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Hering-Breuer Reflex in Normal Adults and in Patients with Chronic Obstructive Pulmonary Disease and Interstitial Fibrosis

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For editorial comment see p. 131.

Key Words

Hering-Breuer reflex · Chronic obstructive pulmonary disease · Interstitial fibrosis

Abstract

Background: It has been suggested that the Hering-Breuer reflex (HBR) is unimportant in adults during normal tidal breathing and that it is elicited only if tidal volume is increased above a certain critical threshold. ***Objective:*** The aim of this study was (1) to study the occurrence of the HBR in adults with normal pulmonary function and (2) to examine if changes in lung mechanics have any effect on the HBR. ***Methods:*** We examined 11 adults with normal pulmonary function, 8 patients with chronic destructive pulmonary disease (COPD) and 3 with interstitial fibrosis (IF). All subjects were lightly sedated with fentanyl, intubated and ventilated with a Servo-900 ventilator. Inspiratory and expiratory flow (and after integration, volume) and mouth pressure were recorded from the endotracheal tube with a pneumotachograph and a pressure transducer. Pressure support ventilation was applied in all patients and functional residual capacity (FRC) was measured with the N_2 washout method. Mean (Te_{mean}) and maximal expiratory time (Te_{max}) were determined for each individual for 20 breaths. Following several breaths to establish a stable baseline the airway was occluded at end inspiration by a shutter. A positive HBR was interpreted as longer Te_{occ} than Te_{max} (Te_{occ}/Te_{max}, %). Occlusion was maintained until negative airway pressure occurred and the occlusion time (Te_{occ}) was measured. We attempted occlusions after the addition of 5 cm H_2O positive end-expiratory pressure (PEEP) and subsequently with 10, 15 and 20 cm H_2O PEEP. Te_{occ} was measured of progressively larger lung volumes. To examine the HBR sensitivity in the three groups, we plotted the lung volumes of occlusion against the corresponding Te_{occ}/Te_{max}. ***Results:*** The ratio Te_{occ}/Te_{max} increased from 167.5 ± 82.5 at normal FRC to 474 ± 200.2 s ($PEEP_{20}$). On the contrary, in patients with COPD, Te_{occ}/Te_{max} increased from 125.2 ± 34 to 193.7 ± 74.2 ($p < 0.05$). ***Conclusions:*** The HBR was positive in all subjects. COPD patients were found to be less sensitive to volume changes when compared with normal controls and with IF patients.

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Table 1. Anthropometric characteristics and spirometric data of normal subjects and patients with COPD and IF

	Age years	Height cm	RR breaths/min	VT ml	FRC ml	FRC_p ml	TLC_p ml
Normal	63 ± 18.2	163 ± 10	18 ± 3.7	485 ± 122	2,986 ± 593	3,015 ± 637	5,165 ± 1,097
COPD	69.1 ± 8.3	162 ± 9.8	19.2 ± 4	422 ± 241	3,352 ± 498	2,982 ± 607	4,971 ± 971
IF	62.3 ± 8.1	170.7 ± 8	32 ± 3.6[a, b]	507 ± 273	2,423 ± 418[b]	3,413 ± 553	5,830 ± 874[b]

RR = Respiratory rate; VT = tidal volume; FRC = functional residual capacity; TLC = total lung capacity; p = predicted.

[a] $p < 0.05$: statistically significantly different from normal values.

[b] $p < 0.05$: statistically significantly different from COPD.

Introduction

Hering and Breuer demonstrated in animals that sustained lung inflation inhibited inspiration and this stretch receptor reflex was inhibited by vagotomy [1]. The Hering-Breuer reflex (HBR) is accepted as an important respiratory control mechanism in the newborn period by the demonstration of a prolongation of expiration following lung inflation [2] and by the increase in the duration of inspiration following end-expiratory occlusion [3]. In healthy full-term infants the HBR can be evoked by brief end-inspiratory airway occlusions during natural sleep and the strength of reflex remains unchanged from birth to 6 weeks of age [4]. Subsequently reflex strength falls by an average of 38% in full-term infants when paired measurements are made at the 6th week and 1 year of age [5]. Adults exhibit a very weak HBR during quiet sleep and the reflex can only be evoked in conscious children and adults at lung volumes well above the tidal range, suggesting that maturation is asociated with a diminution of reflectivity [6].

It is generally recognized that chemical responses are weak at birth and that they develop subsequently. Also, it is known that the HBR is strong at birth and declines as respiratory stability increases. In adults, the HBR is suggested to be unimportant during normal tidal breathing, and only if tidal volume is increased above a certain critical threshold can it be elicited [7]. The aim of this study was to confirm the occurrence of the HBR in normal adults and to examine the effect of changes in lung mechanics – in interstitial fibrosis (IF) or chronic obstructive pulmonary disease (COPD) – on the HBR.

Methods

Subjects

The presence and the strength of the HBR were examined during mechanical support of ventilation:

(1) In 11 patients with normal pulmonary function, mechanically ventilated in an intensive-care unit 6–14 h after an uneventful CI operation (5 cholecystectomy, 4 for enterectomy of intestinal tumor and 2 for left lubinocele). In spirometry conducted the day before the operation, lung volumes and expiratory flow rates were close to predicted values (table 1).

(2) In 3 IF patients (mean age 62.3 ± 8.1 years) with recent spirometric values: forced expiratory volume in 1 s (FEV_1) 0.92 ± 0.21 l/s (30 ± 5% of predicted values) and forced vital capacity (FVC) 1.3 ± 0.4 liters (35.6% of predicted values).

(3) In 8 COPD patients (mean age 69.1 ± 8.3) on ventilatory support because of recent respiratory insufficiency, measurements were made at the end of a successful weaning period and about 24 h before extubation. Recent spirometric values before mechanical ventilation were FEV_1 0.92 ± 0.21 l/s (30 ± 5% of predicted values) and FVC 1.3 ± 0.4 liters (35.6% of predicted values).

Measurements

The study was approved by the ethical committee of G. Papanikolaou Hospital. At the examination time, all subjects were ventilated in pressure support mode with a tital volume of 8 ml/kg (range 7–10 ml/kg) in a Servo-900 ventilator. A pneumotachograph (Flicher No. 3) attached to a Validyne pressure transducer (range ± 2 cm H_2O) was inserted between the endotracheal tube and ventilator circuit. The pneumotachograph measured flow changes, and flow was obtained by electronic integration. Flow, volume (after integration) and mouth pressure changes were recorded simultaneously on a 4-channel recorder (Hewlett-Packard).

One hour before the HBR measurements, all patients were ventilated with a fraction of inspired oxygen (FIO_2) of 0.21 for 30 min. The nitrogen in the subjects' lungs was washed out by inspiration of an FIO_2 of 1.0 from the ventilator, while the expiration was collected from the expiratory port in a bag. The subject was switched to an FIO_2 of 1.0 circuit at the end of a normal expiration. The functional residual capacity (FRC) was estimated from the equation $FRC = (V + V_{DS})(F_E - F_I)/(Fo - F_A)$, where V is the volume of air expired, V_{DS} is

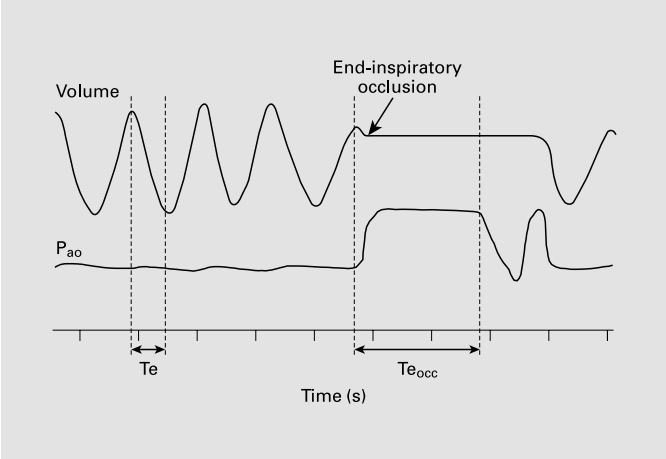

Fig. 1. Calculation of the HBR. Prolongation of Te_{occ} longer than Te_{max} is interpreted as positive HBR. P_{ao} = Airway pressure.

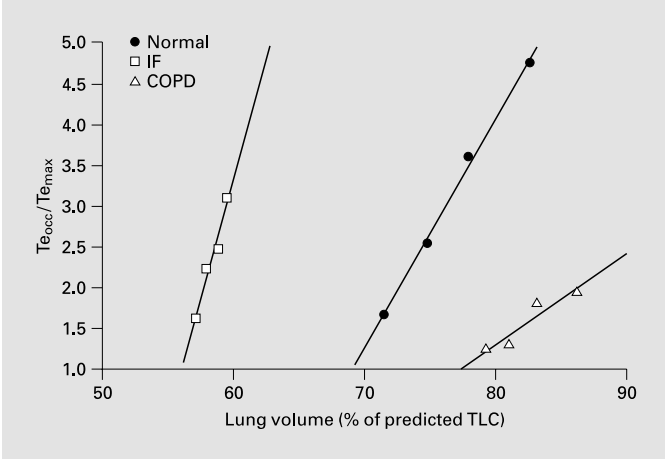

Fig. 2. The strength of HBR in normal subjects and patients with IF and COPD, obtained by plotting Te_{occ}/Te_{max} against the corresponding lung volumes expressed as percent of predicted TLC (V = VT + FRC_m + ΔFRC after PEEP).

Table 2. The mean values of HBR components (Te_{mean}, Te_{max}, Te_{occ}, Te_{occ}/Te_{max}) for normal subjects and patients with COPD and IF

	Te_{mean}, s	Te_{max}, s	Te_{occ}, s	Te_{occ}/Te_{max}, %
Normal	3.34 ± 1.44	4.45 ± 2.01	4.94 ± 2.04	112.2 ± 11.4
COPD	2.7 ± 0.96[a]	3.5 ± 1.4	3.6 ± 1.36	102 ± 8.55[a]
IF	1.48 ± 0.4[a, b]	1.73 ± 0.46[a, b]	2.07 ± 0.5[a, b]	120 ± 5[b]

[a] $p < 0.05$: statistically significantly different from normal values.
[b] $p < 0.05$: statistically significantly different from COPD.

the dead space of ventilator and tubing, F is the concentration of N_2 in the expiratory gas (E), in the inspired oxygen (I) and in the alveoli at the onset of the test (O) and at the end of the test (A) [8].

Experimental Protocols

All patients were lightly sedated with fentanyl (0.05 ml/kg) to avoid anxious reactions. Myelinated fibers which initiate the HBR are not blocked by fentanyl [9]. None of our patients had a PaO_2 <90 mm Hg and a $PaCO_2$ >39 mm Hg 1 h before the study.

Each patient, before any trial, was involved in an initial 10-min observation with at least 8 ml/kg volume, without positive end-expiratory pressure (PEEP), in the absence of air leaks. The mean spontaneous expiratory time (Te_{mean}), prior to each inflation, was determined by the average of about 20 observed breaths. Te_{max} was the biggest of them.

Following several breaths to establish a steady state, the airway was occluded at the end inspiration by the shutter. Occlusion was maintained until negative airway pressure occurred, and the occlusion time (Te_{occ}) was measured (fig. 1). A positive HBR was interpreted as a prolongation of Te_{occ} longer than the Te_{max}.

After the reestablishment of a new baseline tidal volume (VT) tracing, we attempted new occlusions, initially at the first breath after the application of 5 cm H_2O PEEP. Subsequently this procedure was repeated after application of 10, 15 and 20 cm H_2O PEEP, attempting to measure Te_{occ} at progressively larger lung volumes (Te_{occ5}, Te_{occ10}, Te_{occ15}, Te_{occ20}).

Statistical Analysis

The HBR components between normal subjects and patients with IF and COPD were compared with the unpaired t test. The relationship of lung volumes versus strength of HBR between the three groups was calculated by the use of Pearson's correlation coefficient. Significance was set at $p < 0.05$.

Results

The HBR was demonstrated in all normal subjects and patients with IF, but it was not elicited in 2 COPD patients with small lung volumes. The mean values of HBR components, with zero PEEP (Te_{mean}, Te_{max}, Te_{occ}, Te_{occ}/Te_{max}), are demonstrated in table 2. There was no difference in age and the type of medications received by these patients in whom the reflex was not induced.

The Te_{occ} was prolonged as the volume of lung inflation was increased with the application of progressively increased PEEPs. This prolongation – which was interpreted as a positive HBR – was observed in all normal subjects and patients.

The strength of the HBR was expressed as percent prolongation of Te_{occ} in comparison with Te_{max} (Te_{occ}/Te_{max}). In large lung volumes, normal subjects demonstrated higher Te_{occ}/Te_{max} than COPD and IF patients. On the other hand, COPD patients had lower Te_{occ}/Te_{max} than IF patients. To compare the strength of the HBR between normal subjects and patients with different resting lung volumes, we plotted the Te_{occ}/Te_{max} – which was obtained after airway occlusion at progressively increased lung volumes – against the corresponding lung volumes (fig. 2), expressed as percent of predicted total lung capacity (TLC), $\%V = [(VT + FRC_m + \Delta FRC_{PEEP})/TLC_p\ \%]$, where FRC_m is the measured FRC with the N_2 washout method, ΔFRC_{PEEP} is the difference between initial measured FRC and the FRC after application of PEEP and TLC_p the predicted TLC. In patients with COPD, the HBR was elicited with higher inflation volumes (%V) when compared with normal subjects and patients ($p < 0.05$).

Discussion

In this study we defined the presence of the HBR as the Te_{occ} to be longer than the previously recorded Te_{max}.

In patients with IF, with COPD and in normal subjects we noticed a more than 50% prolongation in expiration, as a result of lung inflation. This fact is in agreement with a previous study, which demonstrated that the length of apnea, caused by lung inflation, following a transpulmonary pressure change of 2–3 cm H_2O, was increased over 50% compared to baseline [10].

The Te_{occ} in normal subjects and in patients was progressively prolonged as long as the inflation volume was increased with application of higher levels of PEEP. Earlier workers had also found a relationship between the magnitude of change in lung volume and the stimulation of the reflex. Clark and von Euler [7] found that the magnitude of change in volume was critical to stimulation of the reflex. Other investigators noted that there is no relationship between the timing of inspiratory occlusions and the strength of the HBR [11]. The HBR had been provoked in all our normal subjects and patients with proper lung inflation until a critical change in lung volume was the stimulus which provoked the reflex [12].

A possible problem with the lung inflation technique is that the duration of the apnea may be related to the chemoreceptor input during prolonged periods of stretch receptor stimulation [13]. The duration of hyperinflation in our setting lasted only few seconds and the inflation (PEEP) was applied one breath before the airway occlusion. Another problem is that mechanical ventilation may stimulate various reflexes by changing flow and volume [14]. In order to minimize these effects we used the same type of lung volume change – addition of PEEP – and the same level of consciousness – slightly sedated by fentanyl – for all subjects [15].

Greenought and Pool [16] have studied the HBR in young asthmatic children. The median respiratory system compliance of the children with asthma in whom the reflex was provoked was significantly higher than in those where it was not present. It is also interesting that the healthy children in whom the reflex was not provoked, although their results were within the reference range, had the lower respiratory system compliance than children in whom the reflex was present.

In contrast to the above findings we have demonstrated that in COPD patients (patients with high compliance) the HBR was diminished in comparison to normal subjects. The discrepancies are probably related to the fact that in order to compare different groups of patients we expressed the inflation as a percent of predicted TLC. It has been reported [15] that patients with COPD, any time they suffer from bronchoconstriction, show dynamic hyperinflation (auto-PEEP), especially when they need mechanical ventilation, like our patients. Distension of the thoracic clove – resulting from dynamic hyperinflation – may stress inspiratory stretch receptors diminishing their responses to other stimuli.

Patients with IF had an increased response. This is in agreement with some investigators, who have noted that the HBR is stronger when the respiratory rate is increased [17]. In our work, patients with IF had statistically significantly higher respiratory rates than patients with COPD (table 1).

Our results demonstrated that the HBR may be provoked in healthy adults and in patients with COPD and IF with a proper inflation stimulus. Patients with COPD seem to have a diminished HBR.

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