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 cmH2O 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 cmH2O; 2) tidal volume increased without change in breathing frequency, resulting in hyperventilation; 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

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 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 power 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 cmH2O·l−1·s, 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 (ΔEEELV) 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 nosedip, 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 last 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. ΔEEELV was calculated from the changes in the inspiratory capacity. A volume signal was obtained by numerical integration of flow, V̇t was taken as the maximum excursion of volume during each breath. We also calculated breathing frequency, minute ventilation, inspiratory time (T₁), expiratory time (Tₑ), the ratio of T₁ to total respiratory cycle time (T₁/Tₑ), and mean inspiratory flow (V̇t/T₁). 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 T₁ with inspiratory flow (T₁,flow) was calculated conventionally as the time from the beginning to the end of inspiratory flow. The T₁ for inspiratory muscle contraction (T₁,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

Fig. 1. Schematic illustration of negative pressure inspiratory threshold loading system. See text for further explanation.

Fig. 2. Representative experimental recordings of flow, mouth pressure (Pm), and transdiaphragmatic pressure (Pdi) during an inspiratory threshold load of 10 cmH₂O. Horizontal dashed line, 0 flow; vertical dashed lines a, b, and c: beginning of rise of inspiratory muscle effort from the start of inspiratory flow (T₁,flow). Traces show that start of inspiratory muscle development and beginning of inspiratory flow can be separated clearly. That is, at beginning of inspiratory muscle contraction, Pm develops quickly to attain level of threshold; however, no inspiratory flow is generated before Pm reaches this threshold pressure.
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'T, breathing frequency, and minute ventilation to inspiratory threshold loading. Both V'T and minute ventilation remained unchanged at 2.5 and 5 cmH2O of inspiratory threshold load but increased when the inspiratory threshold load reached 7.5–10 cmH2O. 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 Ti,mus. However, Ti,flow shortened with increasing inspiratory threshold load. This led to a decrease in Ti,flow/TT. V'T/Ti,flow increased significantly at an inspiratory threshold load of 10 cmH2O.

Figure 5 shows that the perceived inspiratory difficulty increased progressively with increasing inspiratory threshold load (r² = 0.68). The inspiratory difficulty was significantly greater than zero even at an inspiratory threshold load of only 2.5 cmH2O. Multiple step-forward linear regression showed that adding V'T and Ti,mus/TT increased r² to 0.73 and 0.75, respectively. Other parameters including breathing frequency, minute ventilation, Ti,mus, Ti,flow, Ti,flow/TT, V'T/Ti,flow, expiratory time, end-tidal CO₂, 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 CO₂
concentration decreased by 0.5%. These changes did not reach statistical significance.

**DISCUSSION**

Our results demonstrated a small but significant increase in VT 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 cmH₂O and began to increase thereafter, suggesting this response to be load dependent. The magnitudes of increase we found in VT and minute ventilation were lower than those reported for higher inspiratory threshold loads (7, 23).

The present VT, minute ventilation, and VT/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).

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, VT 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 VT. 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 TI,mus be increased, both to meet the extra time required to reach the load threshold and to subsequently keep inspired VT at a relatively constant flow rate. The other possibility is that TI,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 TI,mus essentially unchanged while shortening TI,flow. This allowed them to increase VT/TI,flow to preserve VT.

This raises the question as to why our subjects should have dealt with the inspiratory threshold load by reducing TI,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 TI,flow is altered while VT 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. Presumably, under such a condition, despite a relatively constant breathing frequency and magnitude of change in W is relatively small (5.6–1.6%) under all conditions. It thus appears that preserving VT and inspiratory work of breathing (W) calculated by computer simulation, assuming a constant VT and normal respiratory system resistance and elastance. Left: duration of inspiratory flow (TI,flow) is reduced from 1.25 to 1.00 s. Right: TI,flow is increased from 1.25 to 1.50 s. Results are expressed as %fall or rise in PTI and W compared with those with TI,flow of 1.25 s.

Although our subjects did not know the exact level of the loads, they were told that the loads were mild. It is also possible that breathing sensation is not linear with load at the high end of the load range so that the response to higher loads cannot be predicted simply by extrapolating our results. No matter what caused our subjects to “overestimate” the loads, the lowest inspiratory threshold load of 2.5 cmH2O was clearly sensed by the subjects and led to a perceived inspiratory 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 (r2 = 0.68), and adding other breathing parameters to the step regression contributed little to the sensation (r2 = 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 $V_t$. This might explain, for example, why COPD patients tend to choose a $T_i$ 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

$$P(t) = EV(t) + RV(t)$$  \hspace{1cm} (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 $V_t$ is

$$PTI = \int_0^{T_i} P(t) \, dt$$

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

$$= \int_0^{T_i} \frac{V_T}{T_i} (E + R) \, dt$$

$$= V_T \left( \frac{ET_i}{2} + R \right)$$  \hspace{1cm} (A2)

where we have used the fact that $\dot{V}(t)$ is constant, is equal to $V_T/T_i$. Inspection of the last line of Eq. A2 reveals that PTI increases with $T_i$, 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

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

$$= \int_0^{T_i} \frac{V_T^2}{T_i} (E + R) \, dt$$

$$= V_T^2 \left( \frac{ET_i}{2} + R \right)$$  \hspace{1cm} (A3)

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

The above analysis thus shows that, from the perspective of the simple respiratory model considered, $W$ and PTI have opposite dependencies on $T_i$ for a given $V_t$. However, this analysis does not take into account the presence of an inspiratory threshold pressure, $P_{th}$. 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 $P_{th}$, so that

$$\dot{V}_k = 0, \quad P_k < P_{th}$$

$$= (P_k - P_{th} - EV_k/R), \quad P_k \geq P_{th}$$  \hspace{1cm} (A4)

where

$$P_k = ak\delta t$$  \hspace{1cm} (A5)

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

$$V_{k+1} = V_k + \dot{V}_k \delta t$$  \hspace{1cm} (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 $V_T$. We defined the time required to reach $V_T$ to be $T_i, \text{mus}$. Similarly, the time interval over which $V_k$ was nonzero was defined to be $T_i, \text{flow}$. 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 $T_i, \text{flow}$ and $T_i, \text{mus}$ vary for fixed $V_T$.

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Address for reprint requests and other correspondence: S. Yan, Meakins-Christie Laboratories, McGill Univ., Montreal, Quebec, Canada H2X 2P4.

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