Topical Review

Pharmacotherapy of respiratory muscles in chronic obstructive pulmonary disease

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Introduction

Dysfunction of the respiratory muscles frequently occurs in patients with severe chronic obstructive pulmonary disease (COPD). This is of clinical importance since reduced respiratory muscle function may contribute to the sensation of dyspnoea, reduced exercise capacity, alveolar hypoventilation during exercise, nocturnal desaturation, hypercapnia, dyspnoea sensation and prolonged weaning from mechanical ventilation. Indeed, an increased medical consumption was observed recently in COPD patients with weakness of the respiratory muscles (1).

Respiratory muscle dysfunction is caused by weakness and/or fatigue of these muscles. Factors contributing to the development of respiratory muscle dysfunction in COPD include hyperinflation, malnutrition, physical inactivity, prolonged use of oral corticosteroids, abnormalities in gas exchange and electrolyte concentrations, and heart failure. Each of these factors may contribute to weakness of the respiratory muscles, which in turn pre-disposes to fatigue. Hyperinflation causes mechanical disadvantages, increases the work of breathing and attributes to the (already high) energy demands (2). Increased energy expenditure may attribute to loss of body weight and malnutrition which subsequently may reduce muscle mass. These factors in combination with metabolic changes and adverse effects of e.g. steroid treatment, place the respiratory muscles of these patients at risk for fatigue and the subsequent development of respiratory failure (2).

Improvement of respiratory muscle function in severe COPD may be expected to reduce dyspnoea sensation, increase exercise tolerance, improve gas exchange and reduce medical consumption. Several approaches to improve respiratory muscle function have been explored. These include reduction of (increased) respiratory muscle load, specific training to improve respiratory muscle strength and endurance, and respiratory muscle rest using mechanical ventilatory support (3).

This review will focus on pharmacological interventions to improve respiratory muscle function in patients with COPD. Detailed information will be provided on methylxanthines, /β2-adrenoceptor agonists (including clenbuterol), scavengers of reactive oxygen-derived species, anabolic steroids and growth hormone therapy. As for conceptual interest, relevant data from healthy subjects and from animal experiments will also be discussed.

Methylxanthines

The question whether methylxanthines improve respiratory muscle function in humans is a matter of ongoing dispute. This review will focus on human studies and recent new developments in animal experiments. The studies by Aubier et al. showed that theophylline improved respiratory muscle function in normal subjects (4) and COPD patients (Table I) (5,6). In contrast, other investigators, using different protocols in COPD patients, found no effect of theophyllines on respiratory muscle function or onset of fatigue (7–9). The question remains whether a beneficial effect of methylxanthines on respiratory muscle function is the result of direct stimulation of respiratory muscle contraction (intrinsic effect), since a reduction of trapped air volume and airway resistance was also observed (5,6).

Several recent studies, however, showed beneficial effects of methylxanthines in respiratory muscle dysfunction in specific circumstances. Firstly, in
### Table 1 Respiratory muscle pharmacotherapy in human studies: methylxanthines

<table>
<thead>
<tr>
<th>Healthy/COPD</th>
<th>Drug, dose, duration, design</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>Aminophylline i.v., single dose</td>
<td>Fresh and fatigued $Pdi \sim 15% \uparrow$ after infusion (at $\sim 13 \text{mg l}^{-1}$)</td>
<td>(4)</td>
</tr>
<tr>
<td>COPD</td>
<td>Theophylline 13 mg kg$^{-1}$ p.o., 7-30 days (Pl-c)</td>
<td>Fresh $Pdi 16% \uparrow$ at FRC, fatigue $\downarrow$ (at $\sim 13 \text{mg l}^{-1}$)</td>
<td>(5)</td>
</tr>
<tr>
<td>COPD</td>
<td>Theophylline 10 mg kg$^{-1}$ p.o., 2 months, (Pl-c, CO)</td>
<td>$Ppl/Ppl_{\text{max}} \downarrow$ (at $\sim 15 \text{mg l}^{-1}$)</td>
<td>(6)</td>
</tr>
<tr>
<td>COPD</td>
<td>Aminophylline 12 mg kg$^{-1}$ p.o., s.d. (Pl-c, CO)</td>
<td>$Pmax= (at \sim 15 \text{mg l}^{-1}$)</td>
<td>(8)</td>
</tr>
<tr>
<td>COPD</td>
<td>Theophylline 2.5 mg kg$^{-1}$ i.v., s.d. (Pl-c, CO)</td>
<td>$Pdi= (at \sim 5, 12 \text{ and } 19 \text{mg l}^{-1}$)</td>
<td>(7)</td>
</tr>
<tr>
<td>COPD</td>
<td>Theophylline p.o., 3 days (Pl-c CO)</td>
<td>Fresh and fatigued $Pdi= (at \sim 13 \text{mg l}^{-1}$)</td>
<td>(9)</td>
</tr>
<tr>
<td>Healthy</td>
<td>Aminophylline 6 mg kg$^{-1}$ loading – 0.9 mg kg$^{-1}$ h$^{-1}$ (Pl-c)</td>
<td>$Pdi$-sniff and $Pdi$-twitch $\uparrow$ after 'exhaustion', at 90% TLC $\sim 50$–60% $\uparrow Pdi; \text{ fresh } Pdi= (at \sim 14 \text{mg l}^{-1}$)</td>
<td>(11)</td>
</tr>
<tr>
<td>Healthy</td>
<td>Aminophylline 7.6 mg kg$^{-1}$ i.v. (Pl-c)</td>
<td>$Pdi$-twitch $\uparrow$ (fresh and fatigued); near TLC greater effect and prevention of disproportionate decrease in fatigue ($\sim$-two-fold increase in $Pdi$)</td>
<td>(15)</td>
</tr>
</tbody>
</table>

CO, cross-over study design; COPD, chronic obstructive pulmonary disease; FRC, functional residual capacity; $Pdi$, transdiaphragmatic pressure; $Pmax$, maximal inspiratory mouth pressure; Pl-c, placebo-controlled study design; $Ppl$, pleural pressure; rhGH, recombinant human growth hormone; s.d., single dose; TLC, total lung capacity; $\uparrow$, increase; $=$, no change; $\downarrow$, decrease.

**$\beta_2$-Adrenoceptor agonists**

**SHORT-ACTING $\beta_2$-ADRENOCEPTOR AGONISTS**

Respiratory muscles, like other skeletal muscles, contain $\beta$-adrenergic receptors, predominantly of the $\beta_2$-subtype. These $\beta_2$-adrenoceptors are present both in the muscle fibres and in resistance arterioles, regulating muscle blood flow (16,17).

The effects of short-acting $\beta_2$-adrenoceptor agonists on respiratory muscle function have been investigated in vivo in anaesthetized dogs (18-21). Intravenously administered salbutamol increased twitch transdiaphragmatic pressure ($Pdi$) during compensated metabolic acidosis (19). In fatigued diaphragm, $Pdi$ was not improved (18,20). However, terbutaline, in an i.v. dose of $\sim 25 \mu\text{g kg}^{-1}$, did increase $Pdi$ by 12–20% in fatigued, but not fresh, canine diaphragm both after direct and phrenic nerve stimulation (21). Similar findings were reported for fenoterol (22) and broxaterol (23).

To investigate whether salbutamol has a direct effect on rat diaphragm contractile properties, the effects of salbutamol were studied strictly in vitro and after s.c. administration. Salbutamol increased rat contractile properties at low, clinically relevant concentrations in fresh diaphragm (24). A possible explanation for the lack of effect of $\beta$-agonists on fresh diaphragm in the in vivo studies, in contrast to the increase in force generation found in vitro, could
Table 2  Respiratory muscle pharmacotherapy in human studies: $\beta_2$-adrenoceptor agonists

<table>
<thead>
<tr>
<th>Healthy/COPD</th>
<th>Drug, dose, duration, design</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>Salbutamol, 4 mg t.i.d. p.o., 3 days (Pl-c)</td>
<td>Pdi fresh and fatigued</td>
<td>(27)</td>
</tr>
<tr>
<td>Healthy</td>
<td>Salbutamol $\sim$ 0.05 µg kg$^{-1}$ min$^{-1}$ i.v. (Pl-c)</td>
<td>Pmax=, ventilatory endurance=</td>
<td>(28)</td>
</tr>
<tr>
<td>Healthy</td>
<td>Salbutamol, 8 mg b.i.d. p.o., 14–21 days (Pl-c)</td>
<td>Pmax 7 ± 2% † (14 days) and 15 ± 4% † (21 days)</td>
<td>(30)</td>
</tr>
<tr>
<td>COPD</td>
<td>Terbutaline, 2.5 mg t.i.d. p.o., 7 days (Pl-c, CO)</td>
<td>Pdi=, Pmax=</td>
<td>(32)</td>
</tr>
<tr>
<td>COPD</td>
<td>Terbutaline, 500–1500 µg q.i.d. inhaled, 7 days (Pl-c, CO)</td>
<td>Pmax=</td>
<td>(33)</td>
</tr>
<tr>
<td>Healthy</td>
<td>Terbutaline, s.d. 7.5 mg p.o. (Pl-c)</td>
<td>Pmax=</td>
<td>(29)</td>
</tr>
<tr>
<td>COPD</td>
<td>Broxaterol, 200 µg i.v., single dose (Pl-c)</td>
<td>Pmax=, endurance time at 70% Pmax †</td>
<td>(34)</td>
</tr>
<tr>
<td>COPD</td>
<td>Broxaterol, 0.5 mg t.i.d. p.o., 7 days (Pl-c, CO)</td>
<td>Pdi-twitch †, diaphragm fatigue †, endurance time at 60% Pmax †</td>
<td>(35)</td>
</tr>
<tr>
<td>Healthy</td>
<td>Fenoterol, s.d. 5 mg p.o. (Pl-c, CO)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For abbreviations, see Table 1.

be that $\beta$-agonists predominantly stimulate type II muscle fibre contraction, whereas during normal ventilatory manoeuvres in fresh diaphragm, slow motor units are recruited predominantly (25). Type II muscle fibres generate higher forces and fatigue more easily. In this way, the beneficial effect of $\beta$-agonist treatment on fatigued diaphragm could also be explained (21–23). In a recent experiment, it was found that, similar to the effects of methylxanthines, the inotropic effect of salbutamol was potentiated by foreshortening (26).

The effects of $\beta_2$-agonists on diaphragm function in healthy humans are contradicting (Table 2). Javaheri et al. found no effects of salbutamol on maximal Pdi in fresh or fatigued diaphragm after 3 days of oral treatment (4 mg t.i.d.) (27). Violante et al. reported that i.v. administration of salbutamol had no effect on maximal inspiratory mouth pressure (Pmax) and ventilatory endurance (28). Also, a single oral dose of 7.5 or 15 mg terbutaline did not improve Pmax in healthy subjects (29). In contrast, Martineau et al. reported a significant (7% and 15%) increase in Pmax after, respectively, 14 and 21 days of oral salbutamol treatment (8 mg b.i.d.) (30). Recently, Suzuki et al. reported that a single 5 mg oral dose of fenoterol administered to healthy subjects reduced diaphragmatic fatigue and decreased diaphragm motor command (measured by EMG); this resulted in a reduction of inspiratory effort sensation during inspiratory threshold loading and an increase in endurance (31).

In COPD patients, oral terbutaline administration (32), as well as terbutaline inhalation (33), did not improve Pdi (32) or Pmax (32,33). Treatment with broxaterol in COPD patients resulted in a ~17% increase in Pmax after i.v. administration (200 µg in 10 min) (34), but no increase in Pmax after 7 days of oral treatment (0.5 mg t.i.d.) (35). However, this last study did report an increased endurance (35). In contrast to the animal studies, all human studies used maximal voluntary contractions. This could partly explain the difference in positive effects of $\beta$-agonists in fatigued animal in contrast to the absence of effects in human diaphragm. Furthermore, the human diaphragm has a slightly different fibre type composition, but the total amount of oxidative fibres (type I and Ila) is approximately equal (~70% in rats and ~75% in humans) (36,37). Based on these observations, phrenic nerve stimulation seems essential to determine the effects of $\beta_2$-adrenoceptor agonists on respiratory muscle function in both healthy subjects and COPD patients.

LONG-ACTING $\beta_2$-ADRENOCEPTOR AGONISTS

Data with regard to the respiratory muscles' effects of the new long-acting $\beta_2$-adrenoceptor agonists salmeterol and formoterol in humans are not available. One study showed that salmeterol had growth stimulating effects in rat skeletal muscles (38). This effect, however, depended on the route of administration. After oral administration, a growth stimulating effect was found in high salmeterol dosages compared to low clenbuterol dosages, whereas after s.c. and i.p. administration, salmeterol and clenbuterol had approximately equal effects (38). Recently, a preliminary report showed an increase in costal diaphragm shortening in canines after salmeterol infusion (39).
CLENBUTEROL

Within the group of β₂-adrenoceptor agonists, clenbuterol has a special position. This β-agonist is lipophilic and has a long plasma half-life of elimination (approximately 30–35 h in humans). Research of clenbuterol effects on skeletal muscles mainly concentrated on muscle growth enhancement and reduction of fat deposition.

In peripheral skeletal muscles in normal rats, clenbuterol increased muscle cell growth and protein content in vitro (40) and in vivo (41). These growth effects were the result of β₂-adrenoceptor activation (42,43) with increased cAMP levels (44). Stimulation of skeletal muscle growth and metabolism by clenbuterol was also found in pathological situations including denervation (45,46), tenotomy (47), food deprivation (48) and low protein diet (49). In mdx mice, a model for (Duchenne) muscular dystrophy, clenbuterol increased skeletal muscle mass and diaphragm myosin concentration (50,51), and increased soleus muscle twitch force (Pt) and maximal tetanic force (Po) (52). Long-term treatment (1·6 mg kg⁻¹ day⁻¹ for 12 weeks) increased Pt and Po in soleus (SO), a muscle containing predominantly type I muscle fibres, and extensor digitorum longus (EDL), containing predominantly type II muscle fibres (53). However, the increase in force per cross-sectional area (CSA) was small (53). Histological examination showed hypertrophy of both muscles and a 40% increase in type II muscle fibre CSA in SO muscle. In EDL type I and II muscle fibres, the CSA was increased by 36 and 23%, respectively (53).

Little is known of the effect of clenbuterol on respiratory muscles. Prezant et al. reported that 1 mg kg⁻¹ b.i.d. resulted in hypertrophy of both type I and type II muscle fibres in rat diaphragm, but force generation in fresh diaphragm was reduced in female rats, and the fatigue index was reduced in both sexes (54). The effect of i.v. administered clenbuterol on Pdi in dogs was investigated by Numata et al. (20). They found a dose-dependent relationship in which 10 and 20 μg kg⁻¹ increased Pdi significantly (~7–20%) (20). Rothwell (42) reported a significant (approximately 2–3-fold) increase of diaphragm blood flow 1 h after administration of 1 mg kg⁻¹ s.c. in both chronically treated and control groups, but no effect of chronic clenbuterol treatment on diaphragm blood flow. Recently, Rollier et al. reported an increase of scalenus, gastrocnemius and SO muscle mass in male rats after 2 weeks of clenbuterol treatment in addition to inspiratory muscle training (55). In female rats, only parasternal intercostal mass was increased. No effects were found on diaphragm contractile properties and fatiguability, but type IIa muscle fibre CSA was significantly increased in female rats, and type IIb fibre CSA was significantly increased in both male and female rats (55). Clenbuterol treatment also increased diaphragm myosin content in mdx mice, but an increase in diaphragm fatiguability was also found after clenbuterol treatment in both mdx and control mice (51). There are no studies of the effect of clenbuterol on respiratory muscle function in healthy subjects, nor in patients with COPD. In one human study, Maltin reported an accelerated increase of quadriceps muscle strength after surgery (56).

In conclusion, β₂-adrenoceptor agonists could be useful in improving respiratory muscle function. Especially during fatigue, these agents may increase diaphragm contractility. Possibly, clenbuterol might be used to increase respiratory muscle mass.

Scavengers of Reactive Oxygen-derived Species

In skeletal muscles, a low level of reactive oxygen species (ROS) is essential for excitation–contraction coupling and is obligatory for optimal contractile function (57). Removal of hydrogen peroxide in fresh diaphragm strips using catalase, as well as removal of superoxide anions using superoxide dismutase (SOD), depressed diaphragm twitch force generation in vitro (57). This was reversed by addition of hydrogen peroxide (57). In fresh rat diaphragm, in vitro administration of either the hydroxyl scavenger, dimethyl sulphoxide (DMSO) (58), or N-acetylcysteine (NAC), which is a precursor of the anti-oxidant glutathione (GSH) (59), reduced Pt and submaximal tetanic force (58,59).

In case of excessive mechanical loads and fatigue of the respiratory muscles, the levels of ROS are increased, which may contribute to clinically relevant respiratory muscle dysfunction (60). In hamsters, several ROS scavengers were used to determine the contribution of different ROS in diaphragm and intercostal muscle dysfunction in endotoxin-mediated sepsis (61). Three scavengers had equal beneficial effects: the superoxide scavenger, polyethylene glycol-absorbed superoxide dismutase (PEG-SOD); the hydrogen peroxide scavenger, PEG-catalase; and the hydroxyl scavenger, DMSO (61). SOD, DMSO and catalase also inhibited low-frequency, but not high-frequency, fatigue in rat diaphragm (62). Pre-treatment with NAC (150 mg kg⁻¹ i.v.) attenuated the rate of fatigue development in rabbits (63). Reid et al. reported that NAC, concentration of 10 mm, not only inhibited acute fatigue, but also increased in vitro force production in fatigued rat diaphragm strips (59). Recovery
Table 3 Respiratory muscle pharmacotherapy in human studies: anabolic steroids

<table>
<thead>
<tr>
<th>Healthy/COPD</th>
<th>Drug, dose, duration, design</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>Nandrolone decanoate: 25 mg, 50 mg/2 weeks i.m., for 8 weeks (P1-c)</td>
<td>$P_{max}$ 19% ↑ in nutritionally depleted patients, in combination with nutritional support and a rehabilitation programme</td>
<td>(79)</td>
</tr>
</tbody>
</table>

For abbreviations, see Table 1.

From fatigue, however, was not improved (64). Recently, Supinski et al. showed that i.v. administration of NAC (150 mg kg$^{-1}$) increased diaphragm GSH and oxidized glutathione (GSSG) levels in rats exposed to massive inspiratory loading (65). This increased GSH level was accompanied by an approximately 60% increase in fatigue resistance in vitro, but NAC did not alter the time to respiratory arrest during loaded breathing (65). In humans, treatment with NAC (150 mg kg$^{-1}$ i.v.) attenuated the development of fatigue during low-frequency electrical stimulation in tibialis anterior muscle, and increased force output by ~ 15% during fatigue (66). Reports on the effects of reactive oxygen scavengers on human respiratory muscle (dys-)function are not available, except for one preliminary report (67). This pilot study reported an attenuating effect of NAC infusion on the development of diaphragm fatigue in two healthy subjects (67).

In summary, preliminary data suggests that lowering increased levels of ROS may be of clinical importance in critically ill patients and patients with overt or incipient respiratory muscle fatigue. Treatment with ROS scavengers could possibly increase respiratory muscle function in these circumstances, but this needs to be investigated.

Anabolic Steroids

Little is known of the effects of androgens on respiratory muscle function. Human studies have concentrated on peripheral skeletal muscle strength and shown that slight increases in strength are predominantly found in previously trained athletes taking anabolic steroids (68). In animals, treatment with anabolic steroids increased diaphragm muscle weight, percentage and relative CSA of type Ia muscle fibres, as well as capillary : fibre ratio and glycolytic capacity (69,70). Preliminary data in rats suggested that administration of nandrolone decanoate (1.5 and 7.5 mg kg$^{-1}$ week$^{-1}$ i.m.) did not increase respiratory muscle mass : body weight ratio in female rats, and contractile properties in the diaphragm were not altered (71). Also, in combination with inspiratory muscle training, no additive effects of nandrolone decanoate were found in rats (72). In contrast, a preliminary study using dehydroepiandrosterone (DHEA) reported an ~ 24% increase in $P_o$ in rat diaphragm, whereas fatigue index was not changed (73). Furthermore, in male hamsters, continuous s.c. administration of nandrolone significantly increased diaphragm isometric and isotonic contractile properties, and caused hypertrophy of all muscle fibre types, but did not change fatigue resistance (74).

Testosterone administration (9-12.5 mg kg$^{-1}$ day$^{-1}$, 5 days week$^{-1}$ i.m.) in rats increased diaphragm muscle mass and reduced fatigue resistance in female but not in male rats (75). Testosterone treatment increased diaphragm contractility in female rats alone after short-term (2-5 weeks), but not after long-term (10 weeks), treatment; no changes in fibre type proportion or area were found (75). In hamsters, continuous s.c. administration of testosterone for 6 weeks increased diaphragm optimal length, specific force production and relative contribution of type II fibres, but did not change fatigue resistance (76). In rabbits, in vivo administration of testosterone (20 mg kg$^{-1}$ day$^{-1}$, 14 days i.m.) reduced the effects of concomitant corticosteroid treatment (cortisone 10 mg kg$^{-1}$ day$^{-1}$ i.m.) on the diaphragm (77). Testosterone alone had no effect on diaphragmatic strength ($P_{di}$), endurance or biochemistry, but blunted the effects of cortisone on diaphragmatic endurance (77). In a recent experiment in the authors' laboratory, this effect was confirmed. Concomitant administration of nandrolone decanoate completely antagonized methylprednisolone-induced functional changes and partly reversed (immuno-) histochemical changes in rat diaphragm (78).

There is little data on the effects of anabolic steroids on respiratory muscle function in humans (Table 3). Schols et al. reported a significant increase (~ 19%) in $P_{max}$ in COPD patients with nutritional depletion receiving an 8-week treatment of nandrolone decanoate in combination with supplemental nutrition compared to placebo (79). All these patients participated in an intensive inpatient rehabilitation...
Table 4  Respiratory muscle pharmacotherapy in human studies: growth hormone

<table>
<thead>
<tr>
<th>Healthy/COPD</th>
<th>Drug, dose, duration, design</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>rhGH 0-05 mg kg⁻¹ day⁻¹ s.c. for 3 weeks</td>
<td>Pimax 27 ± 8% in malnourished patients, in combination with normally recommended diet</td>
<td>(87)</td>
</tr>
<tr>
<td>COPD</td>
<td>1 week of s.c. rhGH: 30 µg day⁻¹ (3 days) and 60 µg day⁻¹ (4 days)</td>
<td>Pimax = , in malnourished patients, in combination with total parenteral nutrition scheme</td>
<td>(88)</td>
</tr>
<tr>
<td>COPD</td>
<td>rhGH 0-15 U kg⁻¹ day⁻¹ s.c. for 3 weeks (Pl-c)</td>
<td>Pimax = , in underweight patients, in combination with in-hospital rehabilitation programme</td>
<td>(89)</td>
</tr>
<tr>
<td>Acute</td>
<td>rhGH 0-14 mg kg⁻¹ day⁻¹ s.c. for 12 days (Pl-c)</td>
<td>Duration of mechanical ventilatory support= , (critically ill patients with nutritional support)</td>
<td>(90)</td>
</tr>
</tbody>
</table>

For abbreviations, see Table 1.

programme, and the majority of these patients had concomitant corticosteroid medication.

In conclusion, the studies in normal animals found contradicting results and did not show conclusively that administration of anabolic agents improves respiratory muscle function. However, administration of these agents to malnourished, nutritionally depleted, COPD patients may increase respiratory muscle function. There could be a role for anabolic steroids in rebuilding the contractile apparatus but, more importantly, these agents may prove useful in preventing the deleterious effects of corticosteroids on respiratory muscles. This effect appears to be based on a competitive binding of androgens and corticosteroids to the steroid receptor (80).

### Growth Hormone Therapy

Patients with COPD, and particularly those with emphysema, are often underweight and malnourished (81-83). This condition is associated with increased mortality and morbidity, and a decrease in respiratory muscle function (83-86). Often these patients are unable to meet their increased nutritional demands. Besides dietary supplementation, growth hormone therapy may be considered, since this therapy has potent anabolic effects and enhances protein synthesis.

In a non-controlled study in seven malnourished COPD patients (Table 4), human recombinant growth hormone in a dose of 0-05 mg kg⁻¹ day⁻¹ in addition to a balanced diet increased Pimax by ~27% after 3 weeks of treatment (87). In contrast, 1 week of growth hormone treatment in addition to a 2-week parenteral nutrition treatment did not increase respiratory muscle function (88). Similarly, during a 3-week in-hospital rehabilitation period, growth hormone treatment did not increase Pimax (89). Finally, in critically ill patients undergoing prolonged mechanical ventilation, administration of growth hormone did not influence the duration of ventilatory support (90).

Contradicting results have also been reported in studies investigating the effects of nutritional repletion alone. Several studies found no effects of short-term re-feeding (91) or long-term supplemental feeding (92,93) on Pimax in malnourished COPD patients. In contrast, another study reported a ~35-40% increase in Pimax and Pdی after 3 weeks of nutritional repletion (94). Despite these contradictions, nutritional assessment and management is an important therapeutic modality that should be considered in the treatment of COPD patients (81,86).

In animal studies, administration of growth hormones did not prevent rat diaphragm fibre atrophy after acute nutritional deprivation (95), but did reverse the reduction CSA of all fibre types in moderate nutritional deprivation (96). Furthermore, growth hormone accelerated body growth and promoted a selective hypertrophy of IIX fibres (97). This IIX diaphragm fibre hypertrophy, however, was not accompanied by an increase in in vitro contractile properties (97). Further, in a study investigating the recovery from a 25% weight loss after nutritional deprivation, growth hormone administration in combination with re-feeding reversed the atrophy found in every type II muscle fibres in the rat diaphragm (98). In contrast, after re-feeding for 5-9 weeks without growth hormone administration, this return to control value CSA was only observed in I1a muscle fibres and not in type I1b or IIX fibres (98).

Growth hormone therapy might also be of value to prevent the side-effects of corticosteroid treatment on respiratory muscles. Administration of growth hormone prevented prednisone-induced protein catabolism both in healthy subjects treated with high doses of prednisone for 7 days, and in patients with chronic prednisone treatment (99,100). In contrast to...
these human data, growth hormone did not prevent the histochemical and functional changes in rat diaphragm induced by triamcinolone treatment (101).

This may be explained by the fact that triamcinolone treatment also reduced nutritional intake, which was not corrected (101).

In conclusion, growth hormone therapy may, similar to anabolic steroids, increase respiratory muscle mass and possibly prevent steroid-induced muscle wasting. However, the effects on respiratory muscle function in COPD patients with respiratory muscle weakness is not yet established.

Conclusions and Clinical Implications

In patients with severe COPD, several mechanisms impair the respiratory muscle function, whilst the workload of these muscles is already increased and their reserve capacity is reduced. Selective pharmacological interventions may be considered in the treatment of both acute and chronic respiratory muscle dysfunction. Based on the current data, several speculative recommendations may be formulated.

(1) When acute hyperinflation is the most prominent factor reducing respiratory muscle function, treatment with methylxanthines would be appropriate since, at normal plasma concentrations, Pdi was approximately doubled near TLC (15).

(2) In case of overt or developing respiratory muscle fatigue, further cellular damage may be prevented by administering ROS scavengers. Force generation could be increased in fatigued muscles by β2-adrenoceptor agonists and reactive oxygen scavengers in this acute situation. A Pdi increase could be expected of β-agonist treatment, whereas NAC has been shown to increase diaphragm fatigue resistance.

(3) Anabolic steroids and growth hormone therapy could possibly prevent deleterious effects of corticosteroids on respiratory muscles.

(4) The β2-adrenoceptor agonist clenbuterol might be useful in the treatment of chronic respiratory muscle failure by increasing respiratory muscle mass. It is clear, however, that further studies are necessary to determine the clinical benefit of these approaches.

Acknowledgement

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