Breathing responses to small inspiratory threshold loads in humans

SHENG YAN AND JASON H. T. BATES
Meakins-Christie Laboratories and Department of Biomedical Engineering, McGill University, and Montreal Chest Institute, Royal Victoria Hospital, Montreal, Quebec, Canada H2X 2P4

Yan, Sheng, and Jason H. T. Bates. Breathing responses to small inspiratory threshold loads in humans. J. Appl. Physiol. 86(3): 874–880, 1999.—To investigate the effect of inspiratory threshold load (ITL) on breathing, all previous work studied loads that were much greater than would be encountered under pathophysiological conditions. We hypothesized that mild ITL from 2.5 to 20 cmH\textsubscript{2}O is sufficient to modify control and sensation of breathing. The study was performed in healthy subjects. The results demonstrated that with mild ITL 1) inspiratory difficulty sensation could be perceived at an ITL of 2.5 cmH\textsubscript{2}O; 2) tidal volume increased without change in breathing frequency, resulting in hyperpnea; and 3) although additional time was required for inspiratory pressure to attain the threshold before inspiratory flow was initiated, the total inspiratory muscle contraction time remained constant. This resulted in shortening of the available time for inspiratory flow, so that the tidal volume was maintained or increased by significant increase in mean inspiratory flow. On the basis of computer simulation, we conclude that the mild ITL is sufficient to increase breathing sensation and alter breathing control, presumably aiming at maintaining a certain level of ventilation but minimizing the energy consumption of the inspiratory muscles.

control of breathing; breathing pattern; inspiratory muscles; breathing effort

THE EFFECTS OF INSPIRATORY resistive and elastic loading on breathing have been studied extensively (6) because of their obvious relevance to obstructive and restrictive lung diseases. Somewhat less is known about the breathing response to inspiratory threshold loading. Campbell et al. (3) noted that the immediate response to an inspiratory threshold load was a depression in tidal volume (V\textsubscript{T}), which returned to previous levels in about six breaths. Freedman and Campbell (9) reported that the steady-state response to inspiratory threshold loading was an augmentation of V\textsubscript{T}. Later, research on inspiratory threshold loading concentrated on its application as a means for testing respiratory muscle endurance (13). Recently, Yanos et al. (23) and Eastwood et al. (7) systematically studied the ventilatory responses to inspiratory threshold loads, but both studies applied large loads. This led to exhaustion, resulting in large variations in breathing pattern and ventilatory muscle performance.

The purpose of the present study was to investigate the ventilatory effects of mild inspiratory threshold loads (2.5–20 cmH\textsubscript{2}O), because breathing response to these mild loads has not been described in detail previously and the clinically encountered “internal” inspiratory threshold load, the intrinsic positive end-expiratory pressure (PEEP\textsubscript{i}) (17, 18) in patients with chronic obstructive pulmonary disease (COPD), generally falls into this range (1, 10, 19, 21). The characteristic of inspiratory threshold load that makes it differ from other types of breathing loads is its requirement that inspiratory muscles overcome the load before initiating the flow. This feature is known as neuromechanical uncoupling of the ventilatory pump and is believed to mediate the feelings of unrewarded inspiratory effort or inspiratory difficulty (11). We therefore hypothesized that a mild inspiratory threshold load is sufficient to alter breathing control and increase breathing effort sensation in healthy subjects.

METHODS

Subjects. Ten healthy subjects (9 men, 1 woman) participated in the study. All of them were staff members at our institution, and eight of them did not know the purpose of the study. The protocol of the study was approved by the Ethics Committee of the Montreal Chest Institute Research Center.

Inspiratory threshold loading. The inspiratory threshold-loading device we used and its characteristics were recently introduced in detail elsewhere (5). This system is composed of a negative-pressure chamber attached to the inspiratory port of a Hans Rudolph two-way nonrebreathing valve (type 2700, Hans Rudolph, Kansas City, MO) (Fig. 1). There are multiple holes with different sizes in the chamber. The negative pressure in the chamber is produced by a powerful flow generator that circulates the air between the room and the pressure chamber. The desired level of constant negative pressure is created in the pressure chamber by selective occlusion of different combinations of the holes in the chamber, thereby limiting the flow generated. The negative pressure in the chamber is directly applied to the inspiratory port of the Hans Rudolph valve and so closes the inspiratory valve until the negative pressure is exceeded by the inspiratory pressure. The chamber pressure thus constitutes the inspiratory threshold load. Our laboratory has recently shown (5) that the flow resistance of the threshold-loading system, measured as the difference between the mouth pressure and the applied threshold pressure divided by flow, is 0.7–1.1 cmH\textsubscript{2}O·l\textsuperscript{-1}·s\textsuperscript{-1}, which is fully accounted for by the intrinsic resistance of the Hans Rudolph valve and the pneumotachograph. This resistance is independent of either the applied threshold pressure or the inspiratory flow and was the background equipment resistance in the present study during both unloaded and loaded breathing experiments. Our laboratory has also shown (5) that the present system permits the inspiratory valve to open only when the mouth pressure matches the applied threshold pressure. These features guarantee that this system provides a pure threshold load and is therefore suitable for the present study.

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Measurements and procedures. Respiratory flow was measured by a Fleisch no. 2 pneumotachograph (Lausanne, Switzerland) attached between the Hans Rudolph valve and the mouthpiece. Mouth pressure was measured by a differential pressure transducer (Validyne, Northridge, CA) via a tube connected to the mouthpiece. End-tidal CO₂ concentration was measured by a CO₂ analyzer (Ametek CD-3A, Sunnyvale, CA), which was connected to the mouthpiece. Changes in end-expiratory lung volume (ΔEELV) were determined by repeated inspiratory capacity maneuvers (16, 22). The degree of sensation of inspiratory difficulty was quantified by using a modified Borg scale. The subjects were required, at each level of load, to choose a number from 0 to 10 on the basis of their sensations of inspiratory difficulty, with 0 representing no difficulty and 10 the maximal difficulty. The term “inspiratory difficulty” was chosen as the descriptor for the sense of breathing effort because it has been considered the best descriptor for dynamic hyperinflation and PEEPi (15).

Experimental protocol. Maintaining body posture constant throughout the experiment, the subjects, wearing a noseclip, were seated on a high-backed armchair and breathed through a mouthpiece. After a period of quiet breathing, the subjects performed an inspiratory capacity maneuver. Then, they breathed against a fixed inspiratory threshold load for 2 min with expiration unloaded. The subjects were free to choose their breathing pattern during loading. At the end of the trial, the subjects repeated the inspiratory capacity maneuver. The load was removed as soon as the subjects had begun the second inspiratory capacity inspiration, to eliminate the possibility that the inspiratory threshold load might limit the inspiratory capacity. Each subject was loaded with ~2.5, 5, 7.5, 10, 15, and 20 cmH₂O of the inspiratory threshold, presented in random order. The subjects were not told the level of the load applied during each run. Between trials, the subjects were allowed to have 2–5 min of rest. Immediately after the termination of each load, the subjects were asked to report their sensation of inspiratory difficulty.

Data analysis. The breathing signals were preamplified, digitized at 200 Hz, and saved to a desktop computer. The signals were acquired and analyzed by Anadat and Labdat software (RHT-InfoDat, Montreal, Quebec). The 10 breaths during quiet breathing and during each loaded run were ensemble averaged by aligning the breaths by the beginning of inspiratory flow. All the subsequent data analysis was performed on the averaged signals.

The actual inspiratory threshold load applied in each trial was measured as the negative deflection from baseline of mouth pressure at the point where inspiratory flow began. ΔEELV was calculated from the changes in the inspiratory capacity. A volume signal was obtained by numerical integration of flow. VT was taken as the maximum excursion of volume during each breath. We also calculated breathing frequency, minute ventilation, inspiratory time (Ti), expiratory time (Te), the ratio of Ti to total respiratory cycle time (Ti/Tt), and mean inspiratory flow (VT/Ti). As shown in Fig. 2, when inspiratory threshold load is present, inspiratory effort starts before inspiratory flow begins, leading to separation of inspiratory muscle effort from the start of inspiratory flow (24). Accordingly, the Ti with inspiratory flow (Ti,flow) was calculated conventionally as the time from the beginning to the end of inspiratory flow. The Ti for inspiratory muscle contraction (Ti,mus) was calculated as the time from the beginning of inspiratory muscle effort to the end of inspiratory flow. The start of inspiratory muscle effort was determined by the start of increase in transdiaphragmatic pressure, calculated as the difference between gastric pressure and esophageal pressure (20). Gastric pressure and esophageal pressure were measured by conventional balloon-catheter techniques. The results are presented as means ± SE. Dunnett’s test for paired comparisons between several
treatments and a common control was performed to compare the results at each load with those during quiet breathing. P < 0.05 was considered as indicating statistical significance.

RESULTS

Figure 3 shows the responses of V\textsubscript{T}, breathing frequency, and minute ventilation to inspiratory threshold loading. Both V\textsubscript{T} and minute ventilation remained unchanged at 2.5 and 5 cmH\textsubscript{2}O of inspiratory threshold load but increased when the inspiratory threshold load reached 7.5–10 cmH\textsubscript{2}O. There was a slight increase in breathing frequency during loading, which did not reach statistical significance.

As shown in Fig. 4, there was an immediate drop in expiratory time during loading with a constant T\textsubscript{I,mus}. However, T\textsubscript{I,flow} shortened with increasing inspiratory threshold load. This led to a decrease in T\textsubscript{I,flow}/TT. V\textsubscript{T}/T\textsubscript{I,flow} increased significantly at an inspiratory threshold load of 10 cmH\textsubscript{2}O.

Figure 5 shows that the perceived inspiratory difficulty increased progressively with increasing inspiratory threshold load (r\textsuperscript{2} = 0.68). The inspiratory difficulty was significantly greater than zero even at an inspiratory threshold load of only 2.5 cmH\textsubscript{2}O. Multiple step-forward linear regression showed that adding V\textsubscript{T} and T\textsubscript{I,mus}/TT increased r\textsuperscript{2} to 0.73 and 0.75, respectively. Other parameters including breathing frequency, minute ventilation, T\textsubscript{I,mus}, T\textsubscript{I,flow}, T\textsubscript{I,flow}/TT, V\textsubscript{T}/T\textsubscript{I,flow}, expiratory time, end-tidal CO\textsubscript{2}, and total esophageal pressure swing did not contribute significantly to the observed sensation of inspiratory difficulty.

At the highest inspiratory threshold load, the group mean EELV was reduced by 70 ml and end-tidal CO\textsubscript{2}

![Fig. 4. Inspiratory time (T\textsubscript{I}), expiratory time (T\textsubscript{E}), duty cycle (T\textsubscript{I}/T\textsubscript{I}), and mean inspiratory flow (V\textsubscript{T}/T\textsubscript{I,mus}) during inspiratory threshold loading. Solid symbols, parameters based on T\textsubscript{I} or T\textsubscript{E} measured by inspiratory pressure time profile; open symbols, parameters based on T\textsubscript{I} or T\textsubscript{E} measured by inspiratory flow time profile. *Significantly different from unloaded breathing (P < 0.05).](image-url)
concentration decreased by 0.5%. These changes did not reach statistical significance.

DISCUSSION

Our results demonstrated a small but significant increase in V_t and minute ventilation with a relatively constant breathing frequency during inspiratory threshold loading, suggesting the load-induced hyperpnea. As shown in Fig. 3, ventilation was constant when the inspiratory threshold load was below 5 cmH_2O and began to increase thereafter, suggesting this response to be load dependent. The magnitudes of increase we found in V_t and minute ventilation were lower than those reported for higher inspiratory threshold loads (7, 23).

The present V_t, minute ventilation, and V_t/TI response supports and extends the previous observations of Yanos et al. (23) and Eastwood et al. (7) employing large loads. We showed that even a small inspiratory threshold load increases respiratory motor output to the level beyond that needed to maintain ventilation constant. Why respiratory motor outputs increase to induce hyperpnea during inspiratory threshold loading remains unclear. The steady-state breathing response to inspiratory resistive and elastic loadings is “slow deep breathing” and “rapid, shallow breathing,” respectively, without significant alteration of minute ventilation (6). Under these types of loading, inspiratory flow starts at the same time as does inspiratory muscle contraction so that the processes involved in overcoming the load and inflating the lung occur simultaneously. What makes inspiratory threshold loading different from resistive and elastic loadings is “slow deep breathing” and “rapid, shallow breathing,” respectively, without significant alteration of minute ventilation (6). Under these types of loading, inspiratory flow starts at the same time as does inspiratory muscle contraction so that the processes involved in overcoming the load and inflating the lung occur simultaneously. What makes inspiratory threshold loading different from resistive and elastic loading is that, in the former case, the inspiratory effort is separated into two, clear-cut phases (Fig. 2): one before the beginning of inspiratory flow and the other after it. In the first phase, inspiratory effort produces no flow, so the magnitude of the respiratory impedance can be considered infinite. In the second phase, the resistance and elastance of the respiratory system appear normal. Furthermore, the transition between these two phases is extremely rapid so that the feedback information to the respiratory controllers from muscle spindles and tendon organs, as well as from lung and airway mechanoreceptors (25), would have little time to adapt from one phase to the other. It is, therefore, presumably possible that the respiratory controller could overcompensate in the second phase, producing an increase in ventilation.

To limit the following discussion on breathing control to be more practical, the following theoretical analysis is based on what we actually found to be the major response in the present experiment. That is, in response to the load, V_t was unchanged or increased, whereas breathing frequency was constant (Fig. 3). Thus we can now make some inferences about the strategy adopted by the inspiratory controller in our subjects, given that they responded to an increased inspiratory threshold load by maintaining or even increasing V_t. There are, broadly speaking, two distinct ways this could have been achieved. One possibility is that the rate of rise of inspiratory pressure could be kept constant. This would require that T_{I,mus} be increased, both to meet the extra time required to reach the load threshold and to subsequently keep inspired V_t at a relatively constant flow rate. The other possibility is that T_{I,mus} could be kept constant. This would require that the rate of rise of inspiratory pressure be increased both to generate sufficient flows against the greater load and to reduce the time required for inspiratory pressure to reach the load threshold before starting flow. As clearly shown in Fig. 4, our subjects adopted the latter strategy. That is, they kept T_{I,mus} essentially unchanged while shortening T_{I,flow}. This allowed them to increase V_t/T_{I,flow} to preserve V_t.

This raises the question as to why our subjects should have dealt with the inspiratory threshold load by reducing T_{I,flow}. Presumably some additional factor is involved that caused them to respond to the inspiratory threshold load in the present way. We felt it natural to consider that this factor might involve the energy cost of breathing. The APPENDIX shows a model analysis of what happens to the inspiratory pressure-time integral (PTI) and the inspiratory work of breathing (W) when an inspiratory threshold load is applied to the system. We consider how both PTI and W change as T_{I,flow} is altered while V_t is kept constant. The results from computer simulation on the basis of the model described in the APPENDIX are shown in Fig. 6. Assum-
increased VT (7). Presumably, under such a condition, despite a relatively constant breathing frequency and tidal ventilation, it was possible that the subjects had “amplified” the real respiratory difficulty that was significantly greater than zero. This was unlikely due directly to the subjects’ imagination of being loaded because the loads were randomly applied, and in six subjects an additional “load” was imposed without actually applying any, and none reported any degree of inspiratory difficulty. It was previously found that the 50% perception limit for inspiratory threshold loading must have been <2.5 cmH2O in our subjects. The perceived inspiratory difficulty largely reflected the effect of the applied inspiratory threshold load alone ($r^2 = 0.68$), and adding other breathing parameters to the step regression contributed little to the sensation ($r^2 = 0.75$). As a result, the dispersion of the data points in Fig. 5 was mainly due to variation in interpreting the magnitude of the breathing difficulty among our subjects.

In summary, the major findings of the present study are 1) the ventilatory response to mild inspiratory threshold loads (2.5–20 cmH2O) was hyperpnea with an increase in VT and unchanged breathing frequency; 2) during inspiratory effort against mild threshold loading, the total inspiratory muscle contraction time was kept constant, resulting in shortening of the available time for inspiratory flow to develop, a strategy presumably able to minimize the energy cost of breathing by reducing the pressure-time integral of the inspiratory muscles with little influence on W; and 3) inspiratory difficulty could be perceived at an inspiratory threshold load as low as 2.5 cmH2O. Finally, it is of interest to briefly consider what these results might mean for COPD patients experiencing the inspiratory threshold load presented by a significant amount of PEEPi. We must, of course, be cautious in extrapolating our results to patients, not only because, during dynamic hyperinflation in patients, operating lung volume increases dynamically whereas it did not change in our subjects but also because, whereas we studied the effects of an acute load, it is certainly the case that PEEPi in stable COPD patients constitutes a chronically imposed load. Consequently, one might expect some form of adaptation of the breathing response in patients. Indeed, it would be potentially very harmful for COPD patients to respond to PEEPi in the way our healthy subjects did. For example, in most cases PEEPi is due to expiratory airflow limitation (18), and this would become exacerbated by hyperpnea because the flow-limited lung would have even less time to expire.
any increase in VT. This might explain, for example, why COPD patients tend to choose a TI that is reduced compared with normal (12), instead of keeping it unchanged as our subjects did. Thus an adaptive breathing strategy that might be advantageous in health could well be disastrous in disease, which might explain why PEEPi is such a common and troublesome condition in COPD patients.

**APPENDIX**

Consider the single-compartment linear model of the respiratory system governed by equation

\[ P(t) = EV(t) + RV(t) \]  
(A1)

where E and R are the elastance and resistance, respectively, of the model. P(t) is the pressure applied to inflate it, V(t) is the volume in the lungs (above functional residual capacity), and V(t) is the flow into the airway. The pressure-time integral PTI achieved during inflation of the model to a volume VT is

\[ PTI = \int_0^{T_I} P(t) \, dt \]

\[ = \int_0^{T_I} [EV(t) + RV(t)] \, dt \]

\[ = \int_0^{T_I} \frac{V_T}{T_I} (Et + R) \, dt \]

\[ = V_T \left( \frac{ET_I}{2} + R \right) \]  
(A2)

where we have used the fact that \( V(t) \), being constant, is equal to \( V_T/T_I \). Inspection of the last line of Eq. A2 reveals that PTI increases with TI, because all the remaining quantities in the equation are positive.

Calculation of the work W done in the model proceeds in the same way, thus

\[ W = \int_0^{T_I} [EV(t)\dot{V}(t) + RV^2(t)] \, dt \]

\[ = \int_0^{T_I} \frac{V_T^2}{T_I} (Et + R) \, dt \]

\[ = V_T^2 \left( \frac{E}{2} + \frac{R}{T_I} \right) \]  
(A3)

In contrast to the expression for PTI (Eq. A2), Ti appears in the denominator for the expression for W (final line, Eq. A3), which means that W increases as Ti decreases.

The above analysis thus shows that, from the perspective of the simple respiratory model considered, W and PTI have opposite dependencies on Ti for a given VT. However, this analysis does not take into account the presence of an inspiratory threshold pressure, Pth. We now add this feature to the model. However, this also requires that we assume some functional form for P(t) because, during the initial part of inspiration, when V(t) is zero, there is still a contribution to PTI because of the presence of P(t). We therefore assumed that P(t) was a linearly increasing function of time with a slope of a. Analytic solution of the model with these added features is considerably more complicated than that provided above for the simpler scenario (Eqs. A2 and A3). Therefore, we calculated W and PTI by integrating the model equation numerically, as follows. First, we rewrite Eq. A1 in discrete form explicitly in V(t), noting that flow only begins when P(t) exceeds Pth, so that

\[ V_{k+1} = V_k + \dot{V}_k \delta t \]

where

\[ P_k = ak \delta t \]  
(A5)

The subscript k indicates the kth time step, and \( \delta t \) is the duration of each time step. Knowing \( V_k \) and \( V_{k+1} \), we then find \( V_k \) by using first-order Euler integration, thus

\[ V_{k+1} = V_k + \dot{V}_k \delta t \]  
(A6)

We begin with the initial condition that \( V_0 = 0 \).

We used Eqs. A4-A6, using typical normal values of R and E, to calculate the time course of \( V_k \) as it progressed from 0 to VT. We defined the time required to reach VT to be Ti,mus. Similarly, the time interval over which \( V_k \) was nonzero was defined to be Ti,flow. Using \( V_k \) and the corresponding \( P_k \), we then calculated PTI and W by numerically integrating Eqs. A2 and A3 by using the trapezoidal rule. By varying the value of a, we investigated how W and PTI change as Ti,flow and Ti,mus vary for fixed VT.

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Address for reprint requests and other correspondence: S. Yan, Meakins-Christie Laboratories, McGill Univ., Montreal, Quebec, Canada H3X 2P4.

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