Thixotropy of rib cage respiratory muscles in normal subjects

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Homma, Ikuo and Karl-Erik Hagbarth. Thixotropy of rib cage respiratory muscles in normal subjects. J Appl Physiol 89: 1753–1758, 2000.—In this study, we searched for signs of thixotropic behavior in human rib cage respiratory muscles. If rib cage respiratory muscles possess thixotropic properties similar to those seen in other skeletal muscles in animals and humans, we expect resting rib cage circumference would be temporarily changed after deep rib cage inflations or deflations and that these aftereffects would be particularly pronounced in trials that combine conditioning deep inflations or deflations with forcible isometric contractions of the respiratory muscles. We used induction plethysmography to obtain a continuous relative measure of rib cage circumference changes during quiet breathing in 12 healthy subjects. Rib cage position at the end of the expiratory phase (EEP) was used as an index of resting rib cage circumference. Comparisons were made between EEP values of five spontaneous breaths immediately before and after six types of conditioning maneuvers: deep inspiration (DI); deep expiration (DE); DI combined with forceful effort to inspire (FII) or expire (FEI); and DE combined with forceful effort to inspire (FIE) or expire (FEE), both with temporary airway occlusion. The aftereffects of the conditioning maneuvers on EEP values were consistent with the supposition that human respiratory muscles possess thixotropic properties. EEP values were significantly enhanced after all conditioning maneuvers involving DI, and the aftereffects were particularly pronounced in the FII and FEI trials. In contrast, EEP values were reduced after DE maneuvers. The aftereffects were statistically significant for the FEE and FIE, but not DE, trials. It is suggested that respiratory muscle thixotropy may contribute to the pulmonary hyperinflation seen in patients with chronic obstructive pulmonary disease.

IT IS NOW A WELL-ESTABLISHED fact that skeletal muscle fibers possess complex biophysical properties that make the stiffness and resting tension at a given muscle length dependent on the previous history of movements and contractions. These history-dependent properties, referred to as thixotropy, are generally believed to depend on formations and detachments of cross bridges between sliding actin and myosin filaments (5, 22, 23). The original basic observations concerning muscle thixotropy were made on relaxed frog muscle fibers (4, 15), but subsequent studies have shown obvious signs of thixotropy in human skeletal muscles (13, 17, 19, 26). There is also evidence that, in mammalian skeletal muscles, the intrafusal fibers of the muscle spindles have similar thixotropic properties as the extrafusal fibers (23).

A particularly prominent manifestation of muscle thixotropy is that the passive stiffness of a muscle held at an intermediate length is largely dependent on whether the muscle has been held and contracted at a short or at a long length immediately beforehand; the stiffness is enhanced after a hold-short contraction, whereas the muscle fibers will tend to fall slack after a hold-long contraction (12, 23). Thixotropic aftereffects can also be evoked, however, by hold-short and hold-long conditioning maneuvers without concurrent contractions. It is well known that a transient lengthening of relaxed muscle fibers is sufficient to cause a temporary reduction in the short range stiffness and resting tension (4, 5, 15).

In particular, it was the results obtained in a previous study dealing with the thixotropic behavior of human finger flexor muscles that led to the initiation of the present study. Hagbarth et al. (13) noted that, in subjects with totally relaxed finger flexor and extensor muscles, transient high-amplitude finger flexions or extensions had enduring aftereffects on the resting position of the fingers. When released after imposed high-amplitude finger extensions, it took a long time for the fingers to return to their initial semiflexed position, and an analogous positional “creep” of opposite direction was observed after transient high-amplitude finger flexions. These history-dependent changes in resting finger position were regarded as overt signs of extrafusal muscle thixotropy.

Plastic changes in the mechanical properties of the respiratory system have previously been observed as alternations in total respiratory resistance or total respiratory elastance (1, 3). To our knowledge, however, there are, as yet, no studies primarily concerned

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with the respiratory aftereffects of deep inspirations (DI) or expirations (DE) in healthy subjects.

The aim of the present study was to investigate whether human rib cage respiratory muscles possess similar thixotropic properties as those previously described for limb skeletal muscles in animals and humans. If so, a larger passive stiffness (and resting tension) in inspiratory, compared with expiratory, muscles after a conditioning DI (i.e., after a hold-short contraction of inspiratory muscles) and a reverse change after a DE would be expected. As a consequence of such stiffness alterations in inspiratory and expiratory muscles, it is also expected that the rib cage circumference would be temporarily enhanced after a DI and reduced after a DE. The present experiments were designed to test whether such shifts in rib cage circumference do occur and alter the rib cage position at which expiratory movements end during quiet breathing.

Because the end-expiratory position (EEP) provides a measure of the functional residual capacity (FRC) of the lungs, special attention was paid to the question of whether this particular parameter can be affected by conditioning maneuvers. EEP is generally considered to be the equilibrium position at which the elastic recoil of the lungs is balanced by the tendency of the chest wall to expand (24). EEP fluctuates when the balance is disturbed. Pulmonary hyperinflation, commonly observed in patients with chronic obstructive pulmonary disease (COPD), is characterized by an abnormal increase of the FRC, which Gibson and Pride (10) attributed to a decrease in the elastic recoil of the lungs. Contractions of inspiratory muscles at EEP, which have been observed during attacks in asthma patients (20, 21), can hardly be held responsible for the FRC increase in patients with COPD, because, in these patients, the rib cage muscles as well as the diaphragm are electrically silent at the end of expirations (7, 9). The possibility remains, however, that a thixotropy-induced rise in passive muscle stiffness of inspiratory muscles, possibly combined with a “softening” of the expiratory muscles, may contribute to the hyperinflation in COPD patients, a theory supported by the results of the present study.

**METHODS**

**Subjects.** The study was performed on 12 normal men (aged 22–30 yr) with no history of chronic pulmonary and/or neuromuscular disease. All subjects were naive to the purpose of the study and signed an informed consent.

**Measurements.** The circumference of the rib cage was measured by respiratory induction plethysmography using a Respiritrace transducer (Ambulatory Monitoring, Ardsley, NY) (6). The band of the Respiritrace consists of a coil of Teflon-insulated wire, which, in the present study, was attached around the rib cage just below the axilla. Respiratory rib cage movements changed the inductance of the band, and the inductance changes were converted into proportional voltage changes passed through a band-pass filter (0.007–4 Hz). The sensor gain was adjusted so that rib cage movements during breathing at rest gave rise to cyclic voltage variations within a range up to ~0.5 V. The subjects wore a mouthpiece, and a transducer (AR-601G Nihon Koden) attached to the mouthpiece measured the mouth pressure. The mouthpiece was connected to a fast-wire respiratory flowmeter (RF-2 Minato Ikagaku) to monitor flow and volume.

**Experimental procedure.** To avoid effects of posture changes on rib cage circumference, the subjects rested in a comfortable supine position on a bed; their noses were clipped; and the subjects held the mouthpiece in their mouths and breathed quietly. A magnetically driven mouthpiece shutter connected to the flowmeter could be manually triggered to close the airway at the end of DI or DE. Monitoring the airflow with the flowmeter during occlusions verified elimination of airflow.

In each of the subjects, the aftereffects of six different types of conditioning maneuvers on the cyclic rib cage circumference changes during quiet breathing were studied. For quantitative evaluation, a comparison showed the Respiritrace voltage signals at the rib cage EEP of five breathes before and after the conditioning maneuvers described below.

**DI and DE maneuvers.** Quiet breathing was temporarily interrupted by either a DI or DE rib cage movement on command. After these maneuvers, which were short enough (5–10 s) to avoid breathlessness, the subject resumed quiet breathing.

**FII and FEI maneuvers.** Quiet breathing was temporarily interrupted by a DI rib cage movement, and, while the rib cage remained inflated, the airway was closed, and the subject was instructed to make either a forceful inspiratory (FII) or a forceful expiratory effort (FEI) using the rib cage respiratory muscles. After these efforts (3- to 4-s duration), the airflow was opened, and quiet breathing was resumed.

**FEE and FIE maneuvers.** Quiet breathing was temporarily interrupted by a DE chest wall movement, and, while the chest remained deflated, the airway was closed and the subject made either a forceful expiratory (FEE) or a forceful inspiratory effort (FIE) using the rib cage muscles. In these trials, the efforts also lasted 3–4 s and were followed by quiet breathing with open airway.

**Statistical analysis.** To measure EEP levels for individual subjects, a line under the Respiritrace tracings of the rib cage movements was drawn, and the breath-by-breath values between the line and the EEP were measured. For each subject, the values from each of the five breaths before conditioning were averaged, and the averaged value was defined as zero level. This level was compared with the averaged EEP value of the five breaths after the conditioning maneuver and with the EEP value for each of these breaths. For these comparisons, a repeated-measures ANOVA, including the Greenhouse-Geisser correction procedure, was used. The pooled data from the 12 subjects were expressed in bar histograms showing means ± SE of the EEP values for each cycle. Comparisons between the bars were evaluated by the Wilcoxon signed-rank test for nonparametric analysis. P < 0.05 and P < 0.01 were considered significant.

**RESULTS**

**Aftereffects of DI and DE on EEP.** The rib cage records in Fig. 1A show typical examples of respiratory rib cage movements (as sensed by the Respiritrace transducer) for the five breathes before and after a DI or DE. The horizontal lines indicate the mean EEP level before the conditioning maneuvers. Because the mouthpiece shutter was open, there was no change in the pressure transducer signal during the deep rib cage inflations and deflations (top traces). The bar histo-
grams in Fig. 1B illustrate the pooled results of the EEP measurements. For each of the first to the fifth breaths after DI, there was a slight but nonsignificant increase in the EEP value. However, when the mean EEP value of the five breaths after DI are compared with the zero control values, the postmaneuver EEP increase became highly significant ($P < 0.01$). A change in the EEP values in the opposite direction was noted after DE, although, in these DE trials, the EEP reductions did not reach a significant level for either the individual breaths or for the mean EEP value derived from the five postmaneuver breaths.

Aftereffects of FII and FEI on EEP with rib cage held in DI position. Fig. 2 illustrates the outcome of the tests in which the subjects with the mouthpiece shutter closed made strong inspiratory or expiratory efforts while temporarily holding the chest deeply inflated. As shown in Fig. 2A, an obvious rise in EEP levels after both FII and FEI conditioning maneuvers could be observed by mere visual inspection of the Respitrace traces. As expected, it was also noted that the changes in mouth pressure were in opposite directions during FII and FEI. Analysis of the pooled data, illustrated by the bar histograms in Fig. 2B, verified that the after-
effects were similar for the FII and the FEI conditioning maneuvers. Both types of maneuvers caused a highly significant rise in the mean EEP value of the five postmaneuver breaths. Among the individual postmaneuver breaths, the EEP rise was significantly high for the first breath, but, as the aftereffects slowly subsided, the EEP increases for the succeeding breaths did not reach a significant level. We also measured the strength of the forced efforts as expressed by the mouth pressure signals. For the 12 subjects, the mean mouth pressure was $22.7 \pm 9.6$ (SE) and $26.7 \pm 14.5$ cmH$_2$O in the FII and FEI trials, respectively.

**DISCUSSION**

As mentioned, one would expect that, provided the rib cage respiratory muscles possess thixotropic properties, the resting position of the chest wall would not be the same after as before DI or DE rib cage movements. It was expected that the EEP (and FRC) values would be enhanced after a DI (which involved a shortening of the inspiratory and lengthening of the expiratory muscles) and a reverse EEP would change after a DE. It was also expected that these aftereffects would be particularly pronounced in trials where the "hold-short" and "hold-long" conditioning maneuvers are combined with strong contractions of the muscles concerned (23).

All of these expectations were verified by the present results. Even though the aftereffects of unforced deep inspirations and expirations were comparatively weak, the EEP values showed an obvious tendency to change in the expected directions after these types of conditioning maneuvers (Fig. 1). The aftereffects were much more prominent in the trials that combined DI and DE with strong isometric contractions of the respiratory muscles (Figs. 2 and 3).

There was a striking similarity between the aftereffects of the FII and FEI maneuvers and an equally striking similarity between the aftereffects of the FEE and FIE maneuvers. In other words, the direction of the forced efforts (toward inspiration or expiration) was of minor importance for the aftereffects. The determinant factor was whether the rib cage was held in an inflated or deflated position when the strong contractions were performed. One reason the direction of the forced efforts was of minor importance is presumably that all forced voluntary efforts included not only a strong contraction of the muscles generating the desired force but also an involuntary cocontraction of antagonistic respiratory muscles (held long when the force-generating muscles were held short and vice versa).
the rib cage is held in an inflated position would be an enhancement of the stiffness and resting tension in inspiratory muscles combined with a slackness of expiratory muscles, and this would lead to EEP shifts like those shown in Fig. 2. Similarly, strong cocontractions while the rib cage is held in a deflated position would have reverse aftereffects and lead to EEP shifts like those shown in Fig. 3.

The question may be raised whether the observed history dependence of EEP can be ascribed solely to thixotropic behavior of respiratory muscles. Plastic mechanical behavior of other respiratory tissues has been described by Barnas and colleagues (2) and Stamenovic et al. (25) and may possibly contribute to the aftereffects of DI and DE noted in the present study. However, thixotropic behavior of nonmuscular tissues can hardly explain why the aftereffects were particularly pronounced when DI or DE was combined with forceful isometric contractions of the respiratory muscles. This indicates that the aftereffects primarily depend on changes in passive properties that are attributable to actin-myosin cross-bridge kinetics. Stamenovic et al. (25) also considered actin-myosin cross-bridge kinetics to be a determinant factor in the plastic behavior of the respiratory system.

It cannot be maintained that rib cage respiratory muscles alone, by means of their thixotropic properties, are responsible for the aftereffects. Activation of muscles other than those in the rib cage itself may affect rib cage circumference changes during breathing at rest (8), and, if these other muscles also possess thixotropic properties, they may well contribute to the observed EEP aftereffects.

Even though the results presented in this study are explicable in terms of extrafusal thixotropy, it cannot be excluded that intrafusal thixotropy was also partly responsible for the observed aftereffects. There is evidence that indicates that, when human skeletal muscle is returned to an intermediate length after a strong hold-short voluntary contraction, there is enhanced resting tension not only in extrafusal but also in intrafusal muscle fibers, resulting in a raised level of afferent spindle discharge, which, in turn, can give rise to both an error in position sense and to an involuntary, so-called “postural aftercontractions” (11, 14). In the present study, the subjects were not consciously aware of the shifts in rib cage circumference toward inflation or deflation after the conditioning maneuvers, i.e., there was a misjudgment that could possibly be attributed to intrafusal thixotropy. It is still unknown whether postural aftercontractions contributed to the observed EEP shifts in any way.

It is of interest to consider the possible clinical implications of the present results. Because a transient deep and forceful inspiration is sufficient to cause a temporary rise in the EEP (and FRC) values of succeeding breath cycles in healthy subjects, it is not surprising that these values will remain at a high level in COPD patients who, because of airway obstruction, must contract their inspiratory muscles with extra force to obtain sufficient tidal volume. In view of the present results, one would expect that transient forceful expiration and/or a transient forceful inspiratory effort at the DE position (analogous to FEE or FIE, respectively) in COPD patients would temporarily reduce their hyperinflation. One would also expect that, as a consequence of muscle thixotropic behavior, such maneuvers would have a beneficial effect on all types of abnormal hyperinflations, irrespective of their primary causes. On the other hand, in patients with abnormally low FRC values, efforts analogous to FII and FEI are likely to have a temporary normalizing effect. Respiratory muscle stretch gymnastics (16) combines forced breathing with stretching of respiratory muscles. Respiratory muscle stretch gymnastics increases chest wall mobility, decreases FRC, and releases dyspnea in patients with COPD (16, 18). Evidence is now accumulating that respiratory muscle thixotropy is a factor that must be considered in attempts to explain the beneficial effects of respiratory muscle stretch gymnastics observed in patients with respiratory disorders.

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