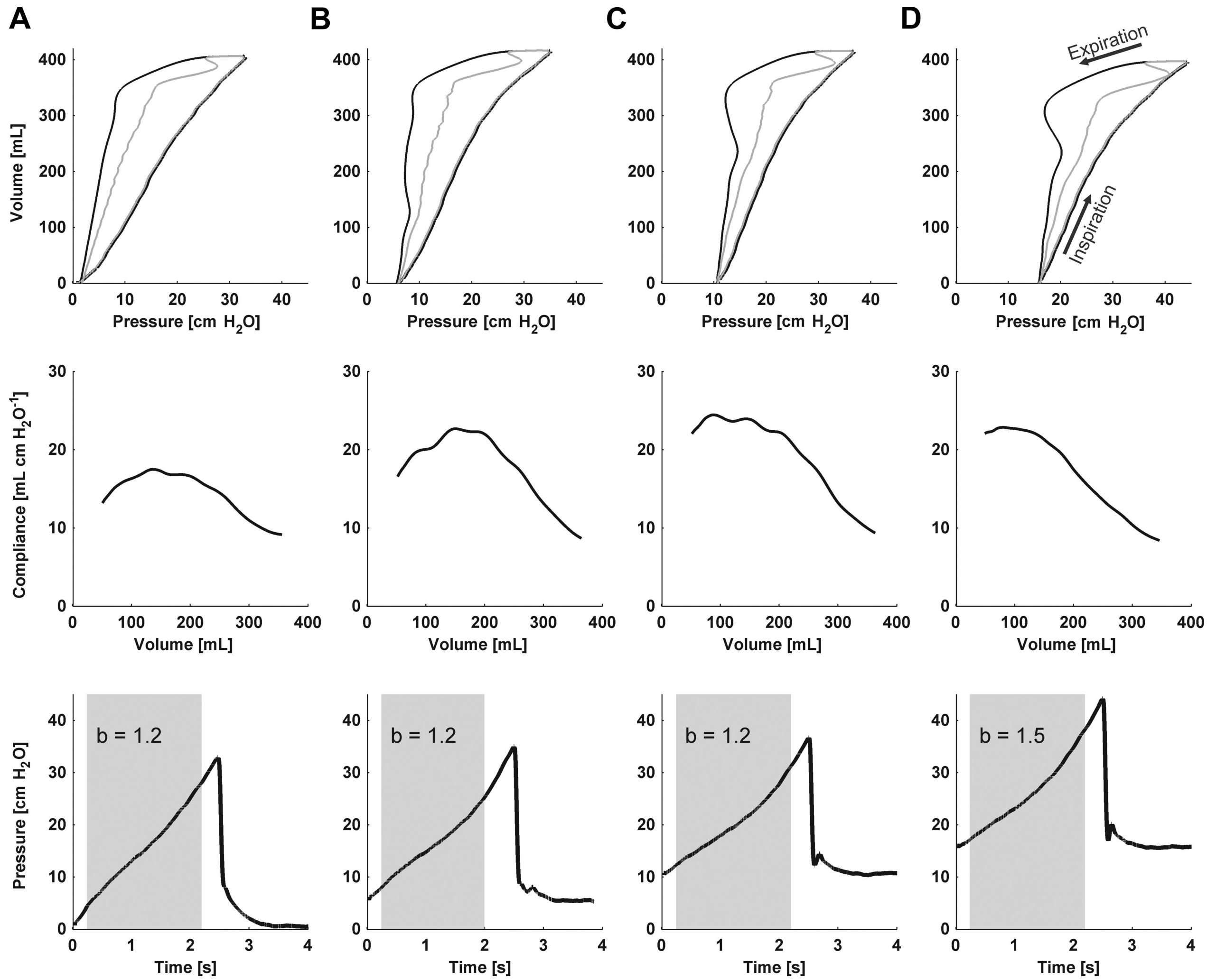


**Fig. 1.** Assessment of intratidal compliance ($C_{RS}$) at different levels of positive end-expiratory pressure (PEEP). Exemplary single breath data are shown from a typical animal. (*A*) PEEP 0 cm $H_2O$. (*B*) PEEP 5 cm $H_2O$. (*C*) PEEP 10 cm $H_2O$. (*D*) PEEP 15 cm $H_2O$. (*Top*) Dynamic pressure-volume curves during ongoing ventilation: airway pressure (black) and tracheal pressure (gray). (*Middle*) Corresponding intratidal compliance profile. (*Bottom*) Corresponding tracheal pressure-time curve (black) with respective stress index (b). Gray shadings indicate the time range, of which the stress index was calculated. The slope of the pressure curve indicates recruitment, then overdistension at zero PEEP and PEEP 5 cm $H_2O$, but only overdistension at PEEP 10 cm $H_2O$ and 15 cm $H_2O$. This is reflected by the course of $C_{RS}$, whereas the stress index indicates overdistension (b more than 1) in all cases.

time and *a* and *c* allowing for adjustment of amplitude and offset, the exponent *b* gives the stress index, indicating a (predominantly) convex, linear, or concave profile of the inspiratory pressure increase if (if more than 1, = 1, or less than 1, respectively). Assuming constant flow, these profiles are associated with (predominantly) decreasing, constant, or increasing compliance, respectively. Because the typical flow profile delivered by any ventilator is not as constant as theoretically required for this method, data points for which flow deviated less than 10% of the maximum instead of the originally proposed 3% deviation were used for estimation of *b* in this study.

### Gliding-SLICE Method

The gliding-SLICE method,[3] being an extension of the established SLICE method,[7] was applied as follows. To eliminate potential influences of nonlinear endotracheal tube resistance, all analyses were based on tracheal pressure calculated from airway pressure as described elsewhere.[8] From this and flow data (integrated to volume), the inspiratory nonlinear compliance of the respiratory system ($C_{RS}$) was then calculated. In brief, from the inspiratory pressure-volume curve, the range of 5–95% of tidal volume was analyzed at subsequent volume steps. For each volume step, $C_{RS}$ was calculated by multiple linear regression analysis from data within a specified volume range (slice) around the volume step. The calculation started using the pressure-volume data of the lowest volume slice. Subsequently, the slice moved up one volume step, simultaneously leaving the very lowest and including the next higher data points, and so on, until all volume steps had been included in the calculation. We chose 91 volume steps to enable the calculation of a smooth course of intratidal compliance by keeping calcula-

**Table 1.** Respiratory Parameters

| | PEEP | | | |
|---|---|---|---|---|
| | 0 cm $H_2O$ | 5 cm $H_2O$ | 10 cm $H_2O$ | 15 cm $H_2O$ |
| $V_T$ (ml) | 356 (322–390) | 355 (321–389) | 354 (320–388) | 340 (307–373) |
| $P_{peak}$ (cm $H_2O$) | 30 (29–31) | 31 (30–32) | 34 (33–35) | 39 (38–41) |
| $P_{plat}$ (cm $H_2O$) | 24 (23–25) | 26 (25–26) | 29 (28–30) | 34 (33–35) |
| $C_{qstat}$ (ml/cm $H_2O$) | 15 (13–16) | 17 (16–19) | 19 (17–21) | 18 (17–20) |
| $C_{RS}$ low (ml/cm $H_2O$) | 15 (13–18) | 21 (18–23)‡ | 25 (22–28)‡ | 25 (22–27)†,‡ |
| $C_{RS}$ mid (ml/cm $H_2O$) | 18 (15–20)§ | 21 (8–23) | 21 (20–23) | 18 (16–20)* |
| $C_{RS}$ high (ml/cm $H_2O$) | 9 (8–10)*,† | 9 (8–10)*,† | 10 (9–10)*,† | 9 (8–10)*,† |

Values in parentheses indicate 95% confidence intervals.

*, † Difference statistically significant, compared with low* and middle† volume slice at the same PEEP level, respectively; ‡ difference statistically significant, compared with PEEP 0 at the same volume slice; § $P = 0.06$, compared with $C_{rs}$ low at PEEP 0.

$C_{qstat}$ = quasistatic compliance; $C_{RS}$ = dynamic compliances of the lowest (low, 1.5 ml/kg), middle (mid, 6 ml/kg), and highest (high, 10.5 ml/kg) volume slice; $P_{peak}$ = peak inspiratory pressure; PEEP = positive end-expiratory pressure; $P_{plat}$ = plateau pressure; $V_T$ = tidal volume.

tion efforts small. Choosing a SLICE volume of one-sixth of $V_T$ and 91 volume steps filtered disturbances induced by cardiogenic oscillations, and the resulting sequential intratidal $C_{RS}$ values were minimally, if at all, influenced by heartbeats (fig. 1).

### *Statistics*

Hemodynamic, blood gas, CT and lung-mechanics data were presented as mean (lower to upper 95% confidence interval [CI]). For the gliding-SLICE, 10 consecutive breaths per measurement for each condition were averaged and the mean was used for further analysis, rather than analyzing one single breath only.

Hemodynamics, blood gases, and CT data at different PEEP levels were compared using the Friedman test (nonparametric repeated measures ANOVA), and differences were evaluated with the Dunn multiple comparisons test (GraphPad Instat, Version 3.05; GraphPad Software, Inc., La Jolla, CA). The gliding-SLICE data were analyzed for differences within a breath ($C_{RS}$ at the lowest, middle, and highest volume slice) at PEEP levels of 0, 5, 10, and 15 cm $H_2O$, respectively, with the Monte Carlo resampling technique (10,000 iterations; PopTools *vs.* 3.1 Hood, G. M., 2010) PopTools# multiple testing was accounted for by applying a Bonferroni correction. Statistical significance was assigned for $P < 0.05$.

## Results

### *CT*

With zero PEEP, 10% (CI, 6.8 to 13.7%) of the lung area was collapsed and 21% (CI, 14.0 to 27.0%) poorly aerated. Increasing PEEP significantly reduced the collapsed and poorly aerated lung areas (from 31% with PEEP 0 cm $H_2O$ to 19% with PEEP 5 cm $H_2O$, 14% with PEEP 10 cm $H_2O$, and 7% with PEEP 15 cm $H_2O$). Normally aerated lung areas increased significantly with PEEP, as did the overaerated areas (from 2% with PEEP 0 cm $H_2O$ to 8% with PEEP 5 cm $H_2O$, 13% with PEEP 10 cm $H_2O$, and 22% with PEEP 15 cm $H_2O$).

### *Lung Mechanics*

**Quasistatic Compliance.** Upon generation of lung collapse by negative pressure application, $C_{qstat}$ decreased significantly (15 [CI, 13 to 16] ml/cm $H_2O$), compared with the noninjured situation (21 [CI, 18 to 23] ml/cm $H_2O$; $P < 0.001$), both measured at PEEP of 0 cm $H_2O$.

With lung collapse, $C_{qstat}$ did not change with PEEP (table 1), except for a minor increase in $C_{qstat}$ from PEEP 0 cm $H_2O$ up to PEEP 10 cm $H_2O$ (19 [CI, 17 to 21] ml/cm $H_2O$; $P < 0.001$).

**Stress Index.** At all PEEP levels, the stress index was clearly larger than 1, indicating overdistension (fig. 2).

### *Intratidal Dynamic Compliance Profile*

Although the individual animals started from different initial $C_{RS}$ levels, the intratidal $C_{RS}$ profiles had similar PEEP-dependent shapes in all animals (fig. 2; table 1).

Once a volume of 5 ml/kg had been delivered, intratidal $C_{RS}$ consistently decreased, suggesting overdistension at volumes above 5 ml/kg irrespective of the particular PEEP level. This was most pronounced at a PEEP of 15 cm $H_2O$, with $C_{RS}$ decreasing from onset of inspiration already.

Below 5 ml/kg, the intratidal $C_{RS}$ profile depended on PEEP: with PEEP 0 and 5 cm $H_2O$, $C_{RS}$ increased up to 5 ml/kg $V_T$, suggesting intratidal recruitment, whereas at PEEP 10 cm $H_2O$, $C_{RS}$ was nearly constant at a high level. For a detailed description of statistical significant differences, see table 1.

## Discussion

The main finding of this study was that the specific intratidal $C_{RS}$ profile is accessible by the gliding-SLICE method in this

# PopTools Version 3.1. Available at: http://www.poptools.org. Accessed November 10, 2010.

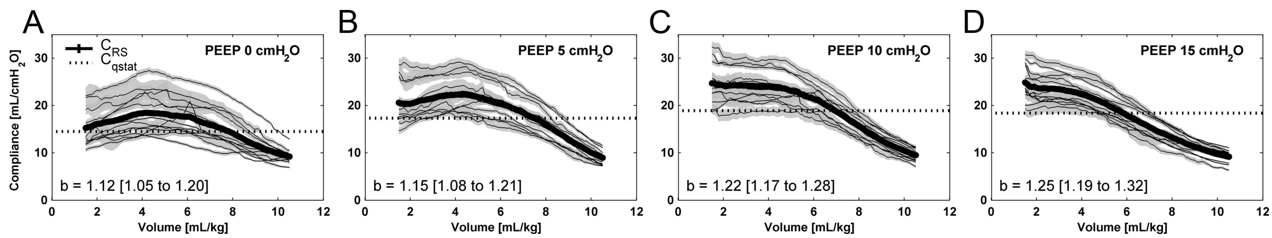


**Fig. 2.** Intratidal nonlinear respiratory system compliance ($C_{RS}$) profiles assessed by the gliding-SLICE method. Intratidal $C_{RS}$ of the respective positive end-expiratory pressure (PEEP) level (*A*, 0 cm $H_2O$; *B*, 5 cm $H_2O$; *C*, 10 cm $H_2O$; *D*, 15 cm $H_2O$) is plotted against the volume level. Thin lines indicate mean values of at least 10 measurements for each animal (enveloping areas indicate lower to upper 95% CI of compliance of each individual animal, calculated for each volume level from all used measurements assessed on the respective PEEP level), and the bold line indicates mean over all animals. Please note: Depending on PEEP and atelectasis, intratidal $C_{RS}$ shows a characteristic profile. Increasing $C_{RS}$ suggests recruitment, which is most pronounced with early inspiration at low PEEP levels (0 and 5 cm $H_2O$), where we assume major lung collapse at end-expiration. A high $C_{RS}$ not decreasing before 5 ml/kg $V_T$ is delivered suggests mechanically beneficial conditions at PEEP 10 and up to a $V_T$ of 5 ml/kg body weight. Decreasing $C_{RS}$, hinting at overdistension, is prominent already upon the start of inflation with PEEP 15 cm $H_2O$. At all other PEEP levels, $C_{RS}$ decreased once a 5-ml/kg inspiratory volume was delivered, suggesting that this volume induced overdistension at all PEEP levels, and this is confirmed by the stress index indicating overdistension (b more than 1) at late inspiration with all PEEP levels. For comparison, $C_{qstat}$ is also displayed, although, by its very nature, not providing information on intratidal events and hence changing very little with PEEP.

lung collapse model. It depends on PEEP in a characteristic way, with initial recruitment prevailing at low PEEP levels and signs of overdistension both with high PEEP levels and high (more than 5 ml/kg) volumes.

### *Interpretation of Nonlinear Intratidal Compliance*

If recorded across a volume range that is much bigger than the physiologic tidal volume, the pressure-volume relation of the respiratory system is sigmoid in shape, with a lower and an upper inflection point and a steep linear segment in between. Already within the narrow range of a $V_T$ of physiologic size, however, a pronounced nonlinear intratidal course of $C_{RS}$ with major deviations from the regular sigmoid course can be observed.[9–11] Tidal volume and PEEP are the key variables affecting the nonlinearity of the intratidal $C_{RS}$. For the protection of injured lungs, it has been suggested to reduce $V_T$ such that ventilation takes place at the linear $C_{RS}$ segment between the lower and upper inflection points (for review, see Tobin *et al.*[12]) and/or to reduce $V_T$ to $\leq$ 6 ml/kg,[12,13] although the latter approach does not explicitly take compliance into account. How to define the optimal PEEP is currently under intensive debate. Unresolved is, moreover, the question whether the same mechanical principles apply to the healthy lungs of patients undergoing general anesthesia.[14–16] Visualizing and quantifying the intratidal $C_{RS}$, which, as we show here, is feasible with the gliding-SLICE technique, offers the opportunity to base the above discussions on mechanical facts that affect the lung parenchyma during uninterrupted dynamic ventilation.[1,2] Differences between quasistatic and dynamic analyses indicate that lung-mechanics properties depend on the inspiratory flow profile and the time allowed for equilibration of viscoelastic forces.[2] The stress index suggested by Ranieri[4,17] and the dynostatic algorithm suggested by Stenqvist *et al.*[1] also analyze lung mechanics dynamically. Here, we present an extension of the SLICE method,[7] the gliding-SLICE technique[3] that generates a high-resolution picture of dynamic intratidal mechanics. The intratidal $C_{RS}$ profile reflects the way lung volume changes during inspiration. Indeed, with low PEEP and hence major lung collapse (as assessed by CT), intratidal recruitment at early inspiration was immediately suggested by an increasing $C_{RS}$ profile. At higher PEEP, lung collapse was reduced and overaeration in the CT became increasingly important, which corresponded to a decreasing $C_{RS}$ profile, suggesting overdistension. The stable high profile of $C_{RS}$ during early inspiration at PEEP 10 cm $H_2O$ reflected fairly stable "open lung" conditions up to 5 ml/kg, with a minimal energy input to the respiratory system up to that point. When inspiration started from pronounced overaeration (PEEP 15 cm $H_2O$), the downhill profile of intratidal $C_{RS}$ signaled overdistension, and this was also true once more than 5 ml/kg volume had been delivered.

The stress index (fig. 1) performs a low-resolution analysis of intratidal mechanics, with the emphasis ostensibly on late inspiration. It has to be noted that Grasso *et al.*, in their description of the method, already stated that a condition of biphasic intratidal behavior (*i.e.*, recruiting plus overdistension) makes correct measurement of the stress index impossible.[4] However, because for $V_T$ above 5 ml/kg overdistension prevailed at all PEEP levels, this index did not differentiate between the variable mechanical loads during early inspiration. In contrast to the gliding-SLICE technique and the dynostatic algorithm (also when tidal volume is limited), the stress index indicates whether nonlinearity is present without indicating what particular volume range is affected from nonlinearity. The examples in figure 1 reveal that without PEEP and at PEEP 5 cm $H_2O$, first increasing then decreasing compliance indicates recruitment in the lower and overdistension in the upper volume range. At PEEP 10 cm $H_2O$ and 15 cm $H_2O$, only overdistension is indicated. By contrast, the stress index indicates overdistension in all cases.

**Table 2.** Hemodynamics and Blood Gases of Animals with Lung Collapse

| | PEEP | | | |
|---|---|---|---|---|
| | 0 cm $H_2O$ | 5 cm $H_2O$ | 10 cm $H_2O$ | 15 cm $H_2O$ |
| Stroke index (ml/m$^2$) | 31 (29–33) | 29 (27–31) | 26 (23–29)* | 21 (17–25)* |
| Mean arterial pressure (mmHg) | 98 (92–103) | 94 (90–99) | 83 (78–88)* | 72 (68–76)*,† |
| $Pa_{O_2}/F_{IO_2}$ (mmHg) | 323 (285–362) | 431 (407–454)* | 540 (525–555)*,† | 583 (571–594)*,† |
| $Pa_{CO_2}$ (mmHg) | 53 (50–55) | 52 (49–55) | 48 (45–51)* | 45 (42–47)*,† |

Values are mean (lower to upper 95% CI).

* Difference significant to PEEP 0 cm $H_2O$; † Difference significant to PEEP 5 cm $H_2O$.

$Pa_{CO_2}$ = arterial partial pressure of carbon dioxide; $Pa_{O_2}/F_{IO_2}$ = quotient of arterial partial pressure of oxygen and fraction of oxygen in inspiration gas; PEEP = positive end-expiratory pressure.

The dynostatic algorithm calculates the intratidal course of alveolar pressure from the tracheal pressure-volume curve. In contrast, the SLICE technique delivers the intratidal profile of compliance. In principle, using the SLICE technique, the intratidal compliance profile could also be calculated from the alveolar pressure-volume relationship, as calculated by the dynostatic algorithm. *Vice versa*, the intratidal alveolar pressure course could be calculated from an intratidal compliance course that is calculated by the gliding-SLICE technique.[3,8]

The compliance-volume curve is the first derivative of the P-V curve displaying the change in volume and pressure of subsequent data points. It is for pure mathematical reasons therefore that the compliance curve displays changes in the P-V curve more sensitively, compared with the P-V curve itself. However, the volume, the respective pressure level at which linearity passes over to nonlinearity, could, in principle, be identified using both the dynostatic algorithm or the gliding-SLICE technique.

Quasistatic methods assume a linear function between start and end of inspiration, disregarding intrabreath changes. $C_{qstat}$ was nearly the same across all PEEP levels, which, again, merely reflects overdistension in these settings. Other than during (quasi-)static measurements, the respiratory system is never in a flowless condition during ongoing breathing. It has been shown in patients with acute respiratory distress syndrome that the mechanics of the respiratory system differ considerably between static and dynamic conditions.[11] In this context, our findings support that overdistension occurs earlier than one would possibly expect from analysis of respiratory system mechanics under static conditions.

### *Critique of Methods*

Instead of the generally accepted $V_T$ level of 6 ml/kg for injured lungs, we here applied 12 ml/kg to lungs that, at onset, were healthy, except for the collapse. Still, this resulted in slightly hypercapnic $Pa_{CO_2}$ values (with a tendency toward lower $Pa_{CO_2}$ values at high PEEP as an indirect sign of recruitment; see table 2). The 12 ml/kg $V_T$ was chosen because we wanted to be sure to have both collapse and overdistension within the same breath, which we felt more important than mimicking the $V_T$ applied in patients in the intensive care unit or during anesthesia. Such high volumes were associated with overdistension at all PEEP levels. However, even at a low PEEP of 5 cm $H_2O$, $C_{RS}$ decreased above 5 ml/kg, indicating the beginning of overdistension. We speculate that in the suction model with high $V_T$ and different PEEP levels, overdistension is induced by two different mechanisms. With PEEP 10 and 15 cm $H_2O$ and high inspiratory airway pressures (table 1), there is global overdistension of the entire lung with ongoing inspiration, with little, if any, lung collapse remaining. By contrast, with 0 cm $H_2O$ and 5 cm $H_2O$, PEEP airway pressure is insufficient for reopening all collapsed areas, and the lung volume accessible for inspiratory gas stays small with the lung partially reopened only. Rather than in the entire lung, overdistension prevails in those areas that do not collapse upon suction or that have lower opening pressures. In patients with lung failure, overinflation has been recently demonstrated, despite small volume ventilation[18,19]; a mechanism similar to that mentioned above might have contributed to this finding.

We did not study here the clinical consequences of repeated suction, a maneuver routinely performed both in intensive care units on patients with diseased lungs and on patients with healthy lungs during anesthesia, nor did we study what suggestions to give avoiding suction-induced lung collapse. In addition, our negative pressure (*i.e.*, suction) model is definitely not a model of acute respiratory distress syndrome. For characterizing the suction model more precisely, additional functional and histologic data would have been helpful, and it is certainly unfortunate that we failed to obtain such data. Clinical experience tells that up to 50–60 cm $H_2O$ pressure is required for reopening a collapsed lung during one lung anesthesia.[20] It was somewhat unexpected to find, in our pilot animals, the lungs remaining partially collapsed, even after controlled mechanical ventilation for more than 2 h. This suggests that forceful suctioning induces some type of surfactant deficiency effect, to which adds the second hit of high tidal volumes, resulting in more than a simple collapse model. Our aim was limited to inducing a standardized stable lung collapse without major impact on hemodynamics or gas exchange, in which high $V_T$ and PEEP would have induced both recruitment and overdistension within the same inspiration. The suction model should be considered therefore a mere proof of principle, rather than a model with immediate clinical impact.

Carryover effects of the different PEEP levels applied at random might be a concern. However, the very similar course of the individual intratidal $C_{RS}$ (see fig. 2) makes major carryover effects unlikely. One might, for example, expect that lungs, once fully recruited with a PEEP of 15 cm $H_2O$, would not recollapse when switched to lower PEEP levels. The narrow CIs of the intratidal $C_{RS}$ course speak against this. Moreover, in pilot animals with this model (please see Supplemental Digital Content 1, http://links.lww.com/ALN/A673), we observed that the lung collapse with negative pressure application is amazingly "sticky,"[21] requiring forceful, sustained reopening procedures, rather than short-lived, PEEP-induced airway increases, for lasting elimination of lung collapse.

Although we compensated for nonlinear endotracheal tube resistance, inertive effects (see overswing in tracheal pressure, fig. 1) related to the large flow peaks in early expiration might have caused artifacts on calculated tracheal pressure during expiration. Therefore, only data from inspiration were used for calculating compliance.

## Conclusions

With lung collapse, the profile of intratidal compliance depends on the actual PEEP/$V_T$ combination. This pattern primarily reflects the mechanical conditions of the respiratory system. From the compliance profile, it is possible to infer whether substantial intratidal recruitment occurs or overdistension prevails. The gliding-SLICE method has the potential to detect those intratidal nonlinearities without interrupting ongoing ventilation or requiring additional technical equipment, making use of the pressure and flow signals that are at hand anyway.

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