Respiratory muscles in endocrinopathies

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Introduction

Respiratory muscles (RM) have the structural, physiological and biochemical characteristics of skeletal muscles. The only difference is that the RM contract continuously and breathing is a lifetime endurance task. Impairment of RM function by myopathy, neuropathy or both, puts life in great danger. The physiological function of the RM, like that of all skeletal muscles, is a multifactorial, complicated procedure. It requires not only the structural integrity of the muscles, their neurons and neuromuscular junction, but also, among others, an adequate energy supply, normal metabolism with intact intracellular biochemical pathways as well as a balance of extra-and intra-cellular electrolytes. It is well known that a number of the above functions are regulated and/or affected by hormones. Therefore, it is not surprising that a variety of endocrinopathies are associated with skeletal myopathies. Recently evidence has accumulated showing that RM function is also impaired in hormonal disturbances. In this paper we will review this evidence but first we will discuss in brief muscle contraction and identify potential mechanisms that could be affected by hormones. Secondly, we will discuss RM function in each endocrinopathy and finally we will propose areas for further investigation.

Theoretical Aspects

Skeletal muscles contain about 80% water and the remaining 20% consists mainly of proteins (1). The basic muscle proteins are the pairs of myosin/actin and tropomyosin/troponin. According to the sliding filament theory (2,3), in a resting state, the myosin head contains adenosinediphosphate and inorganic phosphate (ADP + Pi) and tropomyosin which prevents the combination of myosin to actin. During muscle activation there is a release of Ca2+ causing the myosin’s head to bind with actin and ADP + Pi to dissociate from the actomyosin complex. This results in movement of the thin filament towards the center of the sarcomere thus producing a working stroke, in other words the shortening of the muscle. Next, ATP is taken up and dissociates actin from myosin. The ATP is then hydrolysed and the products ADP, Pi remain in the myosin ready for the next stroke. This procedure continues until Ca2+ is removed to troponin and relaxation occurs. Thus, muscle energy utilization (ATP) is related to mechanical work (stroke).

It is obvious that the high energy phosphate (ATP) is the primary fuel for muscle contraction (4). ATP is restored at the expense of creatine kinase (PCr) which is plentiful and active. This reaction is affected by Mg2+. PCr stores are replenished by glycolysis and oxidative phosphorylation (5). In anaerobic conditions, the breakdown of glycogen towards lactic acid forms 3 ATP molecules. In contrast, in the presence of oxygen, one glycogen molecule produces 36 ATP molecules and no lactic acid. The above chemical reactions are complicated, form pathways, and a number of enzymes and ions are responsible for intermediate steps.

Facilitation of glucose transport across the plasma membrane is observed in active muscles, but first the active muscle utilizes intracellular glycogen which is stored in forms of granules. Thus, the first step in energy supply to the muscle is glycogenolysis. Phosphorylase is the enzyme responsible for glycogenolysis and is activated by Ca2+ release from the sarcoplasmic reticulum, by adrenalin and other circulating hormones. The regulation of glycogenolysis during activation of muscles is not clearly understood but it has been shown that it is closely related to the contraction itself (6,7).

RM, like all skeletal muscles, have to be excited in order to contract. The excitation comes from the motor neurons and crosses towards the muscles at the neuromuscular junction. Acetylcholine (Ach) is the chemical neurotransmitter substance which when it is released from the nerve ending, binds to specific Ach
Table 1 Possible pathophysiological mechanisms of the action of various hormones on the respiratory muscles

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Contractility</th>
<th>Energy/metabolism</th>
<th>Membrane permeability</th>
<th>Protein turnover</th>
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<tr>
<td>Growth hormone</td>
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<tr>
<td>Antidiuretic hormone</td>
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<td>Thyroid hormones</td>
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<td>Parathyroid hormone</td>
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<td>Corticosteroids</td>
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<tr>
<td>Aldosterone</td>
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<tr>
<td>Testosterone androgens</td>
<td>+</td>
<td>?</td>
<td>+</td>
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<tr>
<td>Adrenaline</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Noradrenaline</td>
<td>+</td>
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<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Insuline</td>
<td>+</td>
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receptors at the outer of the postsynaptic membrane (muscle side). This reaction opens ionic channels and allows Na⁺, Ca²⁺, and K⁺ to pass, causing depolarization of the membrane (8). Then an action potential is triggered and moves downward in the muscle fibres. ACh is rapidly hydrolysed by acetylcholinesterase (AChE) and is thus available for the next nerve impulse. Choline is the precursor of ACh and Na⁺ and Cl⁻ affect this metabolic pathway. Ca²⁺, Mg²⁺ and other electrolytes are involved in the storage, or the releasing processes of ACh (9).

The conduction of the action potential (excitation) is along the surface of the sarcolemma and via the sarcotubular system of the muscle. This T-tubular system serves to bring excitation deep into the fibre interior very rapidly. The procedure is Na⁺-dependent. What follows is called the excitation–contraction coupling (E–C). Lately it has been established that the main process in E–C is that of the Ca²⁺ release from the sarcoplasmic reticulum, which occurs between the depolarization of the T-tubules and the development of tension. Critical concentrations of other electrolytes, e.g. K⁺, Mg²⁺ are also important for the E–C coupling process. Finally, Ca²⁺ activates the thin filament of myosin and a muscle stroke begins. Although, the mechanism of E–C coupling is not clearly understood, the integrity of the Na–K pump, the Ca-pump and the so called Ca–Na exchange system of the fibres are vital (10–21).

Mechanisms of the Action of Hormones on Respiratory Muscle Function

The foregoing brief discussion has indicated that a number of possible mechanisms of action could explain the effect of hormonal dysfunction on the RM. However, the main pathophysiological mechanisms by which endocrinopathies affect RM function are four: 1, altering contractility (22–28); 2, altering energy supply and metabolic pathways (29–33); 3, altering membrane permeability (34,35) and 4, altering protein turnover (36–43). Table 1 summarizes the mode of action of various hormones on the muscles. It can be seen that hormones could affect muscle function by a combination of different mechanisms.

PITUITARY DYSFUNCTION

Acromegaly

A number of abnormalities of the respiratory system were reported in patients with excess production of growth hormone in adult life. These reports included early death due to respiratory disease (44), narrowing of the extrathoracic airways (45), sleep apnoea syndrome (46), large lung volumes (47) and abnormal function of small airways (48). The few available reports on values of maximum pressures in acromegaly (49) suggest that RM function is normal but it is worth investigating RM in a larger number of patients.

Hypopituitarism

In patients with a deficiency of growth hormone in adult life, small lung volumes have been reported by Jain et al. (50). In addition, they showed that RM strength was normal in all 12 patients with long standing growth hormone deficiency. Similar results were reported by De Troyer et al. (51). The authors found normal inspiratory muscle strength in four patients and concluded that muscle weakness was not the cause of small TLC. Since these studies were performed in a small number of patients, further studies are needed to clarify RM function in pituitary dysfunction.
Diabetes Insipidus

Antidiuretic hormone (ADH) is produced in the posterior pituitary and exhibits vasopressor and plasma osmolality control. Diabetes insipidus, the disease due to insufficient ADH, is characterized by polyuria, hypertonicity and hypernatremia. These could potentially alter RM function but no relevant study was found in the available literature.

THYROID GLAND

Histopathological studies

In skeletal muscles thyroid hormones have been shown to alter the speed of contraction/relaxation (25) or Ca$^{++}$ pump function (26). In addition thyroid hormones stimulate metabolism, membrane depolarization and myosin ATPase, and influence protein turnover (32,33,40). Experimental studies in rats showed that hypothyroidism increased the proportion of type 1 slow oxidative fibres of the diaphragm and hyperthyroidism decreased type 1 fibres (52). Ianuzzo et al. (53) showed an overall modification of enzymatic capacity of the diaphragm (i.e. glycolysis, tricarboxylic acid cycle, fatty acid oxidation) along with the proportion of alkali-labile to alkali-stable fibre types.

Hyperthyroidism (thyrotoxicosis)

It is well known that skeletal muscle weakness is a very common symptom in thyrotoxicosis. It was shown by Ramsay that 87% of hyperthyroid patients suffer from skeletal muscle weakness and when electromyographic techniques were applied 93% of the patients showed evidences of myopathy (54). Although as early as 1917 it was demonstrated that the respiratory system was affected in hyperthyroidism (55), it was only recently that attention was paid to the function of the RM.

In 1961 Stein et al. first reported that RM strength was reduced in hyperthyroidism (56). These investigators measured maximal expiratory and inspiratory mouth pressures and found them reduced. They concluded that these results are evidence of RM weakness. Later in 1978, Freedman, found small and inconsistent changes in maximal respiratory pressures in six thyrotoxic patients (57). In order to verify these discrepancies Siafakas et al. (58) measured maximum inspiratory and expiratory pressures in a larger group of hyperthyroid patients and found that indeed the pressures were reduced. The authors concluded that both respiratory muscle groups are weak in hyperthyroidism and that the weakness was reversible by medical treatment. Similar findings were reported by Miers et al. in seven patients with hyperthyroidism complaining of dyspnoea (59). These investigators measured muscle strength as well as transdiaphragmatic pressure (Pdi) during sniff and bilateral phrenic nerve stimulation. They concluded that there is RM weakness in thyrotoxicosis. In an effort to relate RM function and breathlessness in thyrotoxic patients McElvaney et al. (60) studied maximal static respiratory pressures, dyspnoea index and exercise parameters in 12 patients. Although they found that maximal pressures were reduced and improved after treatment they failed to show any difference in breathlessness intensity scores between patients and matched controls or a relationship between pressures and thyroid function.

However, recently Siafakas et al. (61) studied 20 consecutive hyperthyroid patients and showed not only that RM were weak but that this weakness was proportional to the degree of thyroid dysfunction. The investigators found a linear relationship between both maximal pressures (insp-exp), triiodothyronine and thyroxine blood levels. They concluded that these results are of clinical importance, since RM weakness is a common finding in thyrotoxicosis and it may cause respiratory failure (pump failure) in the more severe cases.

Hypothyroidism (myxedema)

In 1960 Wilson and Bedell investigated the pulmonary abnormalities in myxedema (62). They showed that maximal breathing capacity was reduced but increased significantly after therapy. They suspected that the RM or the neuromuscular coordination were involved. Freedman, in 1978, studied three hypothyroid patients and reported that one had reduced VC attributable to the decrease of inspiratory muscle force (57). Later, in 1986 and 1987, it was reported by Ashtyani et al. (63) and Siafakas et al. (64) that global RM strength was low in hypothyroidism. In 1988, Laroche et al. (65) by measuring maximal pressures, Pdi and sniff Pdi described a patient with hypothyroidism and respiratory muscle weakness and/or phrenic nerve neuropathy reversible with treatment. Three patients with hypothyroidism and chronic alveolar hypoventilation were studied by Martinez et al. (66) and found to have reversible diaphragmatic dysfunction. In a large series of 43 hypothyroid patients Siafakas et al. (67) investigated respiratory muscle strength before and three months after replacement therapy. They showed that mild RM weakness is a common finding in hypothyroidism and that this weakness is proportional to the degree of thyroid dysfunction. RM weakness was present in both long standing and short-duration hypothyroidism (4 weeks) and RM strength improved after therapy. They
concluded that thyroid dysfunction must be included in the differential diagnosis of unexplained respiratory failure requiring mechanical ventilation (67).

Although the above studies on hyper/hypothyroidism clearly demonstrate that RM weakness is present in thyroid diseases, the exact mechanism is obscure. Therefore, new studies are needed in humans, including RM biopsies and histopathological/enzymatic analyses.

PARATHYROID GLANDS

It is well known that parathyroid hormone regulates Ca\(^{2+}\) levels in the blood. Since Ca\(^{2+}\) is the vital substance of the neuromuscular function it is apparent that parathyroid gland disturbances will be manifested by muscle dysfunction.

Hypoparathyroidism

It causes not only hypocalcemia but also hyperphosphatemia and that leads to neuromuscular irritability, paraesthesias, muscle cramps and tetany. Baker et al. reported the case of a child suffering from hypoparathyroidism and synchronous diaphragmatic flutter (68).

Hyperparathyroidism

Hyperparathyroidism on the other hand, increases blood Ca\(^{2+}\) and reduces pH, and in the majority of cases it is accompanied by proximal muscle weakness, malaise and fatigability. In 1987, Gomez-Fernandez et al. (69) reported an uremic patient on dialysis with severe, secondary hyperparathyroidism, proximal muscle weakness and impaired RM strength. Marked improvement in RM function was observed after subtotal parathyroidectomy. Kristoffersson et al. (70) studies RM in ten hyperparathyroid patients by measuring maximal pressures (P\(_{\text{max}}\), P\(_{\text{nmax}}\)). They reported that only P\(_{\text{Emax}}\) was improved significantly 6–12 months after surgery. P\(_{\text{max}}\) was unchanged. The authors gave no explanation for this discrepancy. It is obvious that further studies are required to investigate RM function in parathyroid diseases in humans.

THE ADRENALS

The adrenal glands are essential to life and produce a number of vital hormones. Among these hormones are corticosteroids, aldosterone, androgens and catecholamines.

Adrenal cortex

Glucocorticosteroids. Steroids have multiple influences on the intermediary metabolism of cells. In brief, steroids affect glucose uptake by tissues and the process of gluconeogenesis, they block the synthesis of protein and nucleic acid and thus increase their turnover, and in addition can produce hyperlipidemia. Therefore, glucocorticosteroids affect muscle function by altering energy supplies, metabolism and protein turnover. In addition, steroids affect Ca\(^{2+}\) metabolism and influence the effect of other hormones, such as insulin and parathormones. Furthermore, glucocorticosteroids are synergistic with adrenaline and glucagon in stimulating gluconeogenesis.

However, most of the evidence concerning the effect of steroids on muscle structure and function are from the administration of these hormones in experimental studies or are due to iatrogenic effects. A number of animal studies have shown that there are a variety of histological/functional changes in the skeletal as well as the RM after chronic or acute administration of corticosteroids (73–77). Diaphragmatic weight loss, of approximately 30%, was a common finding in the above reports (73–77). Vacuolization, fragmentation and rhabdomyolysis were also common but interspecies variations were noted. In addition, histological and biochemical studies showed that there are also fibre-type changes and/or enzymatic alterations of the RM during steroid induced myopathy. In summary, acute steroid induced myopathy involves the RM, which exhibit atrophy and rhabdomyolysis. Chronic myopathy produces selective fibre-type atrophy, alteration in contractile properties and other biochemical and functional changes in the diaphragm. These findings were more profound when fluorinated steroids were used. A recent review on the subject has been published by Dekhuijzen and Decramer (80). In humans there are only a few studies which investigate the effect of the administration of steroids on RM function. Bowyer et al., in 1985, reported that P\(_{\text{max}}\) correlated with hip flexor strength in steroid dependent asthmatic patients (81). Picado et al. (82) studied steroid dependent (12 mg day\(^{-1}\)) and non-steroid dependent asthmatic subjects and found that maximal respiratory pressures (P\(_{\text{max}}\), P\(_{\text{nmax}}\)) and the strength of the deltoid were not significantly different between the two groups. Janssen and Decramer reported two patients with collagen vascular disorders who showed clinical improvement and marked increase in maximal respiratory pressures after gradual steroid tapering (83).

Patients with COPD on steroids showed a correlation between daily steroid dose and RM strength. Recently two patients with asthma and one with
COPD on methylprednisone, who developed RM myopathy, were described (84). However, the results of the above studies have to be read with caution since the underlying disease could influence the RM mechanic due to hyperinflation or due to myopathy itself (collagen disease).

In addition, Wang et al. (85) showed that 20 mg of prednisone for 2 weeks had no effect on $P_{\text{max}}$, $P_{\text{em}}$, $P_{\text{dm}}$, or RM endurance in normal subjects.

**Cushing's disease.** Cushing's disease is the endocrinopathy characterized by high blood levels of corticosteroids. The disease presents with weakness and proximal skeletal myopathy in 80–100% of cases. Although myopathy is very common in Cushing's disease we are not aware of studies investigating RM function in this illness. Therefore, such studies are needed.

**Mineralocorticoids.** Aldosterone is responsible for sodium (Na\(^+\)) ion reabsorption and potassium (K\(^+\)) ion secretion from the kidneys. Thus, an excess of mineralocorticoids results in hypernatraemia, hypokalaemia and alkalosis. In contrast, pure mineralocorticoid deficiency is related to hyponatraemia, hyperkalaemia and acidosis. Both Na\(^+\) and K\(^+\) are vital electrolytes for muscle contraction and aldosterone dysfunction is related to skeletal muscle weakness (86). Hyperkalaemia, in the hypo-aldosteronic state, can be the cause of secondary periodic paralysis. In primary adrenocortical insufficiency (Addison's disease) glyco- corticoids and mineralocorticoids are deficient and muscle fatigue and weakness are very common. However, only Mier et al. (87), in 1988, reported a case of Addison's disease presenting with dyspnoea on exertion that was related to severe RM weakness. RM function returned to within the normal range after treatment.

**Adrenal androgens.** These hormones, as well as testosterone and estrogen, alter protein synthesis and express their androgen action by mild Na\(^+\) retention and protein anabolism. Competitive athletes use androgenic anabolic steroids to improve endurance strength and performance of skeletal muscles but the results are dubious. However, no report was found which investigated in particular the RM function of such athletes.

**Adrenal medulla**

This part of the adrenal glands produces the catecholamines (noradrenaline and adrenaline). Catecholamines, as shown in Table 1, influence muscle function by altering contractility, energy supply and metabolism (glycogenolysis-induced insulin secretion), prolongation of action potential of the membrane and protein turnover. The effects of catecholamines and their derivatives (B\(_2\) adrenergics) on diaphragmatic contraction have not been studied extensively in vivo. However, early studies showed that these hormones when administered could affect diaphragmatic function by producing an abundance of $\beta$ receptors, alteration of metabolic activity and potentiation of twitch response in vitro. More recently, it has been shown that isoprorenaline improves the contractility of a fatigued diaphragm in dogs by approximately 10%. Terbutaline is a $\beta_2$-adrenergic proved to have no effect on a fresh diaphragm preparation but did have an important positive (isotropic) effect on the fatigued diaphragm (88). Clearly more studies in vivo and in humans are needed to elucidate the role of sympathomimetic hormones and their derivatives on the RMs. In diseases of the adrenal medulla, such as pheochromocytoma (excess of catecholamine production) or adrenaline deficiency, RM function has not been studied presumably because these conditions are rare.

**Diabetes mellitus**

Insulin regulates blood glucose, its uptake by various tissues, and has been also shown to induce hyperperfusion of the muscle membrane by increasing K\(^+\) uptake in exchange with H\(^+\). Furthermore, a number of biochemical/enzymatic and functional changes of skeletal muscles in diabetes mellitus have been reported in the literature. Cameron et al. showed that polyol pathway activity was an important factor, probably through the disruption of Ca\(^{2+}\)-handling, explaining functional changes of skeletal muscles in diabetes (89). Borsey et al. reported atrophic manifestations in the small hand muscles of diabetic patients related to autonomic nerve dysfunction (90). In addition, reduction of glucose transporters in the muscles could cause impaired glucose utilization in diabetes.

Recently in experimentally-induced diabetes in animals it was shown that diaphragmatic neuromyopathy appears to be a state of abnormal Ca\(^{2+}\) mobilization secondary to high levels of blood glucose (91). In addition, Nakagawa et al. (92) showed that the diaphragms of diabetic mice were atrophic, with disappearance of the 2-band, disturbed myofibrils and swollen sarcoplasmic reticulum. Furthermore, the investigators found changes in metal content (Ca\(^{2+}\), Mg\(^{2+}\), Fe\(^{+}\), Zn\(^{+}\)) of various muscles including the diaphragm and concluded that the changes induced by the diabetic state may be related to the morphological abnormalities (92).

However, only a few studies have addressed the issue of RM performance in human diabetic patients.
In 1990, Heimer et al. (93) investigated RM strength and endurance as well as lung volume and maximum voluntary ventilation (MVV) in 31 type 1 diabetic patients. The authors reported that no difference was noted in $P_{\text{max}}$ and $P_{\text{Emax}}$ between the diabetic patients and a group of matched subjects. Only RM endurance was lower in diabetics. In addition, they reported that TLC and VC as well as MVV were lower in diabetics and correlated with the duration of the disease. Wanke et al. (94), in 1991, studied inspiratory muscle function in 36 patients with insulin-dependent diabetes. They measured sniff $P_{\text{di}}$ and $P_{\text{es}}$, MVV, lung volumes and maximum expiratory flow – volume curves. In contrast to the results of Heimer (93), Wanke et al. (94) showed that inspiratory muscle performance was restricted in diabetics and both sniff $P_{\text{di}}$ and sniff $P_{\text{es}}$ were lower than in normals. In addition, VC and MVV were also lower. However, they did not find a significant correlation between these volume parameters and the duration of the disease. Wanke et al. concluded that the reduction in VC may have been caused partly by the reduced capacity of the inspiratory muscles (94).

Furthermore, it was reported in case reports that diabetic ketoacidosis could cause hypokalaemic respiratory arrest or hypophosphataemia and acute respiratory failure (95). Thus, it is worth investigating RM function during diabetic ketoacidosis in order to prevent severe respiratory pump failure. In addition, the mechanisms of impairment of RM function in diabetes mellitus could be due to myopathy, neuropathy or both but further investigation is required.

Summary and Conclusions

The aim of this review was to demonstrate that RM function is altered in various endocrinopathies and that RM weakness is a common finding. RM function has been well-studied in diseases such as thyroid dysfunction, and steroid induced RM myopathies. Less well documented reports on RM function were found in parathyroid dysfunctions, disorders of mineralocorticoids and pituitary disturbances. Controversial reports were found in diabetes mellitus. No report was found connecting RM function with androgens, pheochromocytoma or adrenaline deficiency in humans. These diseases could potentially cause RM impairment leading to severe respiratory failure (pump failure) putting life in great danger.

Therefore, it is obvious that further studies are needed to investigate the performance of RMs in endocrinopathies. Such studies are extremely urgent in Cushing’s and Addison’s disease, acromegaly, disorders of the adrenal medulla, and in diabetes insipidus.

References


