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Is pulmonary resistance constant, within the range of tidal volume ventilation, in patients with ARDS?

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When managing patients with acute respiratory distress syndrome (ARDS), respiratory system compliance is usually considered first and changes in resistance, although recognized, are neglected. Resistance can change considerably between minimum and maximum lung volume, but is generally assumed to be constant in the tidal volume range (V_T). We measured resistance during tidal ventilation in 16 patients with ARDS or acute lung injury by the slice method and multiple linear regression analysis. Resistance was constant within V_T in only six of 16 patients. In the remaining patients, resistance decreased, increased or showed complex changes. We conclude that resistance within V_T varies considerably from patient to patient and that constant resistance within V_T is not always likely.

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Acute respiratory distress syndrome (ARDS) is associated with considerable changes in respiratory system mechanics.¹ Clinicians are most interested in the elastic properties of the respiratory system; resistance to gas flow is of less interest. Although resistance is volume dependent when large volume ranges are studied, it is often assumed to be constant within the tidal volume range (V_T). This neglect of resistance in ARDS patients may be because resistance is rarely treated, unlike in obstructive pulmonary diseases. We did not consider resistance when we studied volume-dependent changes in compliance within V_T in 16 patients suffering from ARDS or acute lung injury (ALI).² We determined resistance data but did not evaluate them, considering them irrelevant to the effect of the ventilator settings. However, volume-dependent resistance could be of interest, so we have now considered changes in resistance within V_T on the basis of the same measurements.

Methods

Patients

We studied 16 consecutive adult patients with ARDS or ALI (defined according to Bernard and colleagues³). Compliance measurements from these patients have been reported.² We obtained approval from the institutional ethical committee

and written informed consent of the patients' relatives. Patients' lungs were ventilated⁴ using a Servo 900C ventilator (Siemens-Elema, Solna, Sweden) in the pressure-controlled mode. We used consensus guidelines that have been previously reported in detail.² Since the effects of the given ventilator settings were of greatest interest, the settings were not changed and recruitment manoeuvres were not used.

Determination of resistance: volume-dependent R_{slice} and R_{MLR}

In two patients, gas flow rate was measured with a heated pneumotachograph (Fleisch no. 2; Metabo, Epalinges, Switzerland) connected to the endotracheal tube, which was calibrated with a syringe of 1000 (SD 1) ml (calibration syringe 54500460; Jaeger, Würzburg, Germany). A differential pressure transducer (SPS1, Hoffrichter, Schwerin, Germany) was used to determine the flow proportional pressure difference across the pneumotachograph. Airway pressure was measured by a transducer (1210A; ICSensors, Milpitas, CA, USA) previously tested for linearity between -80 and $+80$ mbar and calibrated using a Revue Thommen calibrator (Waldenburg, Switzerland). Signals were digitized at 100 Hz with 12-bit resolution (SDM863; Burr Brown, Tucson, AZ, USA). In 14 patients a CP-100

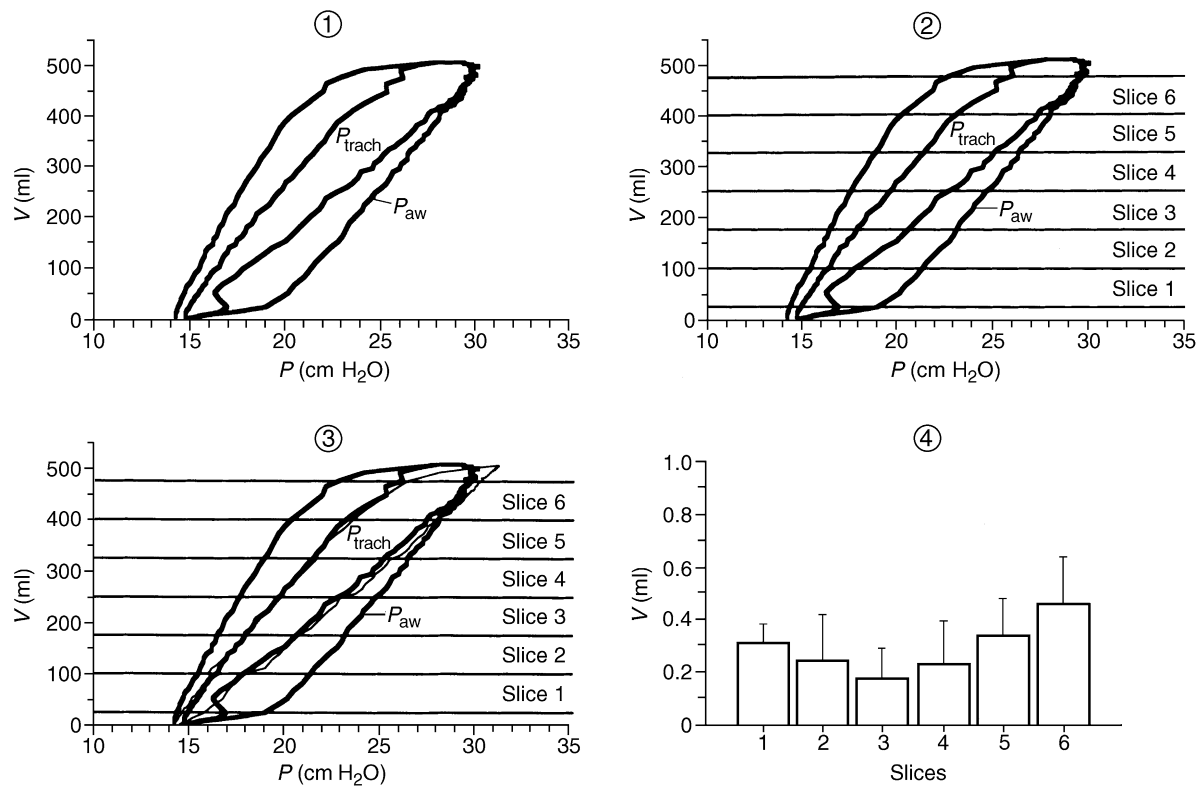


Fig 1 The principle of the slice method involving two steps is shown using an example of a pressure–volume loop. Step 1: the outer loop is based on measured airway pressure (P_{aw}) and volume. Continuous calculation of the flow-dependent pressure drop across the endotracheal tube yields the inner loop, representing tracheal pressure (P_{trach}). Step 2: the loop is divided into six slices of equal volume excluding the uppermost and lowermost 5% of the loop. In each slice, one value of resistance and compliance is calculated based on the simple linear RC model. The resulting R_{slice} and C_{slice} data drawn over volume give the course of these parameters within tidal volume (compare with Figure 2). Two additional steps may be used to verify the quality of the fit. Step 3: the P_{trach} -volume loop (thin line) is reconstructed using calculated respiratory parameters and measured flow and volume. The match of the measured and reconstructed P_{trach} -volume loop give an estimate of the appropriateness of the fit and the model in describing the raw data. Step 4: The absolute difference (mean and SD) between measured and reconstructed P_{trach} -volume-loop (ΔP) is given for each slice.

pulmonary monitor (Bicore Monitoring Systems, Irvine, CA, USA), calibrated according to the manufacturer's instructions, was used for measurements. The raw data were sampled with 50 Hz and passed to a laptop computer. Thereafter, the raw data from both systems were transmitted to a SparcStation 4 workstation (Sun Microsystems, Palo Alto, CA, USA) to calculate volume-dependent respiratory system resistance (and compliance) using the slice method.^{5,6}

The slice method uses multiple linear regression (MLR).⁷ Rather than using data derived from end-inspiratory and end-expiratory airway occlusion manoeuvres, MLR uses flow, pressure and volume data of the whole breath. If resistance and compliance are assumed to be constant within the tidal volume range, a simple linear model is usually used for this calculation to give average values of resistance and compliance by analysing inspiration and expiration signals obtained during mechanical ventilation without flow interruption. Consequently, the resulting 'dynamic' resistance and compliance values include pressure components associated with stored viscoelastic energy and the effects of inhomogeneous gas distribution.

The slice method enhances standard MLR because changes in respiratory variables over the volume of interest (usually the V_T) can be determined. For this purpose, the V_T is first divided into six volume slices of equal size and MLR is done separately for each slice. The resulting plot of R_{slice} (or C_{slice}) over the volume slices give volume-dependent resistance (or compliance) within V_T .

There are other differences between the slice method and standard MLR. With standard MLR, resistance data are affected by the flow-dependent drop in pressure across the endotracheal tube. With the slice method, this effect is eliminated by continuously calculating tracheal pressure (P_{trach}) before the actual slice calculations.^{8,9} To ensure the accuracy of the P_{trach} calculation in this study, obstruction of the endotracheal tube by secretions or kinking was excluded by suctioning of the airways immediately before the measurements and then monitoring the time constant of passive expiration (τ).¹⁰ The uppermost and lowermost 5% of the pressure–volume loop were excluded from the analysis because of distortions caused by operation of the ventilator valves. Another difference is that the slice method automatically

considers intrinsic positive end-expiratory pressure (PEEP).¹¹

The principle of the slice method is shown in an example of a pressure–volume loop (Figure 1). Step 1 involves calculation of P_{trach} . The tidal volume is then divided into six slices (step 2) and resistance and compliance are calculated for each slice separately. To assess goodness of fit, the P_{trach} –volume loop is reconstructed using calculated respiratory parameters for each slice and measured flow and volume data. The match of the measured and the reconstructed P_{trach} –volume loop is shown in part 3 of Figure 1. The absolute deviation (mean plus one SD) of the two loops (ΔP) is shown in part 4 (Figure 1). The quality of the fit and the appropriateness of the model are demonstrated by the small ΔP ; the fit is best in the middle of V_T . Since the uppermost (and lowermost) 5% of the loop are not adequately described by a model not including inertance, these parts of the loop were excluded from the analysis.

In principle, the course of resistance and compliance within V_T would be better described with a higher (ideally infinite) number of slices, thus increasing the volume resolution of the method. However, for stability of a least-squares fit, a sufficient amount of sampling points per slice is required. Cardiac oscillations transmitted to the measured pressure signal cause considerable noise. Use of six slices gives a good compromise between volume resolution and noise.⁵ To reduce noise further, R_{slice} data for 15 breaths were averaged. As well as R_{slice} , we calculated resistance over the entire pressure volume loop (R_{MLR}).^{7,12}

We modified the original slice method⁵ and did not calculate volume-equidistant data sets from time-equidistant raw data. This computation is time-consuming and requires user intervention, which prevents online calculations of mechanical parameters and hinders clinical application. We therefore no longer use this transformation.^{2,6,13} All data are given as mean (SD).

Results

Patient characteristics are presented in Table 1. Patients had both pulmonary and extrapulmonary ARDS/ALI. There was no relationship between resistance (or compliance) data and diagnosis.

The course of R_{slice} within V_T in each patient is shown in Figure 2 (mean (SD) mbar litre⁻¹ s). R_{MLR} is drawn as a horizontal line within each plot and its absolute value and SD are given. R_{slice} was constant or almost constant within V_T in patients A, B, E, H, L and P, and it increased in patients D, G, J, K, M and N. A concave pattern of R_{slice} was observed in patients C and I and a convex pattern in patient O. In patient F, R_{slice} decreased within V_T . The C_{MLR} data are given above each graph. The change in C_{slice} within V_T , which has been reported previously,² is indicated by the symbol above each graph.

To be sure that the resistance–volume pattern did not merely reflect the flow pattern, the absolute gas flow rate in

each slice (mean (SD)) in one representative breath in each patient is shown in Figure 3. As a quality control for the fit, the mean absolute deviation between measured and reconstructed pressure–volume loop is given in Table 2. The mean number of sample points in each slice is given.

Discussion

Resistance often changed within the relatively small tidal volume in ARDS or ALI patients. The course of resistance within V_T varied markedly from patient to patient, with different patterns of R_{slice} . Volume-dependence of resistance in ARDS patients occurs over relatively large volume ranges,¹⁴ but the course of resistance within V_T has not been described before.

Methodological considerations

To determine the course of resistance (and compliance) within V_T , data from the whole breath, i.e. from inspiration and expiration, were used. The resulting mechanical measurements thus represent both phases of the respiratory cycle. Inspiratory and expiratory resistance can be separated by standard (whole-breath) MLR.⁷ However, the stability of the fit procedure would have been overstrained by calculation of volume-dependent resistance separately for inspiration and expiration.

The slice method determines resistance as the sum of airway and tissue resistance. The two can be separated with the interrupter technique using sophisticated technical equipment.^{15–18} However, airway resistance data obtained by the interrupter technique inevitably contain the resistance of the endotracheal tube. By contrast, resistance data obtained by the slice method are based on calculated P_{trach} after elimination of the resistance of the endotracheal tube.^{8,9}

In the slice method, the pressure–volume loop is divided into six slices of equal volume. Potential effects of the gas flow rate on the mechanical parameters are assumed to be negligible. However, the characteristic decelerating flow pattern of pressure-controlled ventilation used here calls this assumption into question. Therefore, we plotted the absolute mean flow rate in each slice for every patient (Figure 3). While slightly differing from patient to patient, the flow rate was distributed over the slices (i.e. the V_T) with a convex pattern. If resistance were to increase with flow rate, a similar pattern would be expected. This pattern was present in patient O and, to a lesser extent, in patients A and H. In all other patients, the course of R_{slice} within V_T was not related to flow values. Consequently, flow has only a minor effect on the course of R_{slice} within V_T . This conclusion supports the findings of Eissa and colleagues,¹⁴ who reported resistance to be grossly independent from the gas flow rate in ARDS patients, although their data were obtained by using the interrupter technique.

Table 1 Patient characteristics and ventilatory parameters. CPR = cardio-pulmonary resuscitation; SIRS = systemic inflammatory response syndrome; MOF = multiple organ failure; HELLP = hypertension, elevated liver enzymes, low platelets. Adapted from reference 2 (p. 1087) with permission from Springer, Heidelberg

Patient	Age (yr)	Gender	Diagnosis	LIS ²⁶	Survived?	PEEP (mbar)	V _T (ml)	RR (min ⁻¹)
A	31	M	aspiration	2.75	yes	11	750	11
B	18	M	after CPR	1.75	no	12	560	11
C	48	F	pneumonia	2.75	no	11	390	15
D	45	M	pneumonia and sepsis	3	yes	14	690	14
E	24	F	malaria tropica	2.5	yes	10	500	10
F	40	M	stab injury of pericardium and liver	2	yes	10	640	13
G	36	F	HELLP syndrome	3.75	yes	15	500	15
H	30	M	rupture of diaphragm	3	yes	10	290	18
I	26	M	pneumonia and sepsis	3.75	no	14	280	11
J	37	M	pneumonia	3.5	no	13	470	8
K	75	M	pneumonia, SIRS, MOF	2.25	no	8	590	12
L	40	M	blunt chest and multiple trauma	2.75	yes	17	500	14
M	23	F	aspiration	3.5	yes	12	650	13
N	24	M	multiple trauma	3.5	no	14	400	11
O	24	M	blunt chest trauma	3.5	yes	14	250	16
P	42	F	peritonitis	3.75	yes	14	21	

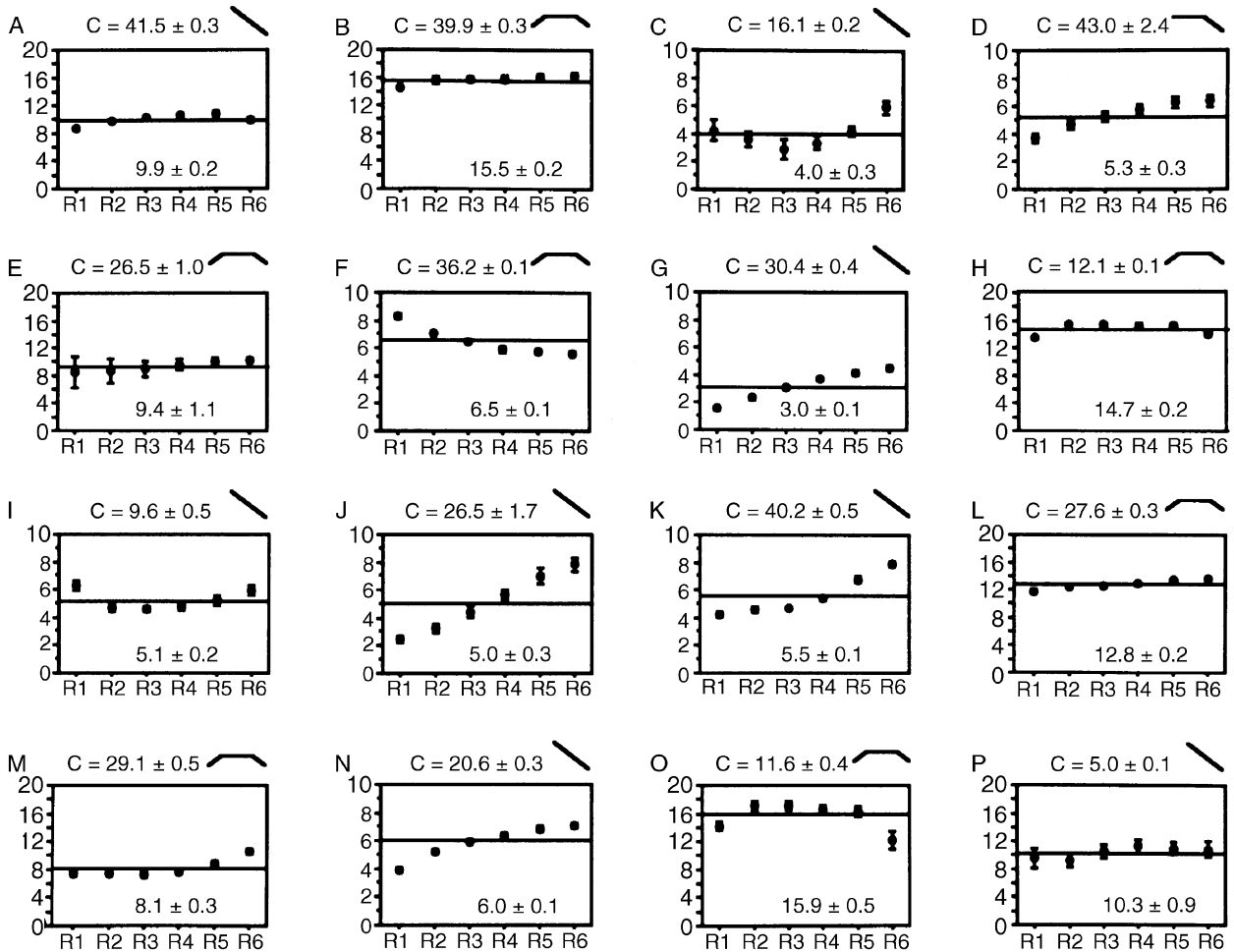


Fig 2 R_{slice} data within V_T (mean and SD, mbar litres⁻¹ s; markers for SD often not visible). Note the different scaling on the y-axis. The numbers (R1–6) refer to slices; volume increases from left to right. R_{MLR} of the same breaths are plotted as a straight horizontal line, mean values (with SD) are given. The letters mark the patients studied. C_{MLR} (ml mbar⁻¹) is given above each plot. A symbol showing the course of C_{slice} over volume as previously described² is also shown.

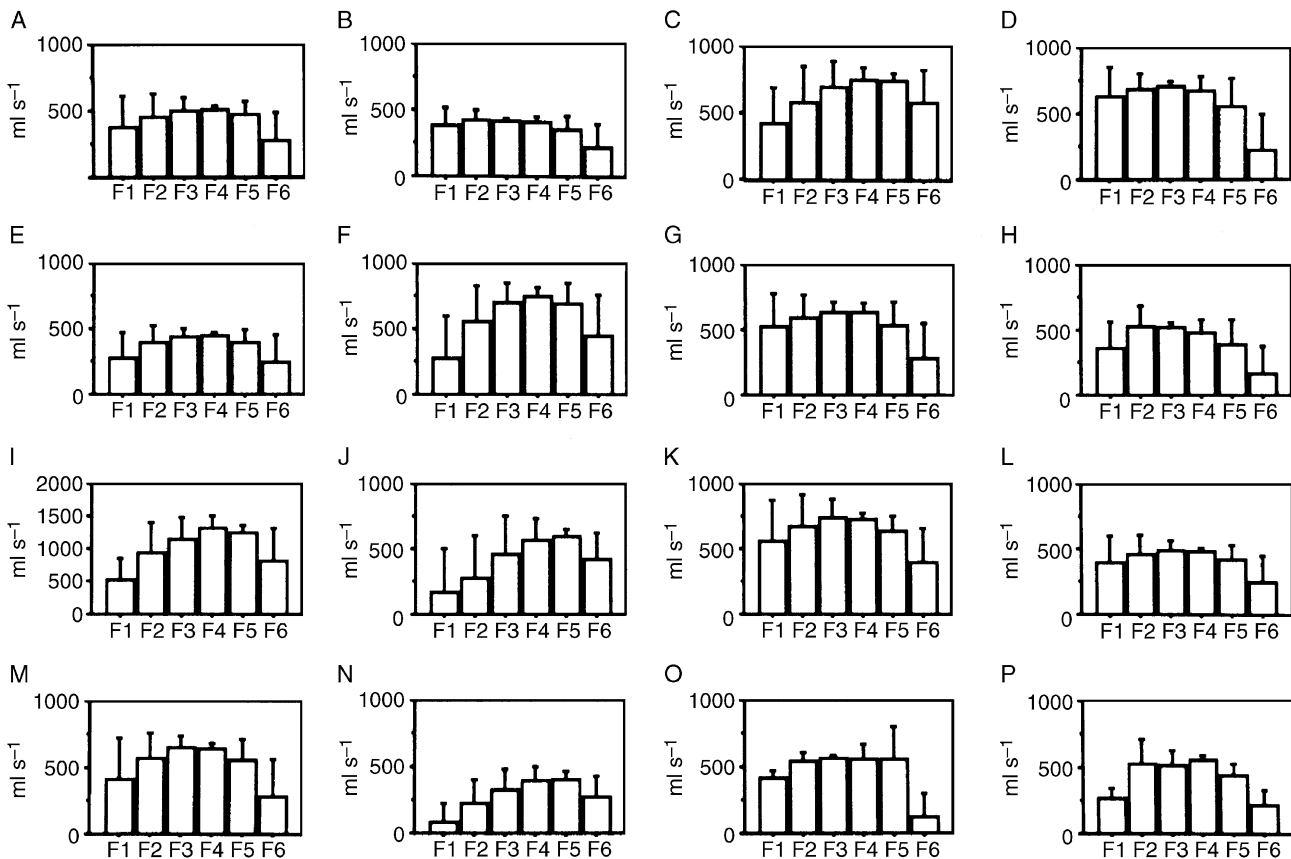


Fig 3 The mean (with SD) flow rate (ml s^{-1}) is shown for each slice in one breath of each patient. The numbers (F1–6) refer to slices; volume increases from left to right. The letters mark the patients studied. Note the different scaling on the y-axis in patient I. The distribution of flow rate over volume (slices) should not be confused with a plot of flow rate over time, which decreases during pressure-controlled ventilation.

Table 2 Quality control of the fit procedure. ΔP =mean absolute difference between original and reconstructed pressure–volume loops (using calculated respiratory parameters for each slice and measured flow and volume data). The number of sample points in each slice was obtained from the first breath, which was recorded in each patient. Data are mean (SD)

	Slice 1	Slice 2	Slice 3	Slice 4	Slice 5	Slice 6
Sample points	31 (25)	21 (11)	18 (11)	17 (8)	19 (8)	34 (14)
ΔP (mbar)	0.8 (0.4)	0.8 (0.4)	0.7 (0.5)	0.9 (0.8)	1.2 (1.2)	1.6 (1.8)

Interpretation of data

Resistance increased considerably in most patients, as often reported in ALI and ARDS patients.^{19–21} Classically, resistance should decrease during lung inflation,²² so a decrease in R_{slice} should also be expected even within the small V_T . Such a pattern of R_{slice} occurred only in patient F, whereas in patient O R_{slice} decreased only at greater lung volume within the tidal volume range. In most of the patients, other patterns of R_{slice} were found. The constant R_{slice} (found in six of 16 patients) is relatively easy to interpret. The studied volume range, i.e. the V_T , may have been too small for a change of resistance to occur.

Other patterns of R_{slice} are more interesting. Several investigators reported an increase of resistance with lung

inflation in ALI patients.^{20 21 23 24} In these reports, however, the studied volume range was larger. Eissa and colleagues¹⁴ investigated the volume dependence of airway resistance in ARDS patients at different PEEP levels, and hence different lung volumes. Although they studied a volume range that was greater than the tidal volumes studied here, they reported an increase of resistance with lung inflation starting from high PEEP levels (10 or 15 $\text{cm H}_2\text{O}$). At lower PEEP levels (0 and 5 $\text{cm H}_2\text{O}$) they observed a concave pattern. These data are not directly comparable because they were obtained with the interrupter technique during constant inspiratory flow. How can we interpret an (unexpected) increase in resistance? Longitudinal stretching of airways at high lung volumes could perhaps decrease their cross sectional area, and thus increase resistance.¹⁴

Our data show no apparent association of PEEP with the course of R_{slice} . This may be because the PEEP was high throughout. Moreover, since larger interindividual differences in lung mechanics exist in ARDS patients, pulmonary overdistension could not be expected at a distinct PEEP level, especially when V_T also differs. However, it may be helpful to consider the C_{slice} data reported previously.² A decrease in C_{slice} is interpreted as overdistension. A decreasing C_{slice} coincided with an increasing R_{slice} , at least in the upper slices, in eight of 16 patients (C, D, G, I, J, K, M and N). These data may support the interpretation by Eissa and colleagues¹⁴ of longitudinal airway stretching at high lung volume. As an alternative explanation for the volume-dependent increase in resistance, Pesenti and colleagues²¹ suggested an increased tissue resistance caused by inhomogeneity of ventilation at high PEEP levels.

Limitations

This study has two limitations. First, it is an incidental observation. The data were obtained with another end in view, i.e. the analysis of volume-dependent compliance within V_T .² The resistance data reported here were not sampled with an *a priori* hypothesis and no plan was followed to investigate the volume dependency of resistance after changes in ventilator settings. Secondly, the resistance data presented here represent the behaviour of the whole respiratory system, containing the lungs and chest wall. While the chest wall's resistance to airflow can be neglected,²⁰ viscoelastic properties of the chest wall may contribute to the 'dynamic' resistance of the respiratory system. It would only have been possible to separate the resistance of the lung resistance from that of the chest wall by measurement of pleural pressure. It is difficult to measure pleural pressure, so oesophageal pressure is often used as a surrogate. In principle, determination of the lungs' inherent resistance based on measurements of oesophageal pressure would be desirable and this could easily be added to the slice method. However, our purpose in measurement of respiratory mechanics with the slice method in this and other studies^{2 6 13} is to develop a concept that will help clinicians to set the ventilator. A non-invasive approach that could be used in standard ventilator equipment is therefore preferable. Measurement of oesophageal pressure is not suited for routine care, because its application is invasive and requires careful adjustment of the catheter's position. Furthermore, oesophageal pressure may not exactly represent pleural pressure, because it is affected by the weight of the mediastinum in the supine position.²⁵

Implications and conclusions

Resistance changes considerably, not only in large volume ranges, but also within the relatively small V_T . The method used allows non-invasive and continuous recording of volume-dependent resistance. Clinical benefits for ARDS

patients will come only if a thorough explanation of volume-dependent resistance can be derived.

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