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Respiratory Muscle Fatigue and Breathing Pattern*

M. Jeffery Mador, M.D., F.C.C.P.

P_{di} = transdiaphragmatic pressure; P_{di}max = maximal transdiaphragmatic pressure; P_m = mouth pressure; I_{time} = time to last failure; T_I/T_{tot} = inspiratory time/total breath duration; TT_{di} = tension-time index; TT_{rc} = tension-time ribcage

The respiratory muscles, like the heart, must work continuously with little opportunity to rest. Pulmonary disease increases the load on the respiratory pump while at the same time decreasing the pressure-generating capacity of the respiratory muscles. If the respiratory muscles are subjected to sufficiently high loads for a prolonged period of time, they will eventually fatigue. It has been postulated that respiratory muscle fatigue causes the respiratory pump to fail resulting in hypercapnic ventilatory failure.[1] This postulate has led to a tremendous interest in respiratory muscle fatigue. In this article, we will focus on the determinants of respiratory muscle fatigue, the effects of respiratory muscle fatigue, the effects of respiratory muscle fatigue on breathing pattern and the clinical significance of these changes in breathing pattern. A complete review of respiratory muscle fatigue is beyond the scope of this article and the reader is referred elsewhere.[2-4]

DEFINITION AND TYPES OF RESPIRATORY MUSCLE FATIGUE

Muscle fatigue can be defined as a condition in which there is a reduction in the force generating capacity of the muscle resulting from muscle activity under load which is reversible by rest.[5] Muscle weakness is a condition in which the capacity of the rested muscle to generate force is impaired. Three general types of fatigue have been described: central fatigue, transmission fatigue, and contractile fatigue. Central fatigue is an exertion-induced reversible decrease in central neural respiratory drive. Transmission fatigue is an exertion-induced reversible impairment in the

transmission of neural impulses through nerves or across neuromuscular junctions. Contractile fatigue is a reversible impairment in the contractile response to neural impulses in an overloaded muscle. Transmission fatigue and contractile fatigue can be grouped together as peripheral causes for fatigue.

DETERMINANTS OF RESPIRATORY MUSCLE FATIGUE

The majority of muscular work required for breathing is performed during inspiration even in patients with chronic obstructive pulmonary disease.[6] Therefore, the inspiratory muscles, including the diaphragm, are the muscles primarily at risk of developing fatigue. In 1977, Roussos and Macklem[7] demonstrated that the diaphragm could be fatigued in normal man when subjected to a sufficiently high load. In these experiments, an inspiratory resistive load was employed to require the diaphragm to generate a given target pressure with each breath until task failure (defined as the inability to generate the target pressure). It was found that a target transdiaphragmatic pressure (P_{di}) less than 40 percent of the maximal transdiaphragmatic pressure (P_{di}max) could be maintained indefinitely while a target P_{di} greater than 40 percent of P_{di}max led to task failure within a finite period of time (less than 45 min). The greater the target pressure, the shorter the time to task failure. Subsequently, these authors have shown that fatigue of both the diaphragm and ribcage muscles can be achieved when subjects generate a high enough mouth pressure (P_m) with each breath during inspiratory resistive loading.[8] A target P_m less than 60 percent of the maximal mouth pressure ($P_m$max) (measured while performing a maximal inspiratory effort against an occluded airway at functional residual capacity) could be maintained indefinitely while a target P_m greater than 60 percent of $P_m$max led to task failure within a finite period of time. These experiments clearly show that the intensity of inspiratory muscle contraction and the strength of the inspiratory muscles are important determinants of the fatiguing process. Thus, increases in inspiratory load (by increasing the required P_m) and decreases in inspiratory muscle strength (by decreasing $P_m$max) will predispose to the development of inspiratory muscle fatigue. It is of interest to note that the target mouth pressure required to induce task failure is larger than

when a diaphragmatic target pressure is employed (60 vs 40 percent). The reasons for this difference are not entirely clear. In these experiments, however, P_{di}max was measured during a Mueller-expulsive maneuver (a maximal inspiration against an occluded airway with simultaneous contraction of the abdominal muscles). The highest P_{di}max values are achieved during a Mueller-expulsive maneuver,[9] but P_{di}max measured during such maneuvers may overestimate the inspiratory pressure generating capacity of the diaphragm.[10]

During breathing, the diaphragm contracts mainly during inspiration and relaxes during expiration. Increases in inspiratory time will increase the duration of diaphragmatic contraction, while decreases in expiratory time will shorten the period in which the diaphragm can relax between contractions. The duty cycle (inspiratory time/total breath duration; T_I/T_{TOT}) is an important determinant of the fatiguing process. Bellemare and Grassino[11] have shown that the duty cycle (T_I/T_{TOT}) is equally as important as the pressure generated during diaphragmatic contraction (P_{di}/P_{di}max) in determining diaphragmatic endurance. These authors found that a tension-time index ($TT_{di} = P_{di}/P_{di}$max$\cdot T_I/T_{TOT}$) could predict diaphragmatic endurance during inspiratory resistive loading. A TT_{di} of less than 0.15 could be maintained indefinitely while a TT_{di} of greater than 0.18 led to task failure within a finite period of time. Thus, the fatigue threshold was 0.15-0.18. A similar tension-time index has recently been devised for the ribcage muscles (TT_{rc}). The $TT_{rc} = P_{es}/P_{es}$max$\cdot T_I/T_{TOT}$ (P_{es}max is measured during a maximal inspiratory effort against an occluded airway at functional residual capacity). Electromyographic (EMG) evidence of fatigue of the sternocleidomastoid muscles and the parasternal intercostal muscles can be demonstrated when the TT_{rc} exceeds 0.26.[12]

The TT_{di} has been measured in patients with COPD.[13] A TT_{di} greater than 0.20 invariably resulted in shifts in the power spectrum of the diaphragmatic EMG consistent with diaphragmatic fatigue. Conversely, a TT_{di} less than 0.12 never produced change in the diaphragmatic EMG. Such studies have resulted in the TT_{di} being widely employed as an index of a potentially fatiguing pattern of contraction. However, it is important to appreciate that the factors incorporated in the TT_{di} are not the sole determinants of diaphragmatic or inspiratory muscle fatigue. Other factors are also important.

Evidence has been provided that diaphragmatic fatigue can occur during high intensity cycle exercise[14] or voluntary hyperpnea to volitional exhaustion.[15] However, the TT_{di} averaged only 0.10 (range 0.06-0.14) in these studies and the fatigue threshold of 0.15-0.18 was never exceeded in any of the subjects. Clearly, in the presence of a marked increase in
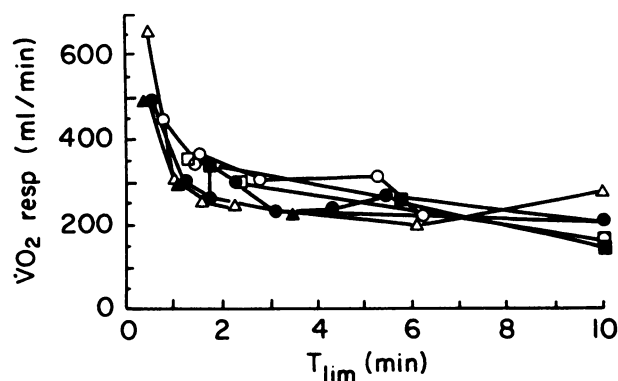

FIGURE 1. Relationship between rate of O_2 consumption due to breathing task (Vo₂ resp) and time to task failure (T_{lim}) in a single subject. There was no systematic difference in the relationship between Vo₂ resp and t_{lim} at different flow rates (low o, medium Δ, high □) or lung volumes (relaxation volume, closed symbols; relaxation volume + 1 L, open symbols). Similar results were obtained in the other subjects. (From McCool FD, Tzelepis GD, Leith DE et al: Oxygen cost of breathing during fatiguing inspiratory resistive loads. J Appl Physiol 1989; 66:2045-55)

ventilatory requirements, TT_{di} threshold values obtained during inspiratory resistive loading are no longer applicable.

What, then, determines diaphragmatic endurance? McCool and colleagues[16] have recently shown that the time to task failure (endurance time) during inspiratory resistive loading is closely related to the oxygen cost of breathing (Vo₂resp). The greater the increase in Vo₂resp, the shorter the endurance time. Furthermore, the relationship between Vo₂resp and endurance time could be described by a single relationship under a wide variety of experimental conditions (Fig 1) while the relationship between the tension-time index and endurance time differed significantly between the various experimental conditions. Field and colleagues[17] have shown that the TT_{di} and Vo₂resp are strongly correlated during inspiratory resistive loading when the pattern of breathing is relatively constrained. Thus, it is not surprising that under these conditions the TT_{di} is an accurate predictor of diaphragmatic endurance. In contrast, when the breathing pattern is not as constrained, the TT_{di} does not uniquely determine Vo₂resp and thus, poorly predicts diaphragmatic endurance.

Collett and colleagues[18] have shown that work rate (mechanical work per breath·respiratory rate) is an important determinant of Vo₂resp. At a constant tension-time index, a doubling of the work rate will lead to a two- to threefold reduction in endurance time[19,20] (Fig 2). Another factor that is very important is hyperinflation. Inspiratory muscle endurance is significantly reduced during inspiratory resistive loading at lung volumes above FRC.[8,21] With increasing lung volume, inspiratory muscles shorten and reduce their ability to generate pressure (length-tension relationship).[22] When the increase in lung volume is
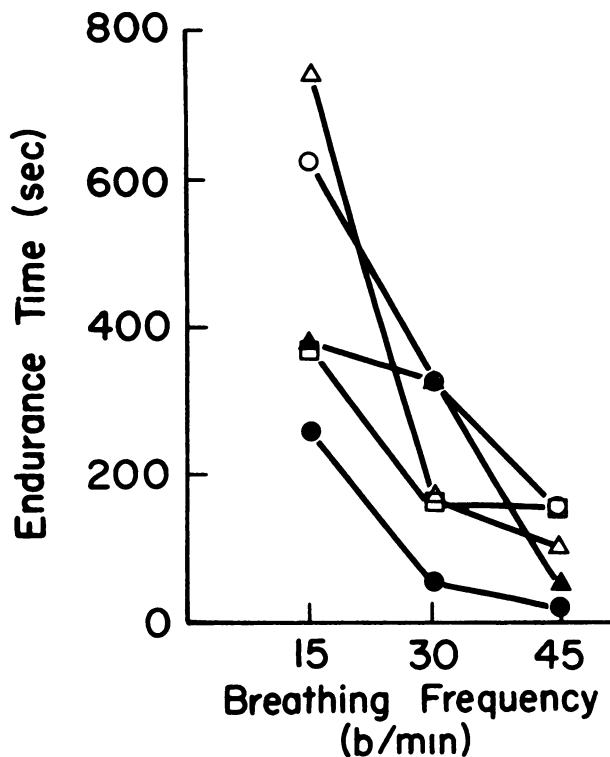
FIGURE 2. Diaphragmatic endurance times of five subjects at three different breathing frequencies. Despite a constant TT_{di}, tidal volume and work/breath, diaphragmatic endurance decreased as breathing frequency and, thus, work rate increased.

achieved by mechanical means, the reduction in inspiratory muscle endurance can be explained solely by the decrease in inspiratory muscle strength (due to muscle shortening).[21] When the increase in lung volume is due to persistent inspiratory muscle activity during expiration (as may occur in patients with asthma[23]), inspiratory muscle endurance is impaired to an even greater extent[8] presumably due to the additional negative work performed by the inspiratory muscles during expiration. Recently, Collett and Engel[24] have measured Vo₂resp in healthy subjects breathing against inspiratory resistive loads at FRC and at a higher lung volume (45 and 66 percent of the vital capacity, respectively). Despite close matching of ventilation, inspiratory flow rate, pressure-time product, and work rate, Vo₂resp was increased at the higher lung volume—an increase of about 1 percent in O₂ cost per unit work for each percentage increase in vital capacity (efficiency was reduced). In this study, increases in tidal volume (from 600 to 1,600 ml) at a constant end-expiratory lung volume had no effect on Vo₂resp suggesting that modest increases in the degree of muscle shortening during inspiration do not affect Vo₂resp. Similarly, a threefold increase in inspiratory flow rate and respiratory rate had no effect on Vo₂resp when the pressure-time product and work rate were held constant during inspiratory resistive loading.[25] Whether more extreme changes in tidal

volume, respiratory rate or inspiratory flow rate would affect Vo₂resp has not been determined.

BREATHING PATTERN IN RESPIRATORY MUSCLE FATIGUE

In a highly influential paper, Cohen and associates[26] measured the diaphragmatic EMG, respiratory rate and ribcage-abdominal motion in 12 ventilator-dependent patients being weaned from mechanical ventilation. Seven patients displayed power spectral shifts in the diaphragmatic EMG consistent with diaphragmatic fatigue. Coincident with the changes in diaphragmatic EMG, the patients developed tachypnea and abnormalities in ribcage-abdominal motion; abdominal paradox, defined as a paradoxic inward abdominal motion during inspiration, and respiratory alternans, defined as phasic alterations between ribcage and abdominal breathing. The abnormalities in thoracoabdominal motion were not observed in the five patients who did not develop EMG evidence of diaphragmatic fatigue. The authors suggested that abdominal paradox and respiratory alternans may be reliable clinical signs of inspiratory muscle fatigue. Implicit in this reasoning is the assumption that the abnormal thoracoabdominal motion was caused by inspiratory muscle fatigue. To determine whether this assumption is correct, Tobin and associates[27] measured ribcage-abdominal motion with a respiratory inductive plethysmograph in healthy subjects during inspiratory resistive loading. Increasing amounts of ribcage-abdominal asynchrony and paradox were observed with increases in respiratory load during nonfatiguing resistive runs. When subjects breathed through an inspiratory resistance to fatigue (defined as the inability to generate a target pressure) increases in abdominal paradox were observed during the first minute of loaded breathing and did not progress during the remainder of the loaded breathing run (Fig 3). Clearly, if fatigue was responsible for the abdominal paradox, the degree of abdominal paradox should have progressed during the loaded breathing run as fatigue developed. The absence of such progression, the immediate appearance of abdominal paradox at the start of the loaded breathing run, and its immediate disappearance when the load was removed, suggest that abdominal paradox was due to the increase in respiratory load rather than to muscle fatigue. Similarly, in a study of patients weaning from mechanical ventilation, an increase in the degree of abdominal paradox was observed immediately following discontinuation of mechanical ventilation without subsequent progression during the remainder of the weaning trial, again suggesting that the increase in abdominal paradox was due to increases in respiratory load rather than to fatigue.[28] In these studies, respiratory alternans was not observed in either the normal
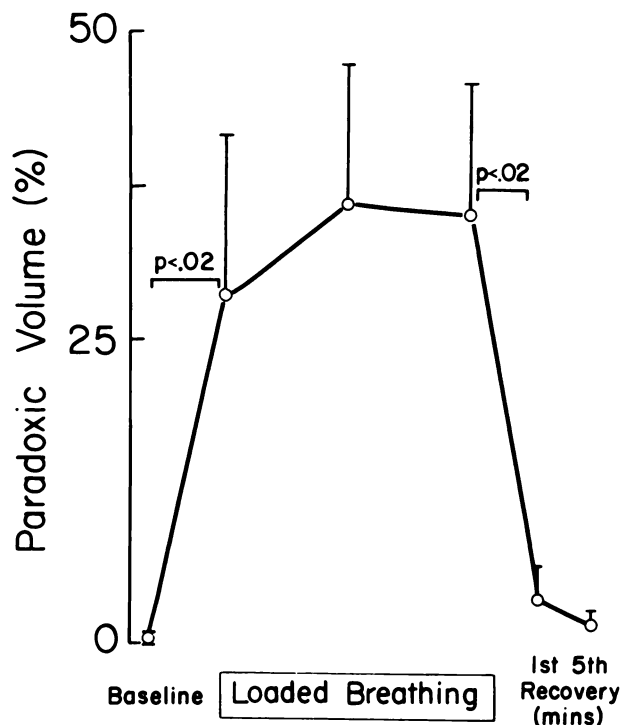
FIGURE 3. Effect of breathing against a fatiguing resistive load on the amount of inspiratory abdominal paradox at baseline, during the first min of loaded breathing, a min at the middle of the run, a min near the end of the run and during the first and fifth min of the recovery period. Values are mean ± SE of six subjects. Abdominal paradox increased during the first min of loaded breathing, did not progress during the loaded breathing run, and returned to baseline levels immediately following discontinuation of the load. (Modified from Tobin MJ, Perez W, Guenther SM, et al. Does ribcage-abdominal paradox signify respiratory muscle fatigue. J Appl Physiol 1987; 63:851-60.)

subjects during resistive loading[27] or in the patients during weaning from mechanical ventilation.[28] Other investigators have also been unable to detect respiratory alternans in patients weaning from mechanical ventilation[29,30] or in subjects breathing against an inspiratory load[31] suggesting that respiratory alternans may be more uncommon than originally believed.

In the study by Cohen and colleagues,[26] all subjects who developed hypercapnia and EMG signs of diaphragmatic fatigue also developed progressive tachypnea during the weaning trials. The question arises as to whether the tachypnea was due to fatigue or to other factors. Road and colleagues[32] have examined the breathing pattern in anesthetized dogs before and after induction of diaphragmatic fatigue by electrophrenic stimulation. Following induction of diaphragmatic fatigue, minute ventilation and respiratory rates were larger while tidal volume was smaller than control values. Oliven and colleagues[33] have measured the breathing pattern during CO_2 rebreathing in awake goats before and after induction of inspiratory muscle fatigue. Fatigue was induced by prolonged inspiratory resistive loading. At any given level of ventilation, tidal volume was reduced and respiratory rate increased

following induction of fatigue. Furthermore, at any given level of CO_2, minute ventilation, peak transdiaphragmatic pressure and peak electrical activity of both the intercostal muscles and the diaphragm were reduced following induction of fatigue. Thus, in this study, induction of fatigue led to a reduction in motor outflow to the inspiratory muscles, a form of "central fatigue." These studies demonstrate that the development of inspiratory muscle fatigue in animals is associated with a rapid shallow pattern of breathing. The mechanism by which fatigue elicits changes in breathing pattern has not been delineated. However, activation of thin fiber afferents within the fatigued inspiratory muscles may be important. Diaphragmatic afferents have been shown to be capable of modulating motor outflow to the respiratory muscles.[34]

Gallagher and colleagues have measured the breathing pattern before and after induction of inspiratory muscle fatigue in healthy human subjects.[35] Fatigue was induced by breathing against an inspiratory resistive load to task failure (inability to generate the target pressure). At the same level of ventilation, breathing was faster and shallower following induction of fatigue compared with control. Since minute ventilation was transiently increased following discontinuation of resistive loading (likely a reflection of neuronal after discharge), ventilation was stimulated during the control period by rebreathing CO_2 to allow comparison of the breathing pattern at the same minute ventilation. However, the breathing pattern may differ depending on the method employed to stimulate ventilation so that CO_2 hyperpnea may not be an optimal control. Nevertheless, the results obtained in this study are quite consistent with the studies in animals and supports the notion that induction of inspiratory muscle fatigue results in a rapid shallow pattern of breathing in conscious humans.

My colleagues and I[36-38] have examined the breathing pattern before and after induction of inspiratory muscle fatigue in healthy volunteers under a variety of experimental conditions. The breathing pattern following induction of fatigue was not significantly different from control during resting breathing and when ventilation was modestly increased by CO_2 rebreathing or exercise.[36,37] In contrast, when ventilation was stimulated more rigorously by high intensity exercise on a bicycle, minute ventilation and respiratory rate were significantly increased following induction of fatigue compared with control (Fig 4) while tidal volume was slightly but not significantly decreased[37,38] (the decrease in tidal volume was less pronounced than the increase in respiratory rate similar to the results obtained by Road et al in the anesthetized dog). It is likely that the degree of peripheral fatigue elicited in healthy volunteers during inspiratory loading is less than that achieved in animal
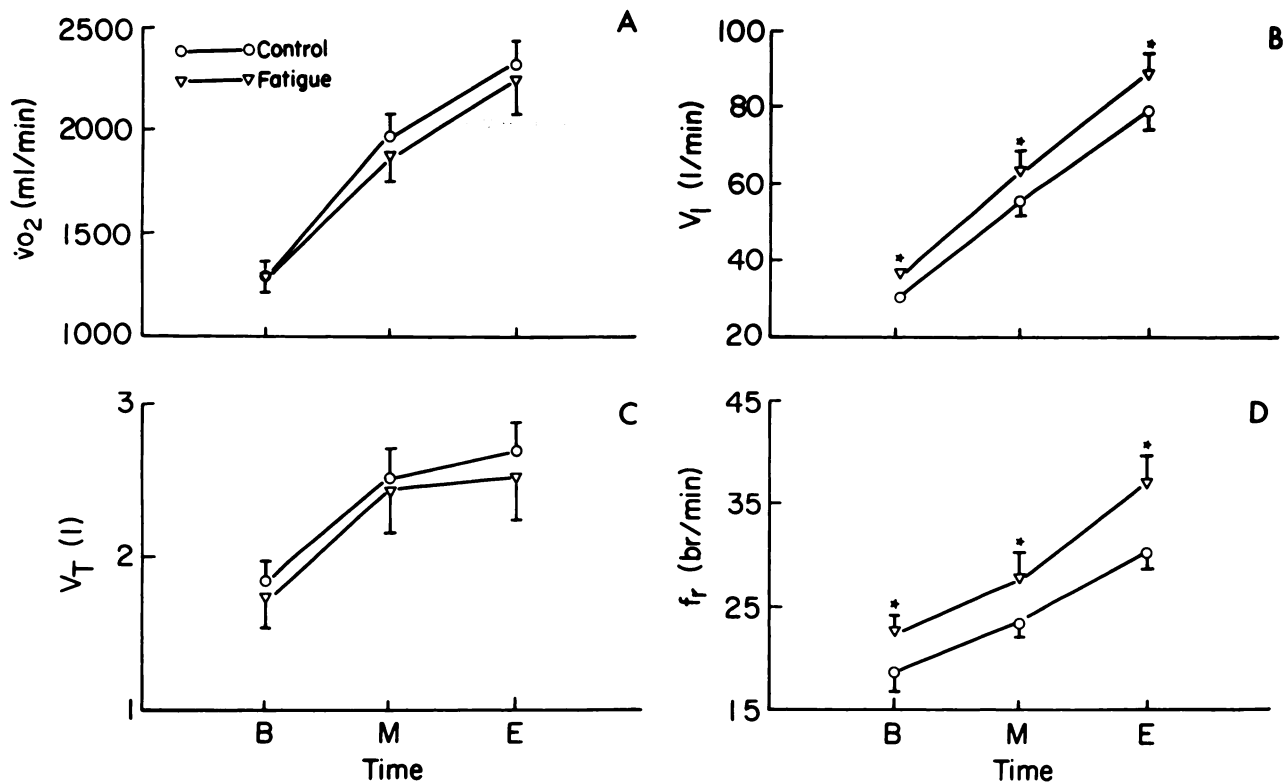
FIGURE 4. Oxygen consumption (Vo₂), minute ventilation (V_I), tidal volume (V_T), and respiratory frequency (f_r) during the first minute (B), the middle minute (M), and the final minute (E) of constant load bicycle exercise at 90% of maximal capacity after induction of fatigue (∇) and during the same time period (isotime) in the absence of fatigue (control exercise, o). Values are means ± SE of 10 subjects. Control curve represents average of 2 control trials. *Significant difference from average of 2 control trials (p<0.01). At any given time during exercise, V_I and f after induction of fatigue were greater than control values. (From Mador MJ, Acevedo FA. Effect of respiratory muscle fatigue on subsequent exercise performance. J Appl Physiol 1991; 70:2059-65.)

models of fatigue possibly accounting for the greater difficulty in eliciting changes in breathing pattern in unstressed human subjects. Nevertheless, it is apparent that induction of inspiratory muscle fatigue in the presence of an increased inspiratory load results in characteristic changes in the breathing pattern in healthy human subjects similar to those obtained in animal models of fatigue.

My colleagues and I[37,38] also found that the ventilatory response to exercise was increased following induction of fatigue compared with control. In these experiments, induction of fatigue resulted in an increase in central respiratory drive. Similarly, Cohen et al[26] observed an increase in minute ventilation in patients undergoing a weaning trial who displayed electromyographic evidence of diaphragmatic fatigue. In contrast, motor outflow to the inspiratory muscles was clearly reduced following induction of fatigue in the awake goat.[33] It has been suggested that the neural response to fatigue may vary with the conditions used to induce fatigue and, thus, both excitatory and inhibitory responses may be seen.

In a subject study, Mador and colleagues[39] examined the breathing pattern during inspiratory resistive loading before and after induction of inspiratory

muscle fatigue. Fatigue was induced by inspiratory threshold loading. Subjects breathed through a large inspiratory resistive load for 5 min before and immediately after induction of fatigue. No differences in breathing pattern were observed following induction of fatigue compared with controls. These results are contrary to what might be anticipated. However, with high external resistances, elastic work is a negligible fraction of total work and mean inspiratory pressure is almost exclusively a function of mean inspiratory flow rate. Under these circumstances, a slow deep pattern of breathing minimizes inspiratory muscle work and respiratory sensation while rapid shallow breathing is maladaptive at least from the point of view of minimizing inspiratory muscle work.[40] These findings suggest that the tachypnea usually elicited by inspiratory muscle fatigue can be suppressed under certain circumstances. It would be of interest to examine the breathing pattern response to elastic loading before and after induction of fatigue. With elastic loading, rapid shallow breathing is the most economical pattern of breathing and we hypothesize that the tachypneic response to fatigue would be enhanced rather than suppressed.

Summary

The major determinants of $\dot{V}O_2$ resp and, thus, diaphragmatic endurance are the tension-time index, work rate and lung volume. Changes in breathing pattern that adversely affect any of these factors can impair diaphragmatic endurance. A TT_{di} above 0.15-0.18 indicates a potentially fatiguing pattern of contraction. However, fatigue may occur at a TT_{di} below 0.15 if the work rate is sufficiently high or the P_{di}max is not measured at the prevailing lung volume.

Inspiratory muscle fatigue usually elicits an increase in minute ventilation and respiratory rate and to a lesser degree a reduction in tidal volume. However, fatigue may not always be accompanied by changes in breathing pattern. Furthermore, fatigue may sometimes result in a reduction rather than an increase in motor outflow to the respiratory muscles. Finally, abdominal paradox initially considered to be characteristic clinical sign of inspiratory muscle fatigue appears to be due to increases in respiratory load rather than to muscle fatigue.

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