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A review of concepts regarding the origin of respiratory muscle fatigue

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In this review, the classification of respiratory muscle fatigue from the perspective of its origin is presented. The fatigue is classified as central or peripheral, and the latter further subdivided into high- and low-frequency fatigue. However, muscle fatigue is a complex process and all three types of fatigue probably occur simultaneously in the overloaded respiratory muscles. The relative importance of each type depends on the duration of respiratory loading and other physiological variables. However, central and high-frequency fatigue resolve rapidly once muscle overload is removed, whereas low-frequency fatigue persists over long time.

Key Words: muscle activation, respiratory failure, excitation-contraction coupling.

Introduction

Muscle fatigue is the temporary reduction in muscle capability of force generation, connected with the accumulation of lactic acid. Fatigued muscle gradually recovers during rest [3], but the recovery is not complete until the lactic acid is removed.

Muscle fatigue should be distinguished from muscle weakness, which is the permanent state caused by a neuromuscular disease or aging [19, 26, 28], and muscle injury, resulting in an irreversible or slowly reversible reduction in muscle contractility [14, 27].

Human respiratory muscle fatigue is caused by excessive effort relative to the strength and endurance of the respiratory muscles [42]. It may develop in healthy subjects in response to

high-intensity exercise [7, 8, 13, 48, 50] or in pathophysiological states induced by lung disease. In the latter case it may contribute to respiratory failure [32, 44, 46]. Respiratory muscle fatigue probably contributes to the difficulties some patients have with weaning from mechanical ventilation, the symptoms of exercise intolerance and dyspnea in chronic lung disease, and to CO_2 retention [3, 22, 24, 39].

Classification of fatigue

On the operational level, fatigue may be classified into different types having different physiological characteristics [12, 15, 20, 29, 35-36, 45]. With respect to the muscle group, in which fatigue is observed, expiratory and inspiratory muscle fatigue may be distinguished [45, 49].

However, the most important classification is related to the origin of fatigue. In this respect, one can distinguish central fatigue (reductions in respiratory synaptic drive [2, 11, 16] and peripheral fatigue [25, 40].

The differentiation between central and peripheral fatigue is usually made on the basis of the results of supramaximal electrical stimulation [13]. When the stimulation produces more force than one generated by maximum voluntary effort, the reduced force output is likely to be caused by the reduction in motor output from central nervous system. When fatigue is due to the failure of peripheral structures (impaired neuromuscular transmission or contractility), the stimulation would produce muscle force decreased with respect to the non-fatigued condition. The peripheral fatigue is further classified into high- and low-frequency fatigue on the basis of the post-fatigue force-frequency relationship obtained in response to the stimulation [5-6, 10].

Some authors distinguished also transmission fatigue, caused by impaired neuromuscular transmission [1, 9] and contractile fatigue related to decreased contractility [4, 32].

The mechanisms involved in muscle fatigue

Nava and coworkers [34] provided evidence of the development of acute diaphragmatic fatigue in a natural condition by measuring the static maximal inspiratory pressure and by analyzing the electromyographic power spectrum of the diaphragm in women during labor.

Central muscle fatigue

To measure As mentioned above, the central fatigue may be revealed as the increase in force output evoked by electrical stimulation above that due to the maximal voluntary contraction. Bellemare and Bigland-Ritchie [10] have shown that well-motivated individuals are able to fully activate rested diaphragm during volitional contractions when asked to make the maximal effort, i.e. that volitional maximal force was equal that obtained by electrical phrenic nerve stimulation. Allen and coworkers [5] found that normal subjects and patients were able to drive the stimulated elbow flexor muscles maximally in about 25% of all trials.

The central component of diaphragmatic fatigue was investigated by Bellemare and Bigland-Ritchie [11]. They measured transdiaphragmatic pressure over time before, during and after inspiratory resistive loading. To assess the central component of fatigue, they employed nerve stimulation at various times during an experiment and found that about one half of the observed reduction in transdiaphragmatic pressure resulted from the reduced central motor drive. McKenzie and coworkers [25] using a modification of the twitch interpolation technique compared the extent of voluntary neural drive to the diaphragm and the elbow flexors during fatigue. The study provided evidence of the development of central diaphragmatic fatigue during repeated maximal and submaximal diaphragmatic contractions. However, the decline in central drive to the diaphragm during inspiratory contractions was not significant in contrast to the limb muscle contractions. Both studies excluded the contribution of neuromuscular transmission failure to observed diaphragmatic fatigue. The diaphragm was also shown to be more resistant to central fatigue than quadriceps muscle [16].

Peripherial muscle fatigue

Whereas the central fatigue refers to a condition in which muscle force generation becomes limited due to a decline in motoneuronal output" [9, 43], peripheral fatigue is due to alterations within the muscle fibre, changes in excitation-contraction coupling or alterations in the neuromuscular junction [6, 31, 34, 41]. This type of fatigue results in changes in propagation of the action potentials along the sarcolemmal membrane or into the t-tubules, reductions in contractile proteins activation in response to the nonimpaired sarcolemmal action potential, and alterations in muscle metabolism.

Hamnegard and coworkers [17] investigated the effect of maximal isocapnic ventilation on twitch transdiaphragmatic pressure elicited by cervical magnetic stimulation. They observed

substantial fall in ventilation of the inspiratory muscles during the first minutes and provided the evidence that it is associated with reduction of diaphragmatic contractility, which may be a limiting factor in maximal ventilation in man.

High-frequency fatigue in humans is presented when fatigue results in depression of the forces generated by a muscle in response to the electrical stimulation in the frequency range 50–100 Hz. The force reductions due to the stimulation in the frequency range 1–20 Hz are associated with the low-frequency fatigue [18, 27, 31, 33-34, 41].

A number of studies have suggested that the high-frequency fatigue is related to alteration in neuromuscular junction transmission, reduction in sarcolemmal membrane excitability or reduction in action potential propagation into the t-tubular system [9, 12, 18, 27, 30-31, 33, 38, 43]. On the other hand, the low-frequency fatigue indicates an impairment of muscle excitation-contraction coupling and a reduction of myofilament calcium sensitivity [27, 33-34] .

Observations have shown that low-frequency fatigue can occur in isolation, but high-frequency fatigue is always associated with low-frequency fatigue [23, 43]. Force generation ability in high-frequency range recovered within 10 min in rabbits [4], whereas low-frequency fatigue persisted for a long time [4, 30].

High-frequency fatigue has been demonstrated in the diaphragm of normal human after a trial of high-intensity inspiratory resistive loading [21, 30, 37, 43]. Low-frequency fatigue has been demonstrated in the diaphragm and sternocleidomastoid muscles of normal subjects breathing against resistive loads [21, 30, 37, 41, 43, 47] and in the diaphragm of normal human asked to sustain maximum voluntary ventilation for 2 minutes [23].

Conclusion

It is convenient to classify fatigue into three different types and to discuss the characteristics of them separately. However, muscle fatigue is a complex process and it is likely that these various phenomena do not occur in isolation during muscle activation.

All three types of fatigue may be operating simultaneously during the respiratory muscles confrontation with an excessive workload. The relative importance of each type depends on the duration of respiratory loading and other physiological variables, i.e., nutritional state, arterial blood gas concentrations, arterial pressure.

Whereas all these three phenomena may participate in the acute response to loading, only low-frequency fatigue is likely to persist over few minutes to hours. Both central fatigue and high-frequency fatigue resolve rapidly once fatiguing levels of muscle contraction cease.

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