Athletes and doping: effects of drugs on the respiratory system

P N R Dekhuijzen, H A Machiels, L M A Heunks, H F M van der Heijden, R H H van Balkom

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 ($\dot{V}O_{2max}$)

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 $\dot{V}O_{2max}$.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 IOC¹)

	Examples
<i>Prohibited classes of substances</i>	
A. Stimulants	Amphetamines, caffeine (urinary concentration >12 mg/ml), ephedrine Salbutamol, terbutaline, (permitted by inhaler) Dextromoramide, dextropropoxyphene
B. Narcotics	Diamorphine (heroin), methadone, morphine Pentazocine, pethidine
C. Anabolic agents	Clostellol, 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)
<i>Prohibited methods</i>	
A. Blood doping	
B. Pharmaceutical, chemical and physical manipulation	Probenecid, epitestosterone

Department of Pulmonary Diseases, Academic Hospital Nijmegen, P O Box 9101, 6500 HB Nijmegen, The Netherlands
P N R Dekhuijzen
H A Machiels
L M A Heunks
H F M van der Heijden
R H H van Balkom

Correspondence to: Dr P N R Dekhuijzen.

Received 10 June 1999
Accepted for publication 12 July 1999

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 arousal²⁰ 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 Blair²³ 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 $\dot{V}O_{2max}$ 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% $\dot{V}O_{2max}$.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 P_{max} or P_{Emax}. 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 $\dot{V}O_{2max}$ 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

Beta₂ 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 three⁴⁹ and nine weeks of treatment.⁴⁶ Ventilatory endurance and P_{max} were also increased by salbutamol treatment.⁴⁹ Clenbuterol in a dose of 20 μ g 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 may⁵³ 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 μ g/day but, when administered intravenously, salmeterol and clenbuterol had similar anabolic effects at equal doses (130 μ g/day and 100 μ g/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 IOC¹)

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**
Beclomethasone 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 $\mu\text{g/kg/day}$ 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.

The authors are grateful to the Dutch Asthma Foundation (grants nos. 95-30, 97-34 and 92-17), Glaxo Wellcome, The Netherlands (grants nos. 92-013 and 97-026), and the Van Walree Foundation of the Royal Dutch Academy of Arts and Sciences for financial support.

- 1 International Olympic Committee. *List of classes of prohibited substances and methods of doping*. 1999.
- 2 Dempsey JA, J. B. Wolffe memorial lecture. Is the lung built for exercise? *Med Sci Sports Exerc* 1986;**18**:143-55.
- 3 di Prampero PE, Ferretti G. Factors limiting maximal oxygen consumption in humans. *Respir Physiol* 1990;**80**:113-27.
- 4 Dempsey JA, Hanson PG, Henderson KS. Exercise-induced arterial hypoxaemia in healthy human subjects at sea level. *J Physiol Lond* 1984;**355**:161-75.
- 5 Williams JH, Powers SK, Stuart MK. Hemoglobin desaturation in highly trained athletes during heavy exercise. *Med Sci Sports Exerc* 1986;**18**:168-73.
- 6 Leith DE, Bradley M. Ventilatory muscle strength and endurance training. *J Appl Physiol* 1976;**41**:508-16.
- 7 Bai TR, Rabinovitch J, Pardy RL. Near-maximal voluntary hyperpnea and ventilatory muscle function. *J Appl Physiol* 1984;**57**:1742-8.
- 8 Bye PT, Farkas GA, Roussos C. Respiratory factors limiting exercise. *Annu Rev Physiol* 1983;**45**:439-51.
- 9 Loke J, Mahler DA, Virgulto JA. Respiratory muscle fatigue after marathon running. *J Appl Physiol* 1982;**52**:821-4.
- 10 Bye PT, Esau SA, Walley KR, *et al.* Ventilatory muscles during exercise in air and oxygen in normal men. *J Appl Physiol* 1984;**56**:464-71.
- 11 Martin B, Heintzelman M, Chen HI. Exercise performance after ventilatory work. *J Appl Physiol* 1982;**52**:1581-5.
- 12 Boutellier U, Piwko P. The respiratory system as an exercise limiting factor in normal sedentary subjects. *Eur J Appl Physiol* 1992;**64**:145-52.
- 13 Gimenez M, Cereceda V, Teculescu D, *et al.* Square-wave endurance exercise test (SWEET) for training and assessment in trained and untrained subjects. III. Effect on $\dot{V}_{O_{2\max}}$ and maximal ventilation. *Eur J Appl Physiol* 1982;**49**:379-87.
- 14 Casaburi R, Storer TW, Wasserman K. Mediation of reduced ventilatory response to exercise after endurance training. *J Appl Physiol* 1987;**63**:1533-8.
- 15 Morgan DW, Kohrt WM, Bates BJ, *et al.* Effects of respiratory muscle endurance training on ventilatory and endurance performance of moderately trained cyclists. *Int J Sports Med* 1987;**8**:88-93.
- 16 Fairbairn MS, Coutts KC, Pardy RL, *et al.* Improved respiratory muscle endurance of highly trained cyclists and the effects on maximal exercise performance. *Int J Sports Med* 1991;**12**:66-70.
- 17 Hanel B, Secher NH. Maximal oxygen uptake and work capacity after inspiratory muscle training: a controlled study. *J Sports Sci* 1991;**9**:43-52.
- 18 Boutellier U, Buchel R, Kundert A, *et al.* The respiratory system as an exercise limiting factor in normal trained subjects. *Eur J Appl Physiol* 1992;**65**:347-53.
- 19 Hoffman BB, Lefkowitz RJ. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, eds. *The pharmacological basis of therapeutics*. New York: McGraw-Hill, 1996; 199-237.
- 20 Clarkson PM, Thompson HS. Drugs and sport. Research findings and limitations. *Sports Med* 1997;**24**:366-84.
- 21 Folgering H. Studying the control of breathing in man. *Eur Respir J* 1988;**1**:651-60.
- 22 Pinter EJ, Pattee CJ. Fat-mobilizing action of amphetamine. *J Clin Invest* 1968;**47**:394-402.
- 23 Chandler JV, Blair SN. The effect of amphetamines on selected physiological components related to athletic success. *Med Sci Sports Exerc* 1980;**12**:65-9.
- 24 Cuthbertson DP, Knox JAC. The effects of analeptics on the fatigued subject. *J Physiol* 1947;**106**:42-58.
- 25 Smith GM, Beecher HK. Amphetamine, secobarbital, and athletic performance. *JAMA* 1960;**172**:1502-14.
- 26 Karpovich PV. Effect of amphetamine sulfate on athletic performance. *JAMA* 1959;**170**:558-61.
- 27 Dollery C. *Therapeutic drugs*. Edinburgh: Churchill Livingstone, 1999.
- 28 D'Urzo AD, Jhirad R, Jenne H, *et al.* Effect of caffeine on ventilatory responses to hypercapnia, hypoxia, and exercise in humans. *J Appl Physiol* 1990;**68**:322-8.
- 29 Supinski GS, Levin S, Kelsen SG. Caffeine effect on respiratory muscle endurance and sense of effort during loaded breathing. *J Appl Physiol* 1986;**60**:2040-7.
- 30 Lindinger MI, Graham TE, Spriet LL. Caffeine attenuates the exercise-induced increase in plasma $[\text{K}^+]$ in humans. *J Appl Physiol* 1993;**74**:1149-55.
- 31 Cairns SP, Hing WA, Slack JR, *et al.* Different effects of raised $[\text{K}^+]$, on membrane potential and contraction in mouse fast- and slow-twitch muscle. *Am J Physiol* 1997;**273**:C598-611.

- 32 Hultman E. Nutritional effects on work performance. *Am J Clin Nutr* 1989;49:949–57.
- 33 Spriet LL, MacLean DA, Dyck DJ, et al. Caffeine ingestion and muscle metabolism during prolonged exercise in humans. *Am J Physiol* 1992;262:E891–8.
- 34 Cheetham ME, Boobis LH, Brooks S, et al. Human muscle metabolism during sprint running. *J Appl Physiol* 1986;61:54–60.
- 35 Jackman M, Wendling P, Friars D, et al. Metabolic catecholamine and endurance responses to caffeine during intense exercise. *J Appl Physiol* 1996;81:1658–63.
- 36 Green HJ, Ball Burnett ME, Morrissey MA, et al. Fiber type specific glycogen utilization in rat diaphragm during treadmill exercise. *J Appl Physiol* 1987;63:75–83.
- 37 Haldi H, Wynn W. Action of drugs on efficiency of swimmers. *Res Q Exerc Sport* 1946;17:17–96.
- 38 Lanigan C, Howes TQ, Borzone G, et al. The effects of beta 2-agonists and caffeine on respiratory and limb muscle performance. *Eur Respir J* 1993;6:1192–6.
- 39 Wemple RD, Lamb DR, McKeever KH. Caffeine vs caffeine-free sports drinks: effects on urine production at rest and during prolonged exercise. *Int J Sports Med* 1997;18:40–6.
- 40 Bell DG, Jacobs I, Zamecnik J. Effects of caffeine, ephedrine and their combination on time to exhaustion during high-intensity exercise. *Eur J Appl Physiol* 1998;77:427–33.
- 41 Bright TP, Sandage BW Jr, Fletcher HP. Selected cardiac and metabolic responses to pseudoephedrine with exercise. *J Clin Pharmacol* 1981;21:488–92.
- 42 Clemons JM, Crosby SL. Cardiopulmonary and subjective effects of a 60 mg dose of pseudoephedrine on graded treadmill exercise. *J Sports Med Phys Fitness* 1993;33:405–12.
- 43 Gillies H, Derman WE, Noakes TD, et al. Pseudoephedrine is without ergogenic effects during prolonged exercise. *J Appl Physiol* 1996;81:2611–7.
- 44 Saux MC, Girault J, Bouquet S, et al. Comparative study of the tissue distribution of two beta-mimetics: clenbuterol and salbutamol in the dog. *J Pharmacol* 1986; 17:692–8.
- 45 Caccia S, Fong MH. Kinetics and distribution of the beta-adrenergic agonist salbutamol in rat brain. *J Pharm Pharmacol* 1984;36:200–2.
- 46 Caruso JF, Signorile JF, Perry AC, et al. The effects of albuterol and isokinetic exercise on the quadriceps muscle group. *Med Sci Sports Exerc* 1995;27:1471–6.
- 47 Malerba M, Boni E, Tantucci C, et al. Ineffectiveness of intravenous beta₂-agonists on improving exercise tolerance in patients with reversible chronic airway obstruction. *Respiration* 1996;63:8–16.
- 48 Maltin CA, Delday MI, Watson JS, et al. Clenbuterol, a β -adrenoceptor agonist, increases relative muscle strength in orthopaedic patients. *Clin Sci* 1993;84:651–4.
- 49 Martineau L, Horan MA, Rothwell NJ, et al. Salbutamol, a β_2 -adrenoreceptor agonist, increases skeletal muscle strength in young men. *Clin Sci* 1992;83:615–21.
- 50 Violante B, Pellegrino R, Vinay C, et al. Failure of aminophylline and salbutamol to improve respiratory muscle function and exercise tolerance in healthy humans. *Respiration* 1989;55:227–36.
- 51 van der Heijden HFM, Dekhuijzen PNR, Folgering HTM, et al. Pharmacotherapy of respiratory muscles in chronic obstructive pulmonary disease. *Respir Med* 1996;90:513–22.
- 52 Freeman W, Packe GE, Cayton RM. Effect of nebulised salbutamol on maximal exercise performance in men with mild asthma. *Thorax* 1989;44:942–7.
- 53 Lemmer JT, Fleck SJ, Wallach JM, et al. The effects of albuterol on power output in non-asthmatic athletes. *Int J Sports Med* 1995;16:243–9.
- 54 McDowell SL, Fleck SJ, Storms WW. The effects of salmeterol on power output in nonasthmatic athletes. *J Allergy Clin Immunol* 1997;99:443–9.
- 55 Meeuwisse WH, McKenzie DC, Hopkins SR, et al. The effect of salbutamol on performance in elite nonasthmatic athletes. *Med Sci Sports Exerc* 1992;24:1161–6.
- 56 Morton AR, Joyce K, Papalia SM, et al. Is salmeterol ergogenic? *Clin J Sport Med* 1996;6:220–5.
- 57 Morton AR, Papalia SM, Fitch KD. Is salbutamol ergogenic? The effects of salbutamol on physical performance in high-performance nonasthmatic athletes. *Clin J Sport Med* 1992;2:93–7.
- 58 Norris SR, Petersen SR, Jones RL. The effect of salbutamol on performance in endurance cyclists. *Eur J Appl Physiol* 1996;73:364–8.
- 59 Moore NG, Pegg GG, Sillence MN. Anabolic effects of the β_2 -adrenoceptor agonist salmeterol are dependent on route of administration. *Am J Physiol* 1994;267:E475–84.
- 60 Emery PW, Rothwell NJ, Stock MJ, et al. Chronic effects of β_2 -adrenergic agonists on body composition and protein synthesis in the rat. *Biosci Rep* 1984;4:83–91.
- 61 Choo JJ, Horan MA, Little RA, et al. Anabolic effects of clenbuterol on skeletal muscle are mediated by β_2 -adrenoceptor activation. *Am J Physiol* 1992;263:E50–6.
- 62 Reeds PJ, Hay SM, Dorwood PM, et al. Stimulation of muscle growth by clenbuterol: lack of effect on muscle protein biosynthesis. *Br J Nutr* 1986;56:249–58.
- 63 Hall IP, Woodhead MA, Johnston IDA. Effect of high-dose salbutamol on cardiac rhythm in severe chronic airflow obstruction: a controlled study. *Respiration* 1994;61:214–8.
- 64 Reeds PJ, Hay SM, Dorwood PM, et al. The effect of β -agonists and antagonists on muscle growth and body composition of young rats (*Rattus* sp.). *Comp Biochem Physiol* 1988;89C:337–41.
- 65 Prakash YS, van der Heijden HFM, Gallant EM, et al. Effects of salbutamol on intracellular Ca^{2+} regulation in skeletal myotubes. *Am J Physiol* 1999;276:C1038–45.
- 66 van der Heijden HFM, Dekhuijzen PNR, Folgering H, et al. Long-term effects of clenbuterol on diaphragm morphology and contractile properties in emphysematous hamsters. *J Appl Physiol* 1998;85:215–22.
- 67 van der Heijden HFM, Dekhuijzen PNR, Folgering H, et al. Inotropic effects of salbutamol on rat diaphragm contractility are potentiated by foreshortening. *Am J Respir Crit Care Med* 1997;155:1072–9.
- 68 van der Heijden HFM, Heunks LMA, Folgering H, et al. β_2 -Adrenoceptor agonists reduce the decline of rat diaphragm twitch force during severe hypoxia. *Am J Physiol* 1999;276:L474–80.
- 69 van der Heijden HFM, van Balkom RHH, Folgering HTM, et al. Effects of salbutamol on rat diaphragm contractility. *J Appl Physiol* 1996;81:1103–10.
- 70 van der Heijden HFM, Zhan WZ, Prakash YS, et al. Salbutamol enhances isotonic contractile properties of rat diaphragm muscle. *J Appl Physiol* 1998;85:525–9.
- 71 Haupt HA, Rovere GD. Anabolic steroids: a review of the literature. *Am J Sports Med* 1984;12:469–84.
- 72 Lewis MI, Fournier M, Yeh AY, et al. Alteration in diaphragm contractility after nandrolone administration: an analysis of potential mechanisms. *J Appl Physiol* 1999;86:985–92.
- 73 Beiner JM, Joki P, Cholewicki J, et al. The effect of anabolic steroids and corticosteroids on healing of muscle contusion injury. *Am J Sports Med* 1999;27:2–9.
- 74 Schols AMWJ, Soeters PB, Mostert R, et al. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease: a placebo-controlled randomized trial. *Am J Respir Crit Care Med* 1995;152:1268–74.
- 75 Sprungen AM, Grimm D, Dumitrescu O, et al. Improvements in diaphragm width and pulmonary function following anabolic steroid therapy in subjects with tetraplegia. *Am J Respir Crit Care Med* 1999;159:A586.
- 76 Bhasin S, Storer TW, Berman N, et al. The effects of supra-physiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med* 1996;335:1–7.
- 77 Hervey GR, Hutchinson I, Knibbs AV, et al. “Anabolic” effects of methandienone in men undergoing athletic training. *Lancet* 1976;ii:699–702.
- 78 Johnson LC, Roundy ES, Allsen PE, et al. Effect of anabolic steroid treatment on endurance. *Med Sci Sports* 1975;7:287–9.
- 79 Freed DLJ, Banks AJ, Longson D, et al. Anabolic steroids in athletics: crossover double-blind trial on weightlifters. *BMJ* 1975;2:471–3.
- 80 Hervey GR, Knibbs AV, Burkinshaw L, et al. Effects of methandienone on the performance and body composition of men undergoing athletic training. *Clin Sci* 1981;60:457–61.
- 81 Clarkson PM, Thompson HS. Drugs and sport. Research findings and limitations. *Sports Med* 1997;24:366–84.
- 82 Yarasheski KE. Growth hormone effects on metabolism, body composition, muscle mass, and strength. *Exerc Sport Sci Rev* 1994;22:285–312.
- 83 Crist DM, Peake GT, Egan PA, et al. Body composition response to exogenous GH during training in highly conditioned adults. *J Appl Physiol* 1988;65:579–84.
- 84 Rudman D, Feller AG, Nagraj HS, et al. Effects of human growth hormone in men over 60 years old. *N Engl J Med* 1990;323:1–6.
- 85 Salomon F, Cuneo RC, Hesp R, et al. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N Engl J Med* 1989;321:1797–803.
- 86 Wagner JC. Enhancement of athletic performance with drugs. An overview. *Sports Med* 1991;12:250–65.
- 87 Deyssig R, Frisch H, Blum WF, et al. Effect of growth hormone treatment on hormonal parameters, body composition and strength in athletes. *Acta Endocrinol Copenh* 1993;128:313–8.
- 88 Yarasheski KE, Campbell JA, Smith K, et al. Effect of growth hormone and resistance exercise on muscle growth in young men. *Am J Physiol* 1992;262:E261–7.
- 89 Yarasheski KE, Zachwieja JJ, Campbell JA, et al. Effect of growth hormone and resistance exercise on muscle growth and strength in older men. *Am J Physiol* 1995;268:E268–76.
- 90 Yarasheski KE, Zachwieja JJ, Angelopoulos TJ, et al. Short-term growth hormone treatment does not increase muscle protein synthesis in experienced weight lifters. *J Appl Physiol* 1993;74:3073–6.