The Control of Breathing in COPD

Neil S. Cherniack, M.D., F.C.C.P.*

Dual drives affect breathing: chemical drives arising from the activity of central and peripheral chemoreceptors link ventilation with metabolic changes in the body; and nonchemical drives originating from mechanoreceptors located mainly in the thorax monitor the performance of the chest bellows and allow respiratory motor output to be adjusted as performance varies. Major subgroups of these nonchemical receptors are located in the airways and lung parenchyma and in the respiratory muscles. The afferent fibers of these receptors are carried in the vagi and spinal nerves.

Ventilation, the conventionally employed index of respiratory output, may be depressed when the mechanical performance of the chest is impaired even if the respiratory controller is normal. However, in the past few years, new measurements of respiratory output have been developed, such as occlusion pressure (the isometric force developed by the inspiratory muscles contracting against an occluded airway) and respiratory muscle EMG. Both methods are less likely to be directly affected by physical factors such as changing airway resistance which can alter ventilatory measurements. With these improved techniques of evaluating the efferent activity of the respiratory controller, we are better able to appreciate the effects of various inputs to the respiratory neurons, discern differences in their action, and evaluate their potential importance during breathing in patients and normal subjects.1,2

Chemical Control

Signals from central and peripheral chemoreceptors clearly play a major role in preserving ventilation. The fact that normal subjects maintain blood gas tensions within narrow limits despite changes in activity and alertness demonstrates that there must be significant chemical regulation of breathing operative over the long term. Severe depression of hypoxic or hypercapnic sensitivity is certainly a “risk” factor in the development of respiratory failure. Recent studies by investigators at McGill University and the University of Colorado3,4 demonstrate that genetic factors are important determinants of chemosensitivity and that families with subnormal inborn responses to CO₂ and hypoxia are more likely to retain CO₂ if chronic obstructive lung disease (COLD) develops. For example, it has been shown that offspring of patients with COLD and CO₂ retention tend to have weaker responses to hypercapnia than do offspring of COLD patients who are able to maintain normal blood gas tensions even when both groups have equally severe disease.3

Regulation of Breathing During Sleep

Breathing patterns in quiet and REM sleep differ from those seen during wakefulness. Sometimes periods of central and obstructive apnea occur. Central apneas are due to the temporary cessation of all respiratory activity. The obstructive apneas occur despite maintained or increased respiratory activity and are believed to be caused by upper airway obstruction due to relaxation of the tongue or pharyngeal muscles or to laryngeal closure during sleep.4-7 These muscles have both tonic and phasic electrical activity with a respiratory rhythm which presumably affects their movement.

Hypercapnia and hypoxia become increasingly severe as both central and obstructive apneas are prolonged. It seems reasonable that individuals who are less responsive to changes in chemical drive would have a longer period of apnea during sleep and a greater reduction in O₂ saturation. Preliminary evidence suggests that, in fact, this occurs.8 Prolonged or recurrent apneas during sleep, in turn, may depress waking chemosensitivity.

There is some evidence that there is greater reduction in the respiratory response to CO₂ than hypoxia during sleep (particularly in the REM stage). Studies in anesthetized cats show that selective depression of CO₂ responses caused by cooling of the ventral surface of the medulla can produce recurrent periods of central apnea (periodic breathing).9 It is well known that during periodic breathing, chemical drive is less during apnea than it is during hyperventilation (i.e., ventilation follows chemical drive).10 Therefore, it may be possible to reduce the occurrence of central apneas by selectively increasing CO₂ drive.

Recurrent cycling in blood gas tensions may also lead to obstructive apnea because the effects of CO₂ on the tongue and the pharyngeal muscles are different from the effects of CO₂ on the diaphragm. The negative airway pressure produced by diaphragm contraction tends to close the upper airway by bringing the tongue in opposition to the pharyngeal wall, but obstruction is prevented by the inspiratory action of the tongue and pharyngeal muscles which maintain upper airway patency.6 Because the threshold and slope of the CO₂ response curve of these muscles seem to be different from that of the diaphragm, decreased CO₂ sensitivity during sleep could eliminate efferent activity to tongue and pharyngeal muscles but not the diaphragm. Diaphragm contraction might then create sufficient negative pressure to close the upper airway producing a period of obstructive apnea. If this sequence of events occurs, it seems possible that respiratory stimulants could be useful in some patients with obstructive apnea and might in some cases eliminate the need for tracheostomy.

*Professor of Medicine and Director, Pulmonary Division, Case Western Reserve University, Cleveland. Reprint requests: Dr. Cherniack, Pulmonary Division, University Hospitals of Cleveland, Cleveland 44106

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NON-CHEMICAL CONTROL OF BREATHING

The acknowledged wide availability of both hypoxic and hypercapnic responses and the fact that some individuals with blunted sensitivity to \( \text{CO}_2 \) and hypoxia can maintain normal blood gas tensions if the lungs are performing normally shows that there must be other drives to respiration that exert significant effects on resting breathing.

An obvious source of additional input to the respiratory neurons are the thoracic mechanoreceptors. In addition, the effects of this receptor input is modified by the activity of higher brain centers and, as a consequence, by the degree of alertness and previous experience. Mechanoreceptors are known to affect breathing patterns and, as a consequence, could affect alveolar ventilation. Sorli \textit{et al.}\(^1\) have observed differences in the resting breathing pattern of eucapnic and hypercapnic \textsc{cold} patients even though they could detect no difference in the two groups in lung function or in respiratory drive as assessed from measurement of occlusion pressure. Average inspiratory airflow was also the same in the two groups, but tidal volume was less in the hypercapnic patients that in the eucapnic because of a decrease in inspiratory time. Inspiratory shortening reflexes arising from deflation or irritant receptors in the lung in the hypercapnic patients could explain the decrease in Ti and the lower tidal volume observed. The lower \( V_T \), in turn, could reduce alveolar ventilation and result in hypercapnia.

Input from mechanoreceptors can also modulate the intensity of respiratory drive as well as modify the respiratory pattern. When normal subjects are made to breathe through external inspiratory resistive or elastic loads which excite mechanoreceptors, respiratory output rises during \( \text{CO}_2 \) rebreathing as measured by either occlusion pressure or diaphragm EMG.\(^{12-14}\)

External loads also produce proportional rises in occlusion pressure in subjects breathing hypoxic or hypercapnic gas mixtures, or \( \text{CO}_2 \) free air or \( \text{O}_2 \).\(^{15}\) When methacholine aerosols are used to produce bronchoconstriction, occlusion pressure also rises proportionally to the airway resistance change; but at the same level of airway resistance, occlusion pressure is greater with methacholine than with the external load.

It is interesting that when the slope of the occlusion pressure response to external loads and to methacholine are compared in different individuals, there is a reasonably good correlation between the two. This suggests that the respiratory response to external loads reflects the response to internal loads and can be employed to evaluate the responses to airway obstruction caused by disease.

Asthmatic patients tend to have higher occlusion pressure responses to \( \text{CO}_2 \) than do patients with COPD, though both tend to be somewhat greater than normal.\(^{16,17}\) Unlike either normal subjects or asthmatic patients, there is not much increase in occlusion pressure in patients with COPD when their airway resistance is increased by external loads. It may be that patients with COPD also fail to increase their respiratory drive as much as asthmatics during bronchoconstrictive episodes and this may account for the greater incidence of respiratory failure in COPD than in asthma.

The blunted response to external resistive loads in COPD may be caused by physical factors which limit the pressures that can be developed by the inspiratory muscles in COPD. There is considerable evidence against this. Alternatively, the weaker response to resistive loads may be caused by dulled mechanoreceptor sensitivity or by altered processing of mechanoreceptor signals within the central nervous system. This might occur through a process of adaptation which occurs with prolonged airway obstruction and which allows increased mechanoreceptor activity to be ignored in patients with COPD.

Measurement of the sensations elicited by loads is a possible, albeit an indirect way, of assessing the combined effects of mechanoreceptor inputs and its handling by higher brain centers. Magnitude estimation has been increasingly employed to evaluate the conscious perception of different stimuli by psychophysicists.\(^{18}\) It has been useful in investigating respiratory sensations both during loaded and unloaded breathing. Gottfried \textit{et al.}\(^{18}\) using this test, presented easily discernible loads to different groups of subjects. The subject assigned a number to each load according to the intensity of the respiratory sensation that load elicited. When the log of the number assigned to each load was plotted against the log of the resistance, the relationship was found to be linear. The slope of this line, which is a measure of the perceptual acuity, is less in COPD than in asthmatics or in normal subjects. Recent unpublished data by Gottfried suggests that there is a relationship between magnitude estimation and occlusion pressure responses such that individuals with the lowest increase in occlusion pressure with resistive loading tend to have the lowest sensory response to resistive loads as determined by the magnitude estimation test.

\textit{In summary}, chemical control of breathing is needed to maintain normal arterial blood gas tensions over long periods of time. However, the sensitivity to chemical stimuli need not be very great since non-chemical input from mechanoreceptors and other receptors in the body stimulated by the environment can amplify the effects of chemical drive. During sleep, the level of chemo-sensitivity may be more important than during wakefulness since the level of non-chemical stimulation is greatly diminished. However, it may be that under all conditions both sorts of input influence breathing although their relative importance may vary. Perceptual tests and tests of responses to mechanical changes may be useful in examining the nonchemical drives. Chemical and non-chemical inputs on the controller can be altered by lung disease. Subnormal responses to nonchemical stimuli occur frequently in COPD. It may be that adequate response to non-chemical stimuli is as important as chemosensitivity in lung disease in the maintenance of normal alveolar ventilation.
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Time Course of the Effects of an Inhaled Bronchodilator on Gas Distribution and Ventilatory Efficiency in Patients with COPD*

Antonio Cutillo, M.D.; Suetaro Watanabe, M.D.; Adelbert H. Bigler, Ph.D.; Rodolfo Ferondi, M.D.; Maurizio Turri, M.D.; and Attilio D. Renzetti, Jr., M.D., F.C.C.P.

Studies of the effects of bronchodilators on the distribution of inspired gas and overall efficiency of ventilation in patients with chronic obstructive pulmonary disease have provided conflicting results. Regional changes after bronchodilator treatment have been found to be variable with the overall response being favorable in some subjects, unfavorable or insignificant in others. In order to establish whether time-related factors may, to some extent, account for the observed variation, we studied the time course of the changes in gas distribution and ventilatory efficiency after bronchodilator treatment in a group of patients with chronic obstructive pulmonary disease.

METHODS

Seven patients with chronic obstructive pulmonary disease were studied: data obtained in three of these patients have been preliminarily presented elsewhere. The distribution of inspired gas and the overall efficiency of ventilation were assessed by the open-circuit nitrogen washout technique; the subject inspired from a bag containing 150-200 liters of oxygen and expired into a recording Tissot spirometer. Nitrogen concentration of respired gas was continuously measured at the mouth with a nitrogen meter. To monitor the breathing pattern, a volume tracing was obtained by electrical integration of the inspiratory flow signal (with automatic zeroing of the tracing at the end of each inspiration). Nitrogen concentration and volume tracings were displayed and photographically recorded by a polygraph. From the washout data, the lung clearance index (LCI) was calculated as the cumulative ventilation, per unit functional residual capacity (FRC), required to reduce the end-tidal N₂ concentration to 1.5%. FRC was measured simultaneously during each N₂ washout by the N₂-dilution method. Semilogarithmic plots of end-tidal N₂ concentration vs breath number were analyzed by the methods of Fowler et al. and Briscoe and Cournand based on a multicompartment lung model, and the pulmonary N₂ clearance delay (PCD) was estimated.

Measurements of airway resistance (R₂ₐₜ) as a function of time after bronchodilator treatment, were made in four subjects, using a constant-volume body plethysmograph; in one patient, lung resistance (Rₐₜ) was determined by a method of electrical subtraction. The anatomic dead space (Vₐ) was estimated in five subjects from simultaneous tracings of expired volume and CO₂ concentration (continuously...