The effect of body temperature on the dynamic respiratory system compliance–breathing frequency relationship in the rat

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Received: 1 December 2012 / Accepted: 11 January 2013 / Published online: 22 February 2013
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Abstract The mechanical inhomogeneity of the respiratory system is frequently investigated by measuring the frequency dependence of dynamic compliance, but no data are currently available describing the effects of body temperature variations. The aim of the present report was to study those effects *in vivo*. Peak airway pressure was measured during positive pressure ventilation in eight anesthetized rats while breathing frequency (but not tidal volume) was altered. Dynamic compliance was calculated as the tidal volume/peak airway pressure, and measurements were taken in basal conditions (mean rectal temperature 37.3 °C) as well as after total body warming (mean rectal temperature 39.7 °C). Due to parenchymal mechanical inhomogeneity and stress relaxation-linked effects, the normal rat respiratory system exhibited frequency dependence of dynamic lung compliance. Even moderate body temperature increments significantly reduced the decrements in dynamic compliance linked to breathing rate increments. The results were analyzed using Student's and Wilcoxon's tests, which yielded the same results ($p < 0.05$). Body temperature variations are known to influence respiratory mechanics. The frequency dependence of dynamic compliance was found, in the experiments described, to be temperature-dependent as temperature variations affected parenchymal mechanical inhomogeneity and stress relaxation. These results suggest that body temperature variations should be taken into consideration when the dynamic compliance–breathing frequency relationship is being examined during clinical assessment of inhomogeneity of lung parenchyma in patients.

Keywords Body temperature · Dynamic compliance · Frequency of breathing · Mechanical ventilation · Rat · Respiratory mechanics

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1 Introduction

The frequency dependence of dynamic respiratory system compliance is a well-established index of mechanical inhomogeneity of lung ventilation [1–5]. Demonstrated at times in normal mammals [6–8], including humans [2, 5], it suggests that regional time constant inhomogeneities can exert mechanically significant effects even in basal conditions, i.e., in the absence of respiratory system diseases.

Respiratory system mechanics has been shown to be temperature-dependent [9]. Although temperature increments are frequent events during acute exacerbations of respiratory diseases in which mechanical inhomogeneity is a common occurrence, their effect on the dynamic compliance–breathing frequency relationship has never been studied.

Data describing airway resistance increments following airway cooling in asthmatic patients with respect to subjects with normal airway resistance [10–12] suggest that temperature may have an effect on the respiratory system time constant regional inhomogeneity and hence on the dynamic compliance–breathing frequency relationship. The cooling-induced increment in airway resistance is all the more evident in already-narrowed asthmatic airways, and a reduction in intraparenchymal mechanical inhomogeneity could be expected to follow body temperature rises.

In addition to mechanical inhomogeneity, stress relaxation-linked phenomena could also theoretically affect the frequency dependence of respiratory system dynamic compliance [13]. In fact, the higher the breathing rate, the lower the stress relaxation-linked pressure drop is expected over time [14–17], and hence the lower the dynamic compliance measures [18, 19].

Stress relaxation has also been shown to be temperature-dependent and to diminish in connection to even moderate body temperature increments [9]. The stress relaxation rate has also been found to increase with temperature [20].

Body temperature alterations are thus expected to affect the dynamic compliance–breathing frequency relationship not only because of mechanical inhomogeneity changes but also because of the reduction in stress relaxation-linked effects.

An increment in body temperature is expected to diminish the effects of both parenchymal inhomogeneity and stress relaxation on the dynamic compliance–breathing frequency relationship.

On the basis of that, the aim of this report was to investigate if dynamic respiratory system compliance exhibits frequency dependence in normal rats and if the dynamic compliance–breathing frequency relationship is affected by even moderate changes in body temperature such as those occurring in spontaneous exacerbations of respiratory system diseases.

2 Materials and methods

The experiments were carried out on eight albino Wistar rats of both genders (four males, mean weight 405 ± 15 g, and four females, mean weight 245 ± 10 g). The animals were housed and treated in accordance with Italian legislation concerning animal experimentation (L.116/92) and the European Community Council directive 86/609/EEC. The experimental protocol was approved by the local animal experimentation ethics committee (C.E.A.S.A.).

The rats were anesthetized by i.p. chloralose (50 mg/100 g) and then placed on a heated operation table. After tracheotomy, a small polyethylene cannula (2 mm i.d., 5 cm long) was inserted through an incision in the second tracheal ring and firmly secured in place.

Positive pressure ventilation (tidal volume 10 ml/kg, breathing frequency 60 breaths per minute, Rodent Ventilator 7025, Basile, Italy) was used throughout the experiment, and limb ECG probes were placed to measure heart rate. Care was taken to monitor that tidal volume remained constant when breathing frequency was altered.

Airway pressure was monitored (142 pc 01d, Honeywell, USA) and recorded (1326 Econo Recorder, Biorad, Italy). After a 5-min stabilization period, the breathing frequency was randomly changed from 60 breaths per minute to 30, 90, and 120 breaths per minute, but tidal volume was left unaltered. Every frequency was maintained for the short period of time (less than 30 s) necessary for a constant pressure signal to become evident and each was separated from one another by 5-min period at 60/min. Care was taken to verify that airway pressure consistently reached atmospheric pressure at the end expiration, i.e., that intrinsic positive end-expiratory pressure did not develop at any of the tested breathing frequencies. Peak airway pressure at point of zero flow was measured on adequately magnified tracings for each breathing frequency imposed, and dynamic compliance of the respiratory system (C_{dyn}) was calculated as $C_{dyn} = \text{tidal volume/peak airway pressure}$.

The same experimental procedure was repeated after the rats were warmed, which was achieved using an infrared lamp (150 W) positioned approximately 30 cm from the rat for about 15 min. Rectal temperature was monitored continuously by a previously calibrated rectal thermistor probe inserted about 1 cm deep. Warming was discontinued when the rectal temperature rose approximately 2 °C degree with respect to control conditions. The entire experimental procedure lasted less than 1 h.

Student's *t* test was used to perform statistical analysis but because of the relatively small sample size, the results were also confirmed by a non-parametric test (Wilcoxon). To further study the frequency of the breathing- C_{dyn} relationship, a linear regression analysis was performed to verify if the slopes obtained at 37.3 and 39.7 °C were significantly different from 0 and from one another. Data are expressed as mean values $\pm$ SE ($n = 8$), and significance was set at $p < 0.05$.

Fig. 1 Linear regression between C_{dyn} mean values and breathing frequency (BF) for data obtained at 37.3 °C. Vertical bars indicate $\pm$ SE ($n = 8$)

Fig. 2 Linear regression between mean Cdyn values and breathing frequency (BF) for data obtained at 39.7 °C. Vertical bars indicate $\pm$ SE ($n = 8$)

3 Results

The mean rectal temperature in control conditions was 37.3 ± 0.3 °C. The rectal temperature rose to 39.7 ± 0.2 °C after the body warming procedure.

Regression lines connecting Cdyn to the breathing frequency for both temperatures tested were drawn. A significant regression was demonstrated for all the animals (r values ranged between -0.88 and -1). Results are summarized in Figs. 1 and 2, and Table 1.

The linear regression between Cdyn mean values and breathing frequencies is depicted in Fig. 1 for the experiments performed at 37.3 °C and in Fig. 2 for those performed at 39.7 °C. Both regressions were highly significant, and both slopes were significantly different from 0 ($p = .009$). These results indicate that there was a significant decrease in Cdyn at increasing breathing frequencies.

Statistical analysis showed that the slope calculated for 37.3 °C were significantly higher than that obtained for 39.7 °C ($p = 0.03$), indicating that the increment in body temperature reduced the Cdyn dependence on breathing frequency. The analysis was performed by comparing the mean slope values of the dynamic compliance/breathing frequency relationships in each rat at the two temperatures tested using both a Student's t test for paired data and a non-parametric test (Wilcoxon). Both statistical approaches yielded the same result ($p = 0.03$ and $p = 0.029$, respectively), indicating that an increment in body temperature reduced the Cdyn dependence on breathing frequency. The same result was produced by the statistical comparison (Wilcoxon) of the decrements in Cdyn due to the increasing breathing frequencies observed at the two temperatures tested.

Table 1 p values from Student's t test describing the differences in mean Cdyn values at different breathing frequencies at different body temperatures

Compared breathing frequencies (breaths/min)	p values at 37.3 °C	p values at 39.7 °C
30–60	.05	.04
30–90	.04	.03
30–120	.02	.01
60–90	.03	.08
60–120	.04	.06
90–120	.07	.05

The p values resulting from the Student's t test describing the differences in the mean Cdyn values measured at the various breathing frequencies are outlined in Table 1 and confirm that Cdyn significantly decreases in conjunction with increasing breathing frequencies for both the temperatures tested.

Increasing body temperature caused a significant increment in heart rate, which rose from 276 ± 38 to 332 ± 31 beats/min ($p = 0.034$).

4 Discussion

Other investigators have already demonstrated that the ventilator settings used here are not injurious per se to the respiratory system [17, 21]. Nevertheless, to further investigate the possibility of any time-related influence, Cdyn mean values calculated at the 60 breaths per minute ventilator setting used throughout the experiments were compared and were not found to be statistically significantly different.

The breathing frequencies tested here included normal rat values [22], and the Cdyn mean values observed were similar to those already reported in the literature [17]. As expected, Cdyn mean values were lower than static compliance values in the rat, which fell within the range of 0.35 and 0.5 ml/cmH₂O [9, 17, 21].

As previously observed in various different mammalian species [2, 5–8], the results presented here demonstrate that dynamic respiratory system compliance is frequency dependent in normal rats (Figs. 1 and 2, and Table 1).

The mechanisms responsible for this interplay include the mechanical inhomogeneities in normal lungs, which are thought to depend primarily on the gravity-dependent vertical gradient of pleural pressure that affects the regional mechanical properties of the lung parenchyma, i.e., the local time constant values [23]. Gravity-dependent effects on respiratory mechanics have been demonstrated even in the small rat's lungs [24]. Stress relaxation-linked phenomena may also be expected to lead to a frequency dependence of dynamic respiratory system compliance [13]. It has been shown in fact that inspiratory pressure decays over time due to stress relaxation [14–17], and the decrement will be lower the higher the breathing frequency. Confirming the results of previous reports [18, 19], this in turn leads to decreased dynamic compliance levels in conjunction with increasing breathing frequency rates, as has just been reported here.

Stress relaxation represents a typical visco-elastic behavior. Visco-elasticity combines the liquid- and solid-like characteristics of the lung tissue, and the main mechanism responsible for macroscopic visco-elastic behavior is the micro-structural rearrangement processes of collagen, elastin, and interstitial liquid. Interstitial liquid movements in the lung parenchyma and interaction phenomena of elastin and collagen fibres, such as reciprocal sliding, could be affected by body temperature as those components are in coordinated thermal motion, the driving force of which is thermal energy.

The study's principal finding is that the dynamic compliance–breathing frequency relationship is significantly affected by even moderate changes in body temperature. This result indicates that body warming reduces time-constant inhomogeneities and stress relaxation-linked effects in the normal lung parenchyma.

Although this interplay has never been investigated before and little or no comparison data are available, the following hypothesis can be proposed.

The findings presented here are supported by results showing that breathing cold air increases airway resistance in asthmatic patients but not in normal subjects [10–12]. Those findings are in agreement with other reports indicating that the effects of temperature on airway resistance is stronger in asthma with respect to basal conditions [25, 26]. Those data suggest that increments in airway resistance linked to cooling could be more effective when airway resistance is already increased as, for example, in asthmatic bronchial segments. It follows that the increment in airway resistance linked to cooling could be greater in parenchymal regions already exhibiting lower conductance leading to increased mechanical inhomogeneity in normal lungs. A reduction in intraparenchymal mechanical inhomogeneity might then ensue as an effect of body temperature increments. As presently shown, body warming is expected to reduce the slope of the dynamic compliance–breathing frequency relationship.

However, it could also be a consequence of the effect of temperature change on stress relaxation. Body temperature increments have been shown to reduce stress relaxation [9], and the stress relaxation rate in lung parenchyma has been found to increase with warming [20]. When breathing frequency is increased by any given amount, the time for stress relaxation-linked pressure decay is reduced, leading to a decrement in the dynamic compliance, but if the rate of pressure decay is increased by body warming [20], the airway pressure drop will be greater, and the fall in the dynamic compliance will be smaller, leading to a reduction in the slope of the dynamic compliance–breathing frequency relationship, as has been shown here.

If tidal volume is unaltered (as in our case), modifications in breathing frequency lead to changes in alveolar ventilation. This in turn might cause variations in the partial pressure values in respiratory gases in the blood, which are known to affect airway resistance and in turn respiratory mechanics and C_{dyn} . According to data in the literature, that effect could be considered negligible in the experimental conditions outlined here because the time intervals of altered ventilation were kept very short [27]. Ventilation variations were, moreover, separated from one another by 5-min intervals during which there was a 60 breaths per minute constant breathing frequency, and hence there was constant alveolar ventilation.

The mean heart rate values reported here are similar to those expected in normal rats under general anesthesia [28]. As expected, body temperature increments caused a related increase in heart rate [9], which could have increased pulmonary blood flow, which is known to affect lung mechanics [29]. It is not possible to exclude or quantify the influence of this effect on the results presented here.

5 Conclusions

Increments in body temperature of the same magnitude outlined here are frequently observed during the clinical evolution of common respiratory diseases such as chronic obstructive pulmonary disease (COPD) or asthma. The degree of mechanical parenchymal inhomogeneity is, particularly in the former case, frequently assessed during clinical evaluation of the disease. The data presented here suggest that the effects of increased body temperature on mechanical parenchymal inhomogeneity indexes such as the dynamic compliance–frequency breathing relationship should be considered when patients are being clinically assessed during disease exacerbations and in the presence of fever.

Body temperature increments are expected to improve the mechanical properties of the respiratory system, primarily by increasing respiratory system compliance and decreasing airway resistance [9]. The frequency-dependence of C_{dyn} could also be increased during hypothermia caused by various conditions as well as during therapeutic hypothermia, which has recently been proposed and applied as a protective strategy primarily in ischemic brain injury. The potentially beneficial consequences of body temperature increments on respiratory patients certainly warrant further investigation.

Conflict of interests The authors have no conflicts of interest to declare.

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