To breathe or not to breathe: the respiratory muscles and COPD

The respiratory muscles are unique among skeletal muscles in that they are required to work without sustained rest throughout life. It is not surprising, therefore, that the ventilatory pump has been the subject of intense investigation over the past 30 years, with particular interest in the ability of the muscles to cope with the increased work of breathing imposed by lung and chest wall pathology. The study of Levine et al. (12) published in this issue of the Journal of Applied Physiology provides the first evidence that appropriate adaptive responses occur in the inspiratory intercostal muscles of patients with chronic obstructive pulmonary disease (COPD).

The diaphragm is the principal inspiratory pump muscle, especially during sleep. In 1973, Dudley Rochester published an article entitled “The diaphragm: nobilissimus post cor musculus” (after the heart, the noblest of muscles), although there were limited data to support the statement at that time (22). However, he and others (for review, see Ref. 14) helped initiate an explosion in knowledge about the physiological, morphometric, and biochemical properties underlying the diaphragm’s adaptation for work.

The diaphragm proved to be more resistant to developing fatigue than limb muscles in vivo and in vitro (7), and, in human subjects, the inspiratory muscles recovered from fatigue 10 times faster than the elbow flexors performing a similar task (15). The upper limit of blood flow (adjusted for muscle mass) to the diaphragm is two to four times that of most limb muscles, and there is a corresponding increase in the capillary density compared with a range of limb muscles across a number of species (for review, see Refs. 14, 21). The volume density of mitochondria, the oxidative capacity of the muscle fibers, and the maximal oxygen consumption of the diaphragm exceed those of limb muscles by two to six times. The relatively small muscle fiber size of respiratory muscles also reduces the diffusion distance for oxygen. The diaphragm also appears to maintain intramuscular perfusion during relatively strong contractions, which would normally cause a rise in intramuscular pressure to levels greater than systolic arterial pressure. This is because the relatively thin sheet of muscle produces a negative intrapleural pressure and provides a pressure gradient across the muscle to facilitate blood flow (Ref. 1, for review, see Ref. 16). Such a mechanism should also apply to the intercostal muscles.

The intercostal muscles, possibly because of their complex anatomical and geometric relationships, have been less intensively studied than the diaphragm, but their role in ventilation is important. Activation of the diaphragm in tetraplegic patients leads to paradoxical inward displacement of the cranial half of the rib cage. The mechanical function and neural activation of the intercostal muscles were poorly understood until recently, although anatomists have speculated about them since the time of Galen (~150 AD). Over the past 15 years, De Troyer and colleagues, through an important series of classical physiological studies in dogs and humans, demonstrated that the mechanical advantage and therefore action of both the internal and external intercostal muscles depend not only on the orientation of their fibers, as classically taught but, more importantly, on the interspace number and the location of the fibers within the interspace (for review, see Ref. 3). Inspiratory action is greatest for the external intercostals in the upper spaces posteriorly and decreases progressively in lower spaces and anteriorly within spaces. Their action is reversed to expiratory in the anterior portion of the lower interspaces. The internal intercostals are predominantly expiratory in the lower chest, but the mechanical advantage decreases progressively in higher interspaces. In the latter spaces, the expiratory action decreases progressively from posterior to anterior, reversing to an inspiratory action for the parasternal intercostals.

There has been considerable interest in whether the central nervous system delivers neural drive, according to anatomic neural pathways or according to muscle function. The pioneering work of Taylor (26) showed that EMG activity of the external and parasternal intercostals was inspiratory, while the internal intercostals were expiratory. In recent years, a systematic series of experiments in dogs and humans showed that inspiratory neural drive is distributed in proportion to the mechanical advantage of the muscle fibers, both between and within intercostal spaces (for review, see Ref. 3). The timing of the onset of electrical activity in relation to onset of airflow also varies between and within spaces in a sequential fashion related to the mechanical advantage of the muscle fibers (2, 5). The close matching between the neural drive and the mechanical advantage of groups of intercostal muscle fibers implies an efficient system, which should minimize the work of breathing. Theoretical analyses of the metabolic cost of muscle contraction using a simple mechanical model supported this suggestion (3).

Given that motoneuronal activity has a crucial role in determining muscle fiber composition, it would be reasonable to expect that there might be a systematic variation in muscle fiber-type proportions of the intercostal muscles between and within spaces. However, this does not appear to be the case in humans, with most sites sampled showing a mixed muscle composition with 60–65% type I slow oxidative fibers, slightly higher than that of the human diaphragm with ~55% (Refs. 17, 18; for reviews, see Refs. 16, 21).

The function of the respiratory muscles is profoundly disturbed in severe COPD because of the resistive and elastic loads imposed by narrowed airways and hyperinflation. The inspiratory muscles probably operate at suboptimal fiber lengths, and the mechanical efficiency of the rib cage is reduced (13). The diaphragm, remarkably, retains near normal pressure-generating ability (24) and capacity to generate tidal volume (9, 25), although its inspiratory capacity is diminished. However, to achieve this near normal tidal volume, the diaphragm requires a 70% increase in motoneuronal discharge frequency (4), whereas the parasternal intercostals and scalene muscles required a 30% increase (6).

There seems little doubt that the respiratory muscles of patients with COPD adapt to the chronic increase in the loads to breathing and remain highly resistant to the development of fatigue, and there is little evidence that the ultimate development of ventilatory failure is related to peripheral respiratory muscle fatigue (for reviews, see Refs. 14, 23). The major mechanism for chronic hypercarbia, therefore, is a failure to increase central drive sufficiently to maintain alveolar ventilation, which is first manifest in sleep.
Several pieces of evidence point to useful ultrastructural adaptations of the diaphragm in patients with COPD (for reviews, see Refs. 19, 21). These include a higher percentage of slow (fatigue resistant) isoforms of myosin heavy chains (type 1) and slow light chains, troponins, and tropomyosin (10). Mitochondrial oxidative capacity was higher in all muscle fiber types compared with control subjects, consistent with increased fatigue resistance (11). A reduction in mean sarcomere length has also been documented, pointing to an adaptation to operating at a shorter muscle length (20). A reduction in sarcomere number has not been documented in patients with COPD.

In this issue of the *Journal of Applied Physiology*, Levine and colleagues (12) report results from biopsies of the parasternal intercostal muscles obtained from the third interspace in seven patients undergoing lung volume reduction surgery for COPD. Immunohistochemical techniques of slow (fatigue resistant) isoforms of myosin heavy chain also increased. In other words, there was a transformation of fiber types from fast to slow, consistent with an adaptation for enhanced endurance capacity.

These results for the parasternal intercostal muscles contrast with the slow to fast transformation reported for the inspiratory external intercostals of COPD patients reported by Gea et al. (8). One explanation for this discrepancy may be that the specimens examined by Gea et al. were taken from lower interspaces, where the external intercostals have primarily a postural rather than inspiratory function. Another possibility is that remodeling of the rib cage in COPD reduces the inspiratory contribution of the external intercostals with a corresponding decline in tonic and/or phasic neural discharge. This hypothesis could be tested by measurement of single motor unit firing frequencies in those muscles. If confirmed, the opposite adaptive responses of these two inspiratory intercostal muscles would point to the remarkable plasticity not only of the inspiratory muscles but also of the central neural circuitry that drives them.

REFERENCES


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