Athletes and doping: effects of drugs on the respiratory system

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Doping is an area of ongoing public, legal, and medical debate and in recent years it has been reported to be connected with many sports including athletics, cycling, body building, soccer, and swimming. Ethical issues related to doping include the honesty of the sports competition and the safety of drugs and other methods applied to improve the physical performance. These issues are of increasing interest and importance since drugs on the prohibited list are easily accessible by medically uncontrolled means such as the Internet.

According to the International Olympic Committee (IOC)[1] doping consists of (1) the administration of substances belonging to prohibited classes of pharmacological agents and/or (2) the use of various prohibited methods. There are five prohibited classes of substances: stimulants, narcotics, anabolic agents, diuretics, and peptide and glycoprotein hormones and their analogues (table 1). Prohibited methods include blood doping and pharmacological, chemical and physical manipulation.

Several respiratory drugs are included in the list of prohibited substances unless they are administered by inhalation. This paper reviews the current literature concerning the effects of respiratory and some other drugs on the respiratory system in the broadest sense—that is, from the respiratory controllers to the respiratory muscles and the lungs themselves. We will focus on the effects in athletes and healthy trained and untrained subjects but, where appropriate, we will also refer to studies in patients, to animal studies, and to studies in peripheral skeletal muscles.

Can the function of the respiratory system be improved in athletes?

In general, the respiratory system does not limit maximal oxygen consumption ($\dot{V}O_2$max) in healthy subjects.[2 3] Only in highly trained endurance athletes may blood oxygen saturation fall during heavy exercise.[4 5]

The maximal sustainable ventilation decreases with time, and the level that can be sustained for more than 15 minutes corresponds to 55–80% of the maximal voluntary ventilation (MVV).[6] This reduction is probably caused by respiratory muscle fatigue, as indicated by a loss of maximal transdiaphragmatic pressure and a shift in the electromyographic (EMG) power spectrum.[7] Respiratory muscle fatigue indeed appears to occur in healthy subjects after strenuous exercise.[6 8] Loke *et al*[9] showed a significant reduction in respiratory muscle strength and endurance in athletes after completing a marathon. Similar changes occurred after cycling at 80% of maximal power output until exhaustion.[10] Induction of fatigue of the respiratory muscles prior to exercise (by prolonged isocapnic hyperpnoea) reduced subsequent endurance running time.[11] Improving respiratory muscle function in normal sedentary subjects by voluntary isocapnic hyperpnoea training was found to increase endurance exercise capacity at 62–75% of $\dot{V}O_2$max.[12] Healthy athletes have well trained respiratory muscles since whole body endurance conditioning has been shown to train the respiratory muscles as well.[13 14] However, additional respiratory muscle training further improved the breathing endurance of trained cyclists.[15 16] This improved breathing endurance did not improve high intensity cycle endurance[15–17] but increased cycle endurance at the anaerobic threshold in normal trained subjects.[18] These data from training studies suggest that there is some physiological room for improvement of the function of the respiratory system. Whether or not pharmacological

Table 1 Prohibited classes of substances and prohibited methods (shortened and adapted from IOC[1])

	Examples
Prohibited classes of substances	
A. Stimulants	Amphetamines, caffeine (urinary concentration >12 mg/ml), ephedrines Salbutamol, terbutaline, (permitted by inhaler)
B. Narcotics	Dextromoramide, dextropropoxyphene Diamorphine (heroin), methadone, morphine Pentazocine, pethidine
C. Anabolic agents	Clostebol, fluoxymesterone, metandienone, nandrolone, stanozolol, testosterone, clenbuterol, salbutamol, terbutaline salmeterol, fenoterol
D. Diuretics	Acetazolamide, bumetanide, chlorthalidone, etacrynic acid, furosemide, hydrochlorothiazide, mannitol, spironolactone, triamterene
E. Peptide and glycoprotein hormones	Human chorionic gonadotropin (hCG), corticotropin (ACTH), growth hormone (hGH) (somatotropin), erythropoietin (EPO)
Prohibited methods	
A. Blood doping	
B. Pharmaceutical, chemical and physical manipulation	Probenecid, epitestosterone

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interventions can improve this system, resulting in better exercise performance, is discussed below.

Prohibited substances

STIMULANTS

Amphetamine

Amphetamines are one of the most potent sympathicomimetic amines in stimulating the central nervous system (CNS).[19] They stimulate the medullary respiratory centre, lessen the degree of central depression caused by various drugs, and increase arousal[20] which might increase ventilation.[21] They bind to α and β adrenergic receptors and exert similar effects to catecholamines such as increased blood pressure, heart rate, and metabolic rate. Amphetamines increase the plasma free fatty acid (FFA) concentration in healthy subjects, mediated by endogenous catecholamine release.[22] Increased concentrations of plasma FFA may have a skeletal muscle glycogen sparing effect and thereby delay the onset of fatigue. Because of the stimulatory effects, it is hypothesised that these drugs may enhance all types of performance.[20]

Limited data are available regarding the effects of amphetamine on the respiratory system. Theoretically, increased arousal or decreased perception of fatigue may increase ventilation. However, it is not known whether exercise performance is enhanced by stimulation of the respiratory system with amphetamines.

Chandler and Blair[23] compared the effects of amphetamines and placebo in six recreationally trained athletes and found significant improvements in knee extension strength, sprint acceleration, and anaerobic capacity. Time to exhaustion and maximal heart rate were also increased after amphetamine administration. Since lactic acid and exercise endurance significantly increased during a maximal exercise test while $\dot{V}O_2$ was not affected, this indicates that, after amphetamine administration, the subjects were able to maintain exercise longer under anaerobic conditions. Thus, amphetamines do not delay fatigue but rather mask its effects, as previously shown in soldiers.[24] Amphetamine sulfate in a dose of 14 mg/70 kg body weight or placebo were administered to highly trained subjects 2–3 hours before exercise.[20] Several exercise tests were performed by 18 swimmers, 26 runners and 13 weight throwers; 73% of the runners, 85% of the weight throwers, and 67–93% of the swimmers performed better with amphetamines than with placebo. With the amphetamine the athletes felt "revved up" before the exercise test and perceived that they had improved coordination, strength, and endurance.[25] In an open study Karpovich *et al*[26] investigated the effects of 10–20 mg amphetamine on exercise performance in untrained individuals. There were no or only minor effects on treadmill run to exhaustion, distance running, and swims of various distances. Thus, the beneficial effects of amphetamines on exercise performance appear to result, at least partially, from masking pain and/or fatigue.

Caffeine

Caffeine is a methylated xanthine alkaloid derivative (1,3,7-trimethylxanthine) which is present in coffee, soft drinks, and many non-prescription drugs. The use of caffeine as an ergogenic substance by athletes has been popular over the years, although the legality of caffeine in athletes has been controversial. The IOC classified caffeine as a doping agent in 1962, removed it from the list of banned substances in 1972, and currently has classified it as a restricted drug (positive at >12 mg/ml in urine).

In vitro studies indicate a variety of effects for caffeine including the inhibition of phosphodiesterase, resulting in increased intracellular concentrations of the second messenger cAMP and alteration of the intracellular translocation of calcium via the ryanodine receptor. Although the concentration of caffeine needed to elicit calcium release through the ryanodine receptor mediated calcium release channel is high, it has recently been shown that cyclic ADPribose can potentiate the effect of caffeine on the calcium induced calcium release mechanism.[27] This indicates that physiological doses of caffeine could alter calcium availability via ryanodine receptors in peripheral and respiratory skeletal muscle and thus excitation-contraction coupling. At pharmacologically relevant concentrations caffeine blocks adenosine receptors. This explains the CNS stimulant, diuretic, metabolic, and cardiac effects of the methylxanthines.[27]

The major respiratory effect of caffeine is an increased output of the respiratory centre. In healthy subjects caffeine significantly increases ventilation at rest, accompanied by a fall in end tidal carbon dioxide tension (P_{CO_2}).[28] Caffeine also increases the metabolic rate at rest, as indicated by increases in both $\dot{V}O_2$ and $\dot{V}CO_2$. $\dot{V}O_2$ and $\dot{V}CO_2$ at moderate exercise were significantly higher after ingestion of caffeine compared with placebo. In healthy subjects caffeine significantly increased task endurance time and reduced the perception of fatigue during inspiratory resistive breathing.[29]

In healthy recreationally trained subjects caffeine ingestion (6–9 mg/kg) attenuated exercise induced increases in the plasma potassium concentration ($[K^+]$).[30] Increased extracellular $[K^+]$ impairs force generation in skeletal muscles in vitro.[31] Potentially, a reduction in plasma $[K^+]$ during exercise by caffeine may delay the onset of skeletal, and possibly respiratory, muscle fatigue and thereby improve exercise performance.

Caffeine increases fat mobilisation and subsequently spares muscle glycogen stores during exercise. The glycogen sparing effect of caffeine is relevant to athletes performing exercise at intensities of 65–85% of $\dot{V}O_2$max since, in this range of exercise intensity, glycogen depletion is a major cause of fatigue.[32] Indeed, a profound glycogen sparing effect was observed after caffeine ingestion (9 mg/kg) in recreationally trained subjects performing exhaustive cycle ergometry at about 80% $\dot{V}O_2$max.[33] The glycogen content of the vastus lateralis muscle 15 minutes after initiation of

exercise was significantly higher after ingestion of caffeine than after placebo. Exercise endurance was also significantly prolonged after caffeine ingestion. If this "glycogen sparing" effect is the only mechanism by which caffeine influences exercise capacity, then caffeine ingestion should have no effect on short term intense exercise since, under these conditions, energy is mainly provided by anaerobic metabolism.[34] The "glycogen sparing hypothesis" was shown to be flawed by Jackman *et al*[35] who found that caffeine, in comparison to placebo, spared vastus lateralis muscle lactate and glycogen during short term intense exercise in recreationally trained subjects. Thus, caffeine increased exercise endurance under circumstances where muscle glycogen availability was not the limiting factor since, at the end of this type of exercise, sufficient glycogen was present within the skeletal muscles.

Since no data are available on the glycogen content of the human diaphragm after an acute bout of exercise, it is difficult to speculate on the beneficial effects of glycogen sparing in the performance of the respiratory muscles. Animal studies have shown severe reductions in the glycogen content of the diaphragm after an acute bout of exhaustive exercise, although at fatigue glycogen was not completely depleted in the diaphragm.[36 37] It is therefore doubtful that caffeine will enhance respiratory muscle function by its glycogen sparing properties.

In a study of six healthy subjects, in whom data on training status were not provided, caffeine did not affect maximal voluntary capacity (MVC).[38] However, a small increase (~4.3%) was observed in the force produced at 20 Hz stimulation. Caffeine did not affect PImax or PEmax. In this crossover trial caffeine increased MVC, both before and after fatiguing stimulations, but did not affect recovery after fatigue. It is therefore unlikely that caffeine affects respiratory muscle performance to a significant degree.

Data on general exercise capacity are conflicting. In highly active subjects maximal exercise capacity after an endurance exercise was not improved by caffeine.[39] In contrast, Jackman *et al*[35] investigated the effects of caffeine ingestion (6 mg/kg) on short term cycle ergometry. Recreationally trained athletes performed two cycle ergometry bouts of two minutes duration requiring $\dot{V}O_2$max and one cycle ergometry bout at the same power output until voluntary exhaustion. After each test six minutes rest was allowed. Caffeine ingestion significantly increased exercise endurance (4.12 (0.36) min vs 4.93 (0.60) min with placebo and caffeine, respectively).

Thus, major effects of caffeine on exercise capacity have not been found, although some small (but, in competitive sports, important) effects may be present.

Other prohibited sympathicomimetic drugs

Phenylpropanolamine and ephedrine are chemically related to amphetamine. Phenylpropanolamine is used for the relief of nasal congestion. The pharmacological actions of phenylpropanolamine and ephedrine are equal in potency except that the former is a less potent CNS stimulant.[19] Both substances have direct and indirect effects on adrenergic receptors. They act indirectly by releasing neurotransmitters from storage sites in the sympathetic nerves to the effector organ.[27] Ephedrine is both an α and β adrenergic agonist and, in addition, it enhances the release of noradrenaline (norepinephrine) from sympathetic neurons. It activates β adrenergic receptors in the lung and thereby promotes bronchodilation, and it is also a potent CNS stimulant.[19] However, 1 mg/kg ephedrine given to healthy subjects did not affect ventilation at rest or during cycle ergometry exhaustive exercise.[40] In a placebo controlled study administration of 60 or 120 mg ephedrine had no effect on the time to reach 85% predicted maximum heart rate, blood pressure, or recovery heart rate.[41] The lack of effect of (pseudo)ephedrine on exercise performance has also been reported in other studies.[40 42 43]

β_2 adrenergic drugs

The IOC has classified β_2 agonists as both anabolic and stimulant agents. Animal studies have shown that, after intravenous administration, the concentration of intact clenbuterol in the brain was 0.7 times that in the plasma, whereas the concentration of salbutamol given under the same conditions was not measurable in the brain.[44] Other animal studies have also found low penetration of albuterol in the brain compared with other tissues.[45] Since no human studies have been published on the effects of β_2 receptor stimulation on the CNS, it is not clear whether these drugs have any effect in this respect in humans.

ANABOLIC AGENTS

β_2 adrenoceptor agonists

$Beta_2$ adrenoceptor agonists such as clenbuterol and salbutamol exhibit anabolic properties. From animal studies it appears that clenbuterol has anti-catabolic effects resulting in skeletal muscle hypertrophy. In addition, a shift towards fast twitch skeletal muscle fibres has been observed, facilitating heavy and rapid contractions (like weight lifting).

Several studies have shown that β_2 adrenoceptor agonists administered orally, intravenously or intramuscularly in high doses may increase skeletal muscle mass or function in animals. In humans a limited number of studies have been published investigating oral or intravenous administration of β_2 adrenoceptor agonists.[46–51] Salbutamol in an oral daily dose of 16 mg increased isokinetic quadriceps force after three[49] and nine weeks of treatment.[46] Ventilatory endurance and PImax were also increased by salbutamol treatment.[49] Clenbuterol in a dose of 20 μg twice daily for four weeks improved rehabilitation of quadriceps force after knee surgery.[48]

In contrast, it has never been shown that *inhalation* of the β_2 adrenoceptor agonists salbutamol or salmeterol increases the performance of healthy or asthmatic athletes.[52–58] These drugs may[53] or may not improve ventilatory capacity in healthy subjects,[52 55 57] but there are

no data showing that bronchodilation in these healthy subjects improves exercise capacity. To the best of our knowledge no studies have been published on the effects of terbutaline, fenoterol, or formoterol on exercise capacity, but there is no apparent reason to believe that inhalation of these drugs would result in ergogenic effects. Indeed, inhalation of these short and long acting β_2 adrenoceptor agonists has been permitted by the IOC, with the unexplained and illogical exception of formoterol.

When administered orally or parenterally clenbuterol has a special position within the group of β_2 adrenoceptor agonists, having the most prominent anabolic effect, being lipophilic, and having a long duration of action (30–35 hours in humans). The anabolic effects of clenbuterol are mediated via β_2 adrenoceptor activation with subsequent cAMP response.[59] The precise mechanism of action of the clenbuterol mediated growth stimulating effect is not clear but it appears not to be mediated by growth hormone or thyroid stimulation nor by increased insulin levels.[60] Several studies have reported that increased muscle growth was accompanied by an increase in protein and RNA content and increased protein synthesis (indicated by an increased RNA:protein ratio).[60 61] A reduction in protein degradation was suggested in another study.[62]

Similar muscle growth potentiating effects were found for salmeterol, another long acting β_2 agonist, by Moore *et al*.[59] The size of this effect depended on the route of administration. In this study the anabolic potency of clenbuterol and salmeterol, given in equimolar doses, was compared in rats. When administered orally the anabolic potency of salmeterol at a very high dose of 2.4 mg/day was comparable to the effect of clenbuterol at a dose of 97 µg/day but, when administered intravenously, salmeterol and clenbuterol had similar anabolic effects at equal doses (130 µg/day and 100 µg/day, respectively). Since the anabolic effects of short acting β_2 adrenoceptor agonists such as salbutamol, fenoterol, or terbutaline are much less pronounced,[60 61 63 64] it is likely that a long duration of action is needed to induce these anabolic effects.

The mechanism by which these β_2 adrenoceptor agonists increase skeletal muscle function is still being investigated. There is evidence that the β_2 agonist salbutamol may increase sarcoplasmic reticulum Ca^{2+} release.[65] Animal studies have also indicated that β_2 adrenoceptor agonists like salbutamol, salmeterol, and clenbuterol may enhance diaphragm muscle contractile properties in vitro.[66–70] However, it is not known if this stimulatory action on the diaphragm muscle found in vitro has any effect on exercise capacity or endurance in healthy subjects.

Anabolic steroids

When androgens became available in the 1930s they were used primarily to restore a positive nitrogen balance in victims of starvation. Anabolic steroids were developed to avoid unwanted effects of androgen treatment. Various mechanisms of action of anabolic steroids have been described. Anabolic steroids promote amino acid incorporation into muscle proteins, reduce amino acid catabolism, and cause nitrogen retention and tissue growth.[71] This results in an increase in muscle protein synthesis and an increase in myosin and myofibrillar protein fraction which theoretically leads to an increase in muscle performance. Indeed, supraphysiological doses of nandrolone decanoate increased specific force and shortening velocity in the diaphragm of male rats.[72] This is caused by hypertrophy of muscle fibres and an increase in cross bridge turnover.[72] Anabolic steroids also improve the recovery of the force generating capacity produced following muscle contusion injury in a rat model.[73]

Several efforts have been made to show the beneficial effects of anabolic agents in humans. In malnourished patients suffering from chronic obstructive pulmonary disease (COPD) nandrolone decanoate was beneficial in regaining respiratory muscle strength.[74] Recent data showed an improvement in expiratory and inspiratory muscle strength following treatment with oxandrolone in patients with tetraplegia.[75] This increase in muscle strength was attributed to the observed increase in diaphragm muscle mass and resulted in an increased vital capacity. Basin and co-workers showed a beneficial effect of a high dose of testosterone on fat free body mass, muscle size, and peripheral muscle strength in normal men.[76] During the 1970s and 1980s several studies were performed to investigate the additional effects of anabolic steroids on a training programme in healthy athletes. The results of these studies varied from no additional effect on muscle force production and no improvement in aerobic capacity[77 78] to a small but significant increase in muscle force.[79 80] All these studies were performed in men. Little is known about the effects of anabolic steroids in women.

From these studies it can be concluded that anabolic agents are able to increase skeletal muscle force production only when administered in supraphysiological doses or, at least in some cases, in combination with excessive training.

PEPTIDE AND GLYCOPROTEIN HORMONES

Human growth hormone (hGH)

Human growth hormone (hGH) or somatotropin stimulates protein synthesis and inhibits glucose utilisation through promotion of lipolysis. It promotes tissue growth via nitrogen retention and increases transport of amino acids into tissues.[81] There is no evidence that hGH increases muscle mass or strength.[82]

Administration of hGH lowers body fat and increases fat-free mass (FFM).[83 84] Body composition and physical performance improve with hGH in patients with growth hormone deficiency.[85] Animal studies have shown an increase in the size and strength of atrophied muscles, but no effect on normal muscle.[86] When given in a dose of 0.09 U/kg/day for six weeks to 22 male power athletes hGH caused no significant change in maximal biceps or quadriceps strength, body weight, or body fat.[87]

Table 2 Respiratory drugs permitted by the IOC (shortened and adapted from IOC[1])

Short acting β_2 adrenoceptor agonists*
Fenoterol
Salbutamol
Terbutaline
Long acting β_2 adrenoceptor agonists*
Salmeterol
Anticholinergics
Ipratropium bromide
Methylxanthines
Aminophylline
Choline theophyllinate
Theophylline
Cromones
Sodium cromoglicate
Inhaled corticosteroids**
Beclometasone dipropionate
Budesonide
Fluticasone
Expectorants and cough suppressants
Bromhexine
Dextromethorphan
Codeine
Antihistamines
All known types

* "Permitted by inhaler only to prevent and/or treat asthma and exercise induced asthma. Written notification of asthma and/or exercise induced asthma by a respiratory or team physician is necessary to the relevant medical authority".[1]
** By inhalation and by nasal administration.

In a study by Yarasheski *et al*[88] untrained individuals were given 40 µg/kg/day hGH or placebo for 12 weeks and participated in a heavy resistance training programme. Quadriceps muscle protein synthesis rate, torso and limb circumferences, and the increase in muscle strength (concentric and isometric knee muscle forces) were similar in the two groups, the whole body protein synthesis rate increased more and the whole body protein balance was greater in the hGH treated group, and FFM and total body water increased more after hGH, probably due to an increase in lean tissue other than skeletal muscle.

Yarasheski *et al*[89] reported that resistance exercise training improved muscle strength, muscle mass, and anabolism in older men, but these improvements were not enhanced when exercise was combined with daily hGH administration. No significant increase in the fractional rate of muscle protein synthesis was observed compared with placebo. There was an increase in FFM with hGH treatment which may have been due to an increase in non-contractile protein and fluid retention.[89]

In another study Yarasheski *et al*[90] found that short term hGH administration did not increase the fractional rate of skeletal muscle protein synthesis, as measured by stable labelled leucine incorporation into vastus lateralis muscle protein in young experienced weight lifters. The whole body protein breakdown rate measured after two weeks of treatment with hGH was the same as before treatment.

Permitted pulmonary drugs

Many respiratory drugs are permitted by the IOC but, in certain cases, they need to be accompanied by a written notification. A list of these medications is shown in table 2.

Conclusions

The studies discussed in this paper show diversity in response to several respiratory and other drugs. In most cases it is not clear whether a beneficial effect on exercise capacity is due to an improvement in the central respiratory controllers, the respiratory muscles, and/or the peripheral muscles. Masking the sensation of (muscle) fatigue seems to be an important determinant of improved performance.

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