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Mechanical and morphometrical changes in progressive bilateral pneumothorax and pleural effusion in normal rats

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ABSTRACT: Respiratory changes resulting from stepwise intrathoracic injections of 4 ml of either room air or warm (37°C) Haemaccel ™, simulating pneumothorax and pleural effusion, respectively, were evaluated in anaesthetized, paralysed, and mechanically-ventilated rats.

Respiratory system, lung, and chest wall resistances and elastances (static and dynamic) were determined in 14 animals. For this purpose, the end-inflation occlusion during constant inspiratory flow method was used. Chest wall configuration at both functional residual capacity (FRC) and end-inspiration tidal volume (*i.e.* FRC+(V_T)) was also evaluated in: 1) 15 rats by measurements of lateral and anteroposterior diameters, and circumferences at the 3rd intercostal space and xiphoid levels; and 2) in 16 rats by measurements of thoracic cephalocaudal diameter. In addition, changes in functional residual capacity were measured.

Both in pneumothorax and pleural effusion, resistances were not altered, but static and dynamic respiratory system and lung elastances increased progressively. Morphometric changes were similar at both functional residual capacity and end-inspiration; however, whereas pleural effusion increased all diameters, pneumothorax did not modify lateral diameter. Functional residual capacity was decreased in both conditions.

In conclusion, pneumothorax and pleural effusion induced similar mechanical changes, but thoracic configuration was differently affected, since lateral diameters were increased in pleural effusion only.

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Pneumothorax and pleural effusion frequently lead to respiratory impairment. There are reports mentioning a few aspects of respiratory mechanics in the presence of pneumothorax (PN) or pleural effusion (PE) [1–10], but most of them deal with spirometry [2, 4–8, 10], pleural pressure topography [1, 9], and pressure-volume curves [4–7]. In pleural effusion, only airway resistive properties [2, 4, 8, 10], and chest wall [10] and lung compliance [4, 10] were determined. Recently [3], the measurement of total resistive and elastic properties of lung and chest wall has provided results in disagreement with those reported previously [2, 4, 8, 10]. By superimposing radiographs, the diaphragmatic position was evaluated in pleural effusion [7]. Distribution of ventilation was also measured in pneumothorax [11] and pleural effusion [12].

Therefore, the aim of the present study was to determine the effects of controlled pleural effusion and pneumothorax (stepwise injections of 4 ml up to 20 ml of air or fluid) on respiratory, pulmonary, and chest wall resistive, elastic, and viscoelastic mechanical properties, thoracic morphometry, and changes in functional residual capacity (FRC) in anaesthetized paralysed rats. Such comprehensive analysis has not previously been performed.

Methods

Forty five adult Wistar rats were sedated with diazepam (5 mg *i.p.*), anaesthetized with pentobarbitone sodium (20 mg·kg^{-1} *i.p.*), and a snugly fitting cannula (1.5 mm internal diameter (ID)) was introduced into the trachea. They were then placed in the supine position on a surgical table. A catheter (1.5 mm external diameter (ED)) was inserted into the pleural cavity at the level of the 2nd right intercostal space. For this purpose, the catheter was assembled inside a needle, the distal extremity of which was airtight. After the introduction of the needle tip into the thoracic cavity, a catheter segment of about 1 cm was then inserted, and the needle removed. The catheter was secured into place and airtightness assured by stitching the skin around the catheter.

In 22 rats, room air was injected through the catheter in 4 ml steps, up to a total of 20 ml, to generate a progressive bilateral pneumothorax. In the remaining 23 animals, the same technique was used to inject warm (37°C) Haemaccel™ (Hoechst do Brasil, São Paulo, SP, Brasil) to simulate pleural effusion.

Respiratory mechanics were measured in 14 rats: six belonging to the pneumothorax group (weight 265–352 g;

mean 310±28 (±SD)g); and eight to the pleural effusion group (weight 230–265 g; mean 246±13 g). A pneumotachograph, constructed according to MORTOLA and NOWORAJ [13], was connected to the tracheal cannula for the measurements of flow ($\dot{V}$) and, by electronic integration, of changes in lung volume. The flow resistance of the equipment (tracheal cannula included) (Req), constant up to flows of 26 $ml \cdot s^{-1}$, amounted to 0.125 $cmH_2O \cdot ml^{-1} \cdot s$. Req was subtracted, wherever appropriate, so that the results reported represent intrinsic resistance values. Because abrupt changes of diameter were not present in our circuit, errors of measurement of flow resistance were avoided [14, 15]. The equipment dead space was 0.4 ml. Tracheal pressure (Ptr) was measured with a Hewlett-Packard 270 differential pressure transducer (Waltham, MA, USA). Changes in oesophageal pressure (Poes) were measured with a 30 cm long water-filled catheter (PE-240), with side holes at the tip connected to a PR23-2D-300 Statham differential pressure transducer (Hato Rey, Puerto Rico). The catheter was passed into the stomach and then slowly returned into the oesophagus; its proper positioning was assessed using the "occlusion test" [16]. The frequency responses of the pressure measurement systems (Ptr and Poes) were flat up to 20 Hz, without appreciable phase shift between the signals. All signals were conditioned and amplified in a Beckman type R Dynograph (Schiller Park, IL, USA) and recorded on paper at a speed of 5 $mm \cdot s^{-1}$. Flow and pressure signals were also passed through 8-pole Bessel filters (902LPF, Frequency Devices, Haverhill, MA, USA) with the cutting frequency set at 100 Hz, sampled at 200 Hz with a 12-bit analogue-to-digital converter (DT2801A, Data Translation, Marlboro, MA, USA), and stored on a computer (PC-AT, IBM, Armonk, NY, USA). All data were collected using LABDAT software (RHT-InfoData Inc., Montreal, Quebec, Canada).

Muscle relaxation was achieved with gallamine triethyliodide (2 $mg \cdot kg^{-1}$ *i.p.*) and artificial ventilation was provided by a Salziner constant flow ventilator (Instituto do Coração-USP, São Paulo, SP, Brazil). During the test breaths, a 5 s end-inspiratory pause could be generated by adjusting the ventilator settings. In order to avoid the effects of different flows and volumes [17, 18] and inspiratory duration [19], on the measured variables, special care was taken to keep tidal volume (V_T) (=2 ml) and flow (=10 $ml \cdot s^{-1}$) constant in all animals.

The measurements were performed before and immediately after the stepwise injection of room air or Haemaccel™ into the pleural space. In addition, to verify the effectiveness of the procedures, the rats underwent radioscopic examination at the end of the experiments. Finally, the abdomen was opened and the injected fluid was aspirated through the diaphragm by means of a syringe-needle assembly. The experiments did not last for more than 60 min.

Respiratory mechanics determination

Respiratory mechanics were measured from end-inspiratory occlusions after constant flow inflations [20]. Although this method has been used for a long time, the significance of the measured variables has only recently been clarified [19, 21–24]. Hence, the interrupter technique allows the determination of respiratory viscous resistance (Rvis,rs), which selectively reflects the combination of airways and chest wall Newtonian resistances in normal animals [17, 22–24]. It also provides another quantity, which reflects stress relaxation, or viscoelastic properties, of the lung and chest wall tissues (Rdiff,rs), together with a small contribution of pendelluft in normal situations [18, 23, 24, 25]. Total respiratory system resistance (Rtot,rs) is equal to the sum of Rvis,rs and Rdiff,rs. This method also allows the determination of dynamic (Edyn,rs) ans static (Est,rs) respiratory system elastances. The same procedures apply to Poes, yielding corresponding values for the chest wall (Rtot,w, Rvis,w, Rdiff,w, Edyn,w, and Est,w). Pulmonary values (Rtot,L, Rvis,L, Rdiff,L, Edyn,L, and Est,L) were calculated by subtracting the chest wall values from the corresponding respiratory system values. Five to eight determinations were performed in each animal in all instances. Before each measurement period, the airways were aspirated to remove possible mucus collection, and the respiratory system was inflated three times to a transpulmonary pressure of +30 cmH_2O.

The delay between the beginning and the end of the valve closure (10 ms) was allowed for by back extrapolation of the pressure records to the actual time of occlusion, and the corrections in resistance, although very small, were performed as described previously [17].

All data were analysed using ANADAT data analysis software (RHT-InfoData Inc., Montreal, Quebec, Canada).

Chest wall configuration

Chest wall configuration and FRC changes [26] were determined in 15 Wistar rats prepared and ventilated as described above. Eight belonged to the pneumothorax group (weight 255–320 g; mean 292±22 (SD) g); and seven to the pleural effusion group (weight 205–240 g; mean 226±11 g). Chest wall circumferences (C), anteroposterior (Dap) and lateral (Dl) diameters at the 3rd intercostal space (ic) and xiphoid (x) levels were measured at control and at each level of pneumothorax and pleural effusion, both at FRC and at end-inspiration (FRC+V_T), as described previously [26]. The measurements were performed three times by the same investigator in each animal under the same circumstances, as described for the mechanical analysis. Special care was taken to perform the measurements at the same reference points and to avoid errors due to the soft tissue compressibility. In addition, the possible changes in FRC induced by the experimental protocol were also measured in all animals [26]. The whole experiment lasted less than 60 min.

Pulmonary cephalocaudal diameter (Dcc), (distance from the lung apex to the diaphragmatic dome) was determined in 16 Wistar rats prepared and ventilated as described above. Eight belonged to the pneumothorax group (weight 255–355 g; mean 293±36 g), and 8 to

the pleural effusion group (weight 160–270 g; mean 214±34 g). Dcc was measured at control and at each level of pneumothorax and pleural effusion, both at FRC and FRC+VT. For this purpose, two needle shafts were transversely introduced through the rat's skin at 90° relative to its body length at the 3rd intercostal space and xiphoid levels. Under radioscopic examination, two lengths were measured on the monitor: 1) between the two needle shafts; and 2) the lung apex-diaphragmatic dome distance. Since the space between the two needles was measured in the rats with calipers and the display was linear, Dcc could be easily calculated. In order to better identify the thoracic cavity during liquid injection, a warm (37°C) mixture of Haemaccel™ (50%) and Hypaque™ 75% (The Sydney Ross Co., Rio de Janeiro, RJ, Brazil) (50%) was used. The measurements were performed three times by the same investigator in each animal under the same circumstances, as described for the mechanical analysis. The experiments lasted less than 30 min.

Statistical analysis

Statistical analysis was performed by means of analysis of variance (ANOVA) for nonindependent samples, followed by Newman-Keul's multiple comparisons test, when necessary, with the significance level established at 5%.

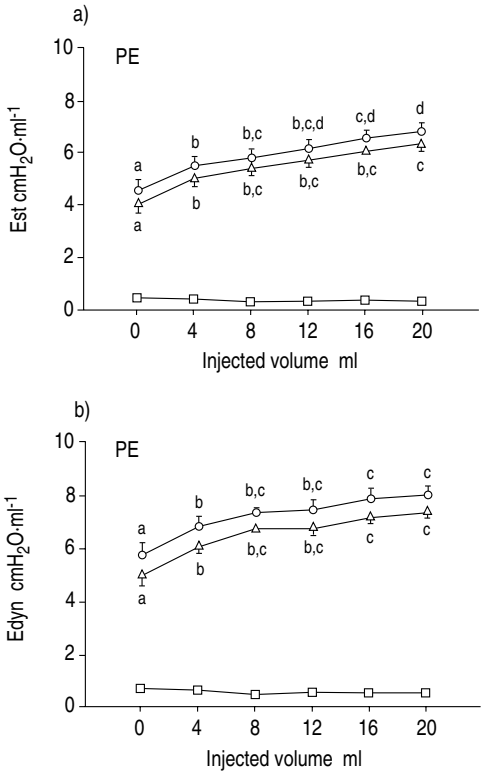

Fig. 1. – Respiratory system (—○—), pulmonary (—Δ—), and chest wall (—□—) a) static (Est) and b) dynamic (Edyn) elastances in control conditions and after progressive pleural effusion (PE). Data are means of eight rats (5–8 determinations·animal^{-1}). Bars represent +/- SEM; when not depicted, bars are smaller than symbols. Different letters indicate significant differences ($p<0.05$) between data-points and same letters indicate no significant difference between data-points.

Results

Intrinsic airway peak pressure (equipment resistive pressure subtracted) varied from 10.4 (control) to 14.8 cmH_2O at 20 ml (pneumothorax). The corresponding values for pleural effusion were 11.0 and 14.9 cmH_2O, respectively.

The mean values (+/- SEM) of respiratory system, lung, and chest wall Est and Edyn in the control condition and after 4 ml intrathoracic injections of Haemaccel™ are shown in figure 1a and b. Respiratory system and lung Edyn and Est increased significantly between control (no Haemaccel™) and different levels of pleural effusion, whereas Edyn,w and Est,w remained unaltered.

Qualitatively similar results were also found for the induction of pneumothorax. There were no statistically

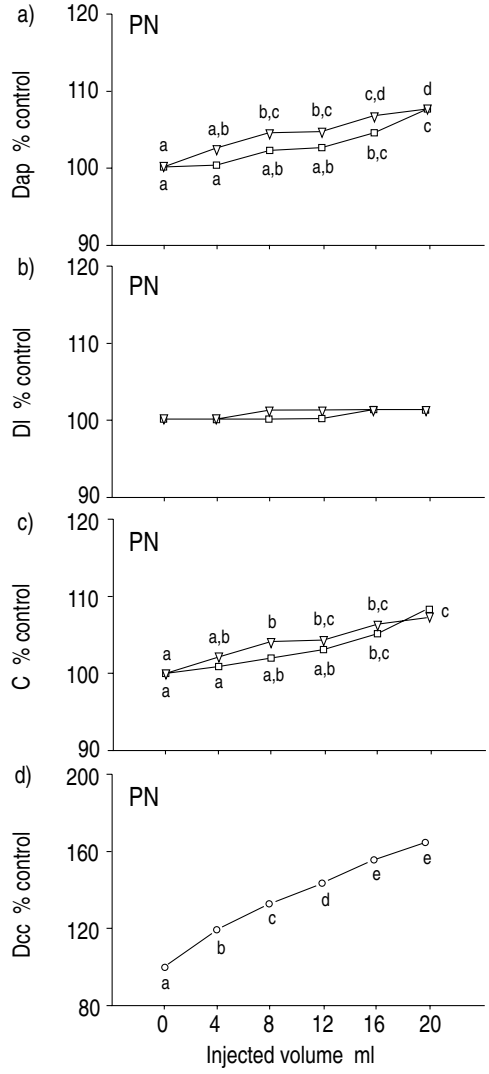

Fig. 2. – Thoracic dimensions measured at functional residual capacity (FRC) in control conditions and after progressive pneumothorax (PN). Data are means of eight rats (3 determinations·animal^{-1}). Bars represent +/- SEM; when not depicted bars are smaller than symbols. Note that a different scale was used in the lower panel. Dap: anteroposterior diameter; Dl: lateral diameter; C: circumference; Dcc: cephalocaudal diameter; —▽— : 3rd intercostal space; —□— : xiphoid rib cage level. Different letters indicate significant differences ($p<0.05$) between data-points and same letters indicate no significant difference between data-points.

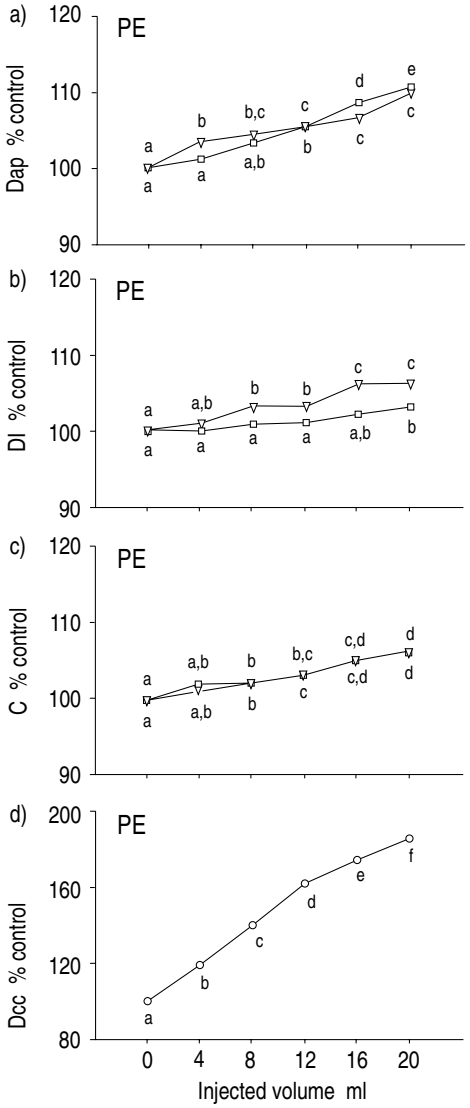

Fig. 3. – Thoracic dimensions measured at functional residual capacity (FRC) in control conditions and after progressive pleural effusion (PE). Data are means of seven rats for anteroposterior and lateral diameters, and circumferences; and 8 rats for cephalocaudal diameter (3 determinations·animal^{-1}). Bars represent +/- SEM; when not depicted bars are smaller than symbols. Note that a different scale was used in the lower panel. For abbreviations see legend to figure 2. —▽—: 3rd intercostal space; —□—: xiphoid rib cage level. Different letters indicate significant differences ($p<0.05$) between data-points and same letters indicate no significant difference between data-points.

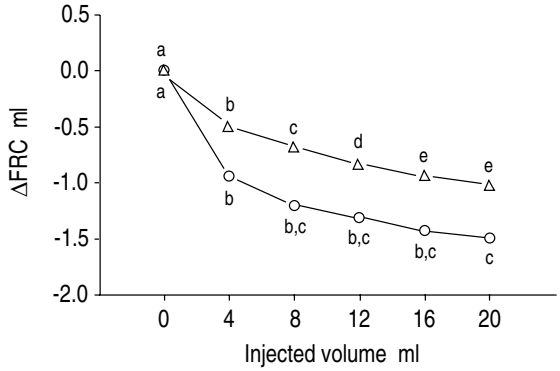

Fig. 4. – Changes in functional residual capacity (ΔFRC) at control and after progressive pneumothorax (—○—) and pleural effusion (—Δ—). Values are means of 6 (pneumothorax) and 8 (pleural effusion) rats. Different letters indicate significant differences ($p<0.05$) between data-points and same letters indicate no significant difference between data-points.

significant changes in the various resistance variables during progressive pneumothorax or pleural effusion.

Figures 2 and 3 depict thoracic configuration parameters at FRC in pneumothorax and pleural effusion, respectively. It can be seen that Dap increased progressively in both cases (figs 2a and 3a). Dl remained unaltered in pneumothorax but increased with each injection of Haemaccel™ in pleural effusion (figs 2b and 3b). Progressive increases in C are seen in figures 2c and 3c. Dcc increased progressively in both cases (figs 2d and 3d). The overall mean and standard deviations of Dap, Dl, C and Dcc in the control condition are listed in table 1. The same behaviour was found when the measurements were performed at FRC+VT.

The changes in FRC during progressive pneumothorax and pleural effusion are depicted in figure 4. FRC was significantly smaller than control value at all levels of pneumothorax; a difference was also found between 4 and 20 ml of injected air. FRC values differed significantly among themselves at all levels of pleural effusion, thus showing a progressive decrease with increasing injected volume of liquid.

Discussion

Pneumothorax and pleural effusion may play an important role in determining respiratory impairment. Hence,

Table 1. – Thoracic dimensions in control conditions before pneumothorax and pleural effusion at functional residual capacity

	Dap,ic	Dap,x	Dl,ic	Dl,x	C,ic	C,x	Dcc
Pneumothorax (n=8)							
	3.68	3.61	4.53	5.61	13.54	15.46	2.46
	(0.19)	(0.13)	(0.24)	(0.36)	(0.61)	(0.54)	(0.41)
Pleural effusion (n=7)							
	3.47	3.41	3.85	5.26	12.22	14.54	2.53†
	(0.22)	(0.18)	(0.16)	(0.29)	(0.50)	(0.45)	(0.34)

Data are presented as mean, and SD in parenthesis. In each animal, three measurements were performed. Dap,ic and Dap,x: 3rd intercostal space and xiphoid rib cage anteroposterior diameters, respectively; Dl,ic and Dl,x: 3rd intercostal space and xiphoid rib cage lateral diameters, respectively; C,ic and C,x: 3rd intercostal space and xiphoid rib cage circumferences, respectively; Dcc: cephalocaudal diameter. †: n=8.

in the present study, we sought to determine the mechanical alterations, body conformational changes, and decreases in FRC secondary to progressive pneumothorax and pleural effusion.

Mechanical alterations

Progressive pleural effusion (fig. 1) and pneumothorax yielded higher Est,L and Edyn,L, which led to greater Est,rs and Edyn,rs, respectively. Est,L was also found to increase in pneumothorax [5] and pleural effusion [3–5]. Conversely, KRELL and RODARTE [7] found that the slope of pulmonary pressure-volume (P-V) curve was not changed by pleural effusion. However, the highest volume injected into the pleural space in their experiment amounted to only 45% of control total lung capacity (TLC), whereas in the present work approximately 200% of TLC was used [27, 28]. The higher lung elastance during pneumothorax and pleural effusion could be secondary to microatelectasis and a lower FRC value (see below), thus moving resting volume to lower values along the P-V curve of the lung. Est,w fell in dogs [3], in disagreement with the present results in pleural effusion (no change, fig. 1). However, in rats, a great deal of change was found in chest wall dimensions (see below), which could explain the discrepancy.

By contrast, no changes in respiratory system, lung, and chest wall resistances could be identified in either pneumothorax or pleural effusion. These results are in line with the findings of unaltered airway specific conductance reported previously [2, 4, 8, 10]. In one study [3], however, increases in respiratory system and pulmonary total resistances were identified. The reason for this discrepancy is not readily apparent. It should be noted, however, that in the present investigation the lungs were passively inflated before each measurement, whilst in the work of DECHMAN *et al.* [3] no measurement was made during incremental loading but only after the end of fluid loading. It is possible that all measurements in our study were affected by lung re-expansion, since DECHMAN *et al.* [3] found a partial and temporary (about 5 min) reversal of the changes after lung inflation.

In summary, the mechanical profiles in pneumothorax and pleural effusion are identical, irrespective of the different distribution of air and liquid, and both in the presence (pleural effusion) and absence (pneumothorax) of pleural pressure gradient [11, 12]. Supporting this finding, pleural effusion and its attendant changes in pleural pressure had no influence on regional lung expansion [12], which was also found to be homogeneous in pneumothorax [11].

Body conformational changes

The conformational changes in pneumothorax (fig. 2) and pleural effusion (fig. 3) follow different trends. In the pleural cavity, gas would tend to collect at the nondependent sites, whereas liquid would be accomodated in the lower portions and move the rib cage laterally. Furthermore, air is compressible, whereas liquid is not. Together, these considerations would indicate that larger conformational changes occur in the pleural effusion group. Finally, it can be concluded that the addition of VT to the FRC does not seem to modify the pattern of alteration of chest wall configuration both in pneumothorax or pleural effusion.

After a fluid injection of 20 ml, the increase in Dcc was strikingly greater than that found in other dimensions (+68% in pneumothorax and +86% in pleural effusion). In spite of the high compliance of the rib cage in rats, the present results suggest that the diaphragm-abdomen is even more compliant, as indicated by the aforementioned configurational changes. Interestingly, in dogs Dcc was also found to increase in pleural effusion but Dap and Dl were not modified [7].

Functional residual capacity

FRC decreased more in the pneumothorax than in the pleural effusion group (fig. 4) but the pneumothorax group mean body weight (BW) was higher than that of the pleural effusion animals. Indeed, taking into account BW, ΔFRC/BW (after 20 ml of fluid had been infused) equaled 4.6 and 5 $ml \cdot kg^{-1}$ in pleural effusion and pneumothorax groups, respectively; thus, implying that pleural effusion and pneumothorax induce the same proportionate change in FRC. Furthermore, according to CROSFILL and WIDDICOMBE [29], in both cases the total exhaled amount of gas was similar to FRC, since their FRC/BW was 6 $ml \cdot kg^{-1}$.

Methods

The infusion of saline solution to simulate pleural effusion in dogs allowed recovery of at least 90% of the injected amount [3, 7]. In previous experiments, we introduced warm (37°C) 0.9% NaCl solution in the pleural space, and after 60 min only 50% of the amount used could be recovered. In order to use a fluid with higher colloidal osmotic pressure, warm Haemaccel™ was substituted for saline solution in the present work, and in all instances the same injected volume was recuperated. Moreover, in the pneumothorax experiments, the volume of injected air was always recovered.

Before the aspiration of the pleural content the animals underwent radioscopic examination, and in all instances a bilateral and almost symmetrical pneumothorax or pleural effusion was found, because in rats the pleural cavities normally communicate [30]. The validity of the Poes measurement was assessed with the occlusion test [16] in six additional anaesthetized spontaneously breathing rats (three from the pneumothorax series and three from the pleural effusion group). Up to 8 ml of infused fluid, the Poes measurement was found to be correct. Beyond this limit, the animals showed severe respiratory failure and the experiment was interrupted. Interestingly, using infusion volumes in dogs (60 $ml \cdot kg^{-1}$) comparable to those in the present investigation, the validity of the oesophageal pressure measurement was

also confirmed [3]. The same result was found in humans [4].

Although the methods used to measure configuration parameters could be subject to error in the measurements, great care was taken to minimize this. Thus, the highest intra-animal value of SD/mean (n=3) in the determination of Dap, Dl and C amounted to only 3.8%; when Dcc was measured the greatest ratio was 5.7%.

In conclusion, pneumothorax and pleural effusion generated identical mechanical changes (unaltered viscous and viscoelastic properties but increased lung and respiratory system elastances); progressive pleural effusion augmented anteroposterior, lateral, and cephalocaudal diameters, as well as thoracic circumferences, whereas pneumothorax did not induce changes in lateral diameters; morphometric results were similar at FRC and FRC+VT; and pneumothorax and pleural effusion yielded proportionate stepwise decreases in FRC. Since the data on respiratory mechanics in pneumothorax and pleural effusion are very scanty, the present results may prove useful as a starting point for further studies to apply our findings to humans.

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