Exercise and the lungs: From physiology to pathophysiology – a narrative review

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Exercise represents a dynamic integration of rapidly activated respiratory, cardiovascular and musculoskeletal responses to meet rising metabolic demands. While the human body has a remarkable ability for exertion and endurance, in disease states, and particularly in respiratory disease, these mechanisms are often compromised, resulting in dyspnoea and reduced exercise tolerance. This review outlines normal exercise physiology, including cardiac, ventilatory and skeletal muscle adaptations to enhance oxygen uptake and delivery to working muscle, and examines how these are altered in conditions such as asthma, chronic obstructive pulmonary disease, interstitial lung disease and pulmonary hypertension. Key management considerations are highlighted to support and optimise functional capacity in patients suffering from these conditions. The unique challenges of exercise, with and without respiratory disease, in specific contexts – including underwater diving, high-altitude exposure, and pregnancy – are also discussed. We briefly review policies and prohibitions on medications for competitive athletes with respiratory disease, where adherence to anti-doping regulations, especially regarding inhaled beta-agonists and corticosteroids, is crucial. Overall, understanding the physiological basis for exercise limitation enables clinicians to be more effective in their assessment, therapeutic intervention and counselling for patients seeking to maintain activity and quality of life despite respiratory compromise.

Keywords. Exercise physiology, cardiopulmonary physiology, respiratory disease and exercise, exercise limitation, effort intolerance, competitive sport and respiratory disease.

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Exercise is an intrinsic part of life, and the human body has a remarkable ability for exertion and endurance, with a unique capacity for efficient locomotion and long-distance running.[1] Daily activities are generally conducted without significant perceived exertion as physiological changes occur to accommodate minor increases in work and oxygen demand. During exercise, rapidly activated and integrated responses from the lungs, heart and skeletal muscle are evoked that aim to optimise delivery of oxygen to myocytes and allow fuels to be converted to adenosine triphosphate (ATP), the energy supply that drives actin-myosin linking and muscle contraction. In disease and exercise, the requirements for oxygen delivery and ability to deliver sufficient oxygen to maintain cellular activity are challenged. Here, normal responses to exercise may be hampered by the underlying disease state and its impact on the cardiac, ventilatory and pulmonary vasculature systems.

For clinicians, understanding exercise physiology is key to understanding why patients may report dyspnoea and decreased exercise tolerance, and how best to integrate exercise and pulmonary rehabilitation into long-term therapy. In this review, exercise physiology will be briefly reviewed, as well as the pathophysiological responses to exercise in common respiratory conditions, during underwater diving, at altitude and in pregnancy. Additionally, a brief review of medications permitted and prohibited during competitive sport is included. While cardiopulmonary exercise testing (CPET) offers an essential tool to dissect the relative contributions of cardiac, pulmonary or other elements to exercise-associated dyspnoea, the role of CPET is outside the scope of this article but has been well reviewed elsewhere.[2-4]

Exercise physiology

Exercise performance (measurable external work) is tightly coupled to oxygen consumption (VO_2). This coupling requires integration of the cardiovascular, respiratory and musculoskeletal responses to exercise.[5] External work depends upon energy production in the cell which, in turn, depends upon fuel availability, VO_2 and carbon dioxide (CO_2) removal in the working muscle. Oxygen delivery to the muscle

is determined by cardiac output (product of heart rate (HR) and stroke volume (SV)) and systemic oxygen extraction (difference in oxygen content between arterial and venous blood). CO_2 clearance depends predominantly upon ventilatory function.

Cardiovascular adaptations in exercise

At exercise onset, increases in HR and SV drive a rise in cardiac output. HR increase, chiefly due to vagal withdrawal and sympathetic stimulation, parallels the rise in VO_2 and reaches a maximum at peak exercise. While training lowers resting HR, it does not appear to affect maximal HR, which is predominantly influenced by age. A number of formulae are available to estimate age-predicted maximum HR (e.g. maximal HR = 208 – 0.7 × age with standard deviation ~10).[6]

SV is influenced by preload, afterload and contractility, and can increase by up to 100% with exercise training.[7] Contraction of exercising muscles around veins in the extremities enhances return of venous blood to the heart, and preload is further augmented by negative intrathoracic pressures, stretching of the myocardium, and increasing SV. Vagal withdrawal and sympathetic activation increase inotropy, or force of contraction, at a cardiac myocyte level, where depolarisation activates intracellular calcium release, inducing myocyte shortening with force (and calcium sensitivity) relative to the degree of myocyte stretch. Afterload is influenced by left ventricular wall thickness and cavity size (both of which steadily increase with training)[8] as well as systemic vascular resistance (SVR). Overall, SVR drops as a result of the locally induced vasodilator response in working muscle, prioritising muscle perfusion away from vasoconstricted beds in non-working tissues such as the gut and kidney.

Pulmonary adaptations in exercise

Minute ventilation (V_E) rises with exercise, initially through increasing tidal volume (Vt) and later through increasing respiratory rate (RR),[9,10] and is regulated by complex brain, muscle, chemoreflex and metabolic signalling, particularly by rising CO_2 production (VCO_2) during mild to moderate exercise. Vt is optimised by decreasing end-expiratory lung volume and increasing end-inspiratory lung volume and, in healthy individuals, increases to ~60% of vital capacity (VC), at which point work of breathing increases unacceptably.[3,4]

While pulmonary blood flow increases with exercise and cardiac output, pulmonary vascular resistance (PVR) falls as a result of passive vascular distension and recruitment and active nitric oxide (NO)-mediated vasodilation.[11] Larger tidal breaths distend the conducting airways and increase anatomical dead space, but this is attenuated by recruitment of at-rest hypoventilated lung units. Augmented cardiac output with improved distribution of pulmonary blood flow optimises matching of ventilated and perfused units and hence gas exchange. Oxygen diffusion across the alveolar-capillary membrane is enhanced by hyperventilation (which lowers the partial pressure of alveolar CO_2, resulting in increased partial pressure of alveolar oxygen) and a higher respiratory exchange ratio (VCO_2/VO_2). Increasing exercise intensity results in buffering of hydrogen ions by bicarbonate, resulting in increased VCO_2. Accelerated VCO_2 results in increased V_E relative to power output and VO_2. This phenomenon has been variously described as the metabolic threshold or ventilatory threshold, corresponds closely to the lactate threshold (level of VO_2 where a sustained rise in lactate is observed),[12] and is a marker of maximal steady-state exercise.

Skeletal muscle level and substrate use

The motor unit is made up of many muscle fibres, divided into types I and IIA (red, with high myoglobin content, therefore intrinsic oxygen stores, and a high concentration of oxidative enzymes) and type IIX (white, predominantly anaerobically metabolising with low myoglobin content).[13] A constant supply of ATP is needed in working muscles, and it is the hydrolysis of ATP that releases the energy required for myosin heads to row and slide along actin filaments and contract skeletal muscle. The chief fuels used for generation of ATP depend on intensity and duration of exercise, patient nutritional composite and physique, and diet.[14,15] These are glucose and glycogen (especially with short bouts of intense exercise where glycolysis predominates, supplemented by conversion of phosphocreatine to ATP by creatine kinase) and free fatty acids (the choice of fuel at rest, or for prolonged submaximal exercise). Mitochondrial respiration is the common final pathway of all aerobic metabolism of fuels, where, in these cellular powerhouses and in the presence of oxygen, coenzyme A (CoA) derivatives rotate through the Krebs cycle to produce nicotinamide and flavin adenine dinucleotide, donating electrons that move through enzyme complexes of the oxidative phosphorylation pathway, in turn converting adenine diphosphate (ADP) to ATP, with water and CO_2 as waste products.

Lactate is produced continuously during exercise, as the reaction from pyruvate is catalysed by lactate dehydrogenase with the equilibrium constant strongly in favour of lactate production. This reaction rate is also higher than the pyruvate dehydrogenase reaction that converts pyruvate to acetyl-CoA.[16] Lactate is re-used as fuel within the muscle, and effluxes into the bloodstream where it is metabolised in other skeletal muscles, heart and liver. Increasing exercise intensity results in progressive inability to metabolise lactate both locally and in distant sites, resulting in accumulation. Furthermore, increasing recruitment of fast-twitch glycolytic fibres and progressive saturation of entry of pyruvate into the mitochondria result in insufficient ATP for energy needs, with accumulation of ADP, phosphate and hydrogen ions. These hydrogen ions efflux into the bloodstream, where they are buffered by bicarbonate with subsequent increased CO_2 production. Critically, phosphofructokinase, an essential enzyme in the glycolytic process, is pH-dependent, and this protects against uncontrolled glycolysis and acidosis.

Skeletal muscle vasodilation, driven by drops in pH and rises in NO and other mediators,[17] with local acidosis causing a right shift in the oxyhaemoglobin dissociation curve and increased oxygen offloading, optimises muscle oxygen extraction. With training, fibre size and mitochondrial and capillary density increase,[18] with adaptive capacity for transition to use fatty acids, a particularly high-yield ATP substrate, as fuel.[19]

Respiratory disease and exercise

In most respiratory disorders, including chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PH) and interstitial lung disease (ILD), exertional dyspnoea stems primarily from mismatches between demand and ventilatory capacity, with added factors such as mood state and environmental factors that induce a subjective feeling of being short of breath. Overlapping comorbidities, including smoking and cardiovascular disease, may further contribute to exercise intolerance. Furthermore, sarcopenia is

frequent in these patient groups, evolving out of the disease process itself as well as ageing, deconditioning and demotivation, and is a common contributor to inactivity. Exercise as therapy is therefore an essential addendum to respiratory care and may reduce mortality and improve quality of life.

Asthma and exercise

Asthma is a common and heterogeneous disease, usually associated with chronic airway inflammation, with intermittent and variable symptoms of cough, wheeze and dyspnoea, associated with expiratory airflow limitation, that vary with intensity and time.[20] Exercise-induced bronchoconstriction, induced mainly by hyperventilation of dry cool air, with downstream effects on airway reactivity, may occur as an isolated entity, but is observed in at least 90% of patients with symptomatic asthma.[21] It may be accompanied by additional symptoms of cough, chest tightness and excess mucus production. Exercise-induced laryngeal obstruction is a paradoxical physical narrowing of the laryngeal passage, which should also be considered when basic asthma testing is negative; it requires specialised visualisation during exercise, and a recent review provides a detailed overview of the phenomenon.[22]

Pathophysiology

Cold and dry air exposure results in osmolarity changes and dehydration of respiratory mucosa, activating mast and epithelial cells with release of histamine, leukotrienes and chemokines resulting in bronchoconstriction.[23] Prolonged cold air exposure in itself has been found to be associated with a bronchial inflammatory cell infiltrate in both asthmatic and non-asthmatic elite athletes, without a consistent correlation between inflammatory infiltrate and airway reactivity.[24-26] Other sequelae of cold air exposure that may contribute to airway narrowing in asthmatics include pulmonary vasoconstriction with rebound reactive hyperaemia with bronchial congestion.[27] Exercise-induced bronchoconstriction (EIB) is more common in endurance compared with non-endurance athletes, and is also sport-specific.[28]

Suggestions for patient care

Regular use of inhaled corticosteroids (ICS) is essential for asthma control, but may not prevent EIB. In mild asthma, as-needed ICS with a long-acting beta-2-agonist (LABA) can be used. Useful adjunctive measures to reduce EIB include pre-exercise use of a bronchodilator, slow warm-up, and avoiding exercise during times of high allergen, pollen or pollution exposure, and at extreme temperatures. If ongoing symptoms occur during exercise, or added medication is being contemplated, review by a 'sports-asthma' specialist is advised to avoid over- or undertreatment, and in professional athletes, to ensure compliance with anti-doping policies and the significant restrictions that are in place for asthma (see below).

Chronic obstructive lung disease and exercise

COPD is a common and heterogeneous respiratory condition, often related to cigarette smoking, and characterised by persistent abnormalities of the airways with resultant airflow limitation.[29] Gas exchange impairments primarily evolve out of severe architectural alveolar damage (emphysema). Dyspnoea with exercise is frequent and multifactorial, and given common comorbidities such as hypertension, ischaemic heart disease and deconditioning that may contribute to depleted exercise capacity, the evaluation of a COPD patient with dyspnoea on exertion needs to be comprehensive.

Pathophysiology

In COPD, abnormal lung mechanics that are present at rest are often amplified by exercise. Narrowed and floppy airways with decreased elastic tissue support tend to collapse on expiration, and as RR increases with exertion, dynamic hyperinflation results, with increased dead space, suboptimal respiratory muscle mechanics and increased work of breathing.[30,31] Hyperinflation also compromises perfusion. Deranged gas exchange from ventilation/perfusion (V/Q) mismatches is further compounded by pulmonary microvascular dysfunction, and failure to adequately recruit pulmonary capillaries, which, in the context of a reduced alveolar-capillary interface, results in diffusion limitation.[32] Increased reflex chemo-stimulation, driven by both respiratory (inadequate alveolar ventilation) and metabolic (deconditioning and elevated lactate at low workloads) acidosis, and sympathetic activation are further drivers of dyspnoea.[33] Furthermore, central haemodynamic sequelae, with high negative intrathoracic pressures and high expiratory pressures, have been shown to increase afterload and lower SV, with the net effect of lowering cardiac output.[34] Finally, respiratory and limb muscle weakness, fatigue and remodelling[35,36] may occur, which further limits exercise capacity.

Suggestions for patient care

Patients with COPD will have exercise limitation by definition. Ensuring maximal bronchodilatation with regular inhaled long-acting bronchodilators (long-acting muscarinic antagonist (LAMA) with/without a LABA) is imperative. Managing comorbid disease is essential, since patients without cardiac disease will be limited by respiratory capacity (airflow and gas exchange), requiring bronchodilator optimisation, but those with coexisting cardiac dysfunction will also require dedicated heart failure, angina and other cardiac impairment optimisation. Pulmonary rehabilitation is very useful in COPD to improve overall respiratory-musculoskeletal conditioning and quality of life, although it is frequently underutilised.

Interstitial lung disease and exercise

Although less common than asthma or COPD, ILDs are not infrequently diagnosed during the work-up for unexplained dyspnoea. ILDs tend to occur in older patients, with insidious onset, therefore often presenting late in the disease course with the hallmark features of exertional dyspnoea, cough and inspiratory crackles on auscultation. This group of diseases includes a wide range of inflammatory and fibrosing diseases of lung parenchyma, triggered by autoimmune, exposure-related or idiopathic causes.[37] Gas exchange limitation with exertion is the predominant issue in ILD, where thickened alveolar membranes and fibrotic parenchymal destruction disrupt and widen the fragile gaseous diffusion barrier. Resting hypoxaemia and PH may also develop, further worsening the ability to exercise.

Pathophysiology

Patients with ILD typically have reduced total lung capacity and VC, due to stiff and scarred lungs that are poorly compliant. The inability

to increase Vt appropriately during exercise, within this restricted VC, results in a marked increase in RR in order to try to achieve suitable $V_{E.}$.[38,39] Work of breathing is further compounded by frequently coexisting and multifactorial skeletal and respiratory muscle dysfunction that, beyond deconditioning, may be secondary to immunosuppression or extrapulmonary manifestations of systemic connective tissue disease (CTD). In ILD, pulmonary capillary architecture is distorted and the alveolar-capillary interface thickened. With exercise, increased cardiac output and reduced transit time of red blood cells through the capillary beds further limit time for oxygenation, resulting in or aggravating arterial hypoxaemia. V/Q mismatches due to higher anatomical dead space from tethered airways and regional alveolar dead space also contribute to gas exchange impairment.[40-42]

Suggestions for patient care

ILDs have a significant impact on quality of life, where, in particular, severe progressive subtypes are frequently associated with incremental loss in exercise capacity. Pulmonary rehabilitation, along with supplemental oxygen in selected cases, may improve patients' ability to complete activities of daily living. For patients being considered for lung transplantation, maintenance of exercise capacity and muscular strength is critically important.

Pulmonary hypertension and exercise

PH, a syndrome of vascular remodelling in pulmonary beds, essentially results in an inability to deliver enough blood to the lungs for oxygenation during exercise. PH is categorised into five clinical groups based on pathophysiological and haemodynamic characteristics.[43] Depending on the underlying reason for the PH, coexistent cardiac or respiratory disease may be worsened by PH, or PH can complicate an underlying CTD such as systemic sclerosis. If PH is suspected, careful work-up is required, as exercise testing in a patient with PH is fraught with challenges and complications.

Pathophysiology

The normal SV increases seen during exercise are inhibited by high right ventricular afterload and reduced contractile reserve.[44] Loss of pulmonary vascular distensibility results in climbing of pulmonary arterial pressures and PVR with exertion,[45] aggravating at-rest V/Q mismatch and right-to-left shunting. Together with increased dead space ventilation, the subsequent gas exchange limitation (with arterial hypoxaemia and respiratory acidosis) triggers increased ventilatory drive with resulting dyspnoea.[46] Limited right ventricular reserve and output during exercise may impair left ventricular filling, with resultant impairment in oxygen delivery to working muscles,[47] early anaerobic glycolysis, excess lactate generation and delayed CO_2 clearance contributing to fatigue.[46] With advanced disease, presyncope or syncope may result from failure to appropriately augment systolic blood pressure with exertion and is a poor prognostic feature.[48] Incremental right heart failure with fluid overload, with or without left ventricular failure, further compromises mobility and lung compliance, and decreases effort tolerance.

Suggestions for patient care

Patients with PH should attempt to maintain their physical activity as best they can, but should not attempt excessive exercise. Desaturation with exercise may be overcome with a portable oxygen concentrator to allow for longer durations of exercise, since, as is the case with ILD, maintenance of exercise capacity is especially important if a transplant is being considered.

Respiratory disease in specific contexts

Respiratory disease in underwater diving

The physiological changes that occur with scuba diving are multiple. Work of breathing is increased even in health owing to the effect of underwater pressures on shifting abdominal contents, reduced compliance of lung soft tissues with immersion, increased inhaled gas density with depth, and intrinsic resistance and increased dead space of scuba breathing apparatus.[49] Broadly, the effects of diving and the impact of respiratory disease can be divided into immersion, pressure and decompression effects.

On immersion, there is peripheral vasoconstriction, and fluid shift from extravascular tissues into the circulation, with increased intrathoracic blood volume and right heart pressures and increased diuresis. However, pulmonary capillary congestion and oedema may occur with increased exertion in susceptible individuals, especially those with raised pulmonary vascular pressures at rest.[50]

Pressure effects and barotrauma are more frequently encountered on ascent, when expanding gas in the lungs can cause lung over-expansion with alveoli rupture, pneumothorax, and most severely, pulmonary arterial gas embolism. A small study showed increased risk for barotrauma in divers with pre-existing cystic or obstructive lung physiology at rest.[51] However, asthmatics with normal airway function at rest, with little exercise- or cold-induced bronchial reactivity, do not seem to be at increased risk of pulmonary barotrauma.[52]

Decompression sickness may occur on descent or ascent. With descent and increasing partial pressure, metabolically inert gases diffuse down a concentration gradient into tissues, either producing immediate harm (nitrogen narcosis, oxygen toxicity, helium-associated high-pressure nervous syndrome) or, on rapid ascent with decreasing partial pressures, forming free gas, with bubbles in supersaturated tissues and venous blood ('the bends').

Commercial diving activities are regulated by international (e.g. the International Marine Contractors Association)[53] and national authorities (e.g. the South African Department of Employment and Labour),[54] where formal medical review and clearance of employees is required. Patients with significant respiratory disease will not be able to undertake underwater diving, and excellent control of asthma is essential in any person with asthma considering partaking in scuba diving recreationally.

Respiratory disease and altitude

With ascending altitude, barometric pressure decreases linearly, and the atmospheric partial pressure of oxygen (PaO_2) reduces proportionally (hypobaric hypoxia). Acclimatisation describes the progressive physiological adaptations that allow toleration of extremely low oxygen partial pressures.[55,56] Such adaptations include hypoxia-driven hyperventilation (resulting in hypocarbic alkalosis that is slowly compensated for by increased renal bicarbonate excretion), pulmonary circulatory changes (including hypoxic pulmonary vasoconstriction), and ventilatory changes (including VC reduction

but increased residual capacity). Furthermore, increased sympathetic activity and HR drives an increase in cardiac output. Acutely, blood is haemoconcentrated, and with time, erythropoietin drives increased red blood cell production.

In patients with COPD, ILD or other hypoxic respiratory diseases, tolerance of altitude-related hypobaric hypoxia is variable. Significant drops in PaO_2 with altitude in patients with COPD and mean sea-level PaO_2 of 8.8 kPa have been described.[57] There are well-established recommendations for supplemental oxygen for patients with sea-level PaO_2 <6.7 kPa, or desaturation on hypoxic challenge, for use on commercial flights,[58,59] which may be extrapolated to adults engaging in altitude travel. The risk of bullae or bleb expansion, of theoretical concern due to falling ambient pressure with altitude, seems to have been largely disproven, perhaps because of these lesions' communication with the airways. However, the risk of expanding pneumothoraces remains a concern.[60]

In patients with PH of any cause, their limited pulmonary vascular distensibility means that hypoxia-mediated pulmonary vasoconstriction is poorly tolerated. They tend to develop exaggerated haemodynamic changes, accelerated right ventricular dysfunction, and increased risk for high-altitude pulmonary oedema.[61,62]

Key recommendations on the management of pre-existing lung disease with altitude travel are well explored in a recent revised review.[56,63] Central to travel planning is stabilisation of disease prior to travel, establishing monitoring and response plans in case of exacerbations, and ensuring that rescue and oxygen therapy is available and functional at altitude.

Respiratory disease in pregnancy

Pregnancy results in several physiological changes in the lungs that may be challenged further in the context of respiratory or cardiac disease. Physiological changes to the chest wall, with outward flaring of the ribs in early pregnancy and an increase in chest diameter, allow for preservation of VC and maximum excursion of the diaphragm despite the enlarging uterus and reduced residual volume.[64] Elevated progesterone levels are thought to drive physiological dyspnoea and hyperventilation of pregnancy, starting in the first or second trimester and stabilising in the third, allowing for a significant rise in Vt and V_E at term, with generally increased arterial oxygenation and a relative respiratory alkalosis.[65] While many women experience upper respiratory tract mucosal congestion, changes in gas exchange and diffusion capacity are usually not of clinical significance.

While asthma remains stable in most pregnant women, it may worsen in approximately a third of pregnancies, usually in the third trimester.[66,67] Poorly controlled asthma has been shown to be associated with a small increased risk of pre-eclampsia and preterm birth among other complications in some studies.[66,68] The use of common asthma medications, including beta-agonists and corticosteroids, is largely safe in pregnancy, although there are fewer published data on use of theophylline, leukotriene antagonists, muscarinic agonists and biologic therapy.

Distinguishing physiological dyspnoea of pregnancy from complications such as infection, aspiration or disease progression can be challenging in patients with ILD. However, any decline in baseline pulse oximetry, forced vital capacity or diffusing capacity of the lungs for carbon monoxide, a metric of gaseous exchange efficiency, during pregnancy should alert to disease progression or complication.[69] Patients with underlying ILD should be extensively counselled about the risks of pregnancy and immunosuppressive medications on pregnancy outcomes. While some patients may have stabilisation or improvement of their autoimmune disease with pregnancy, approximately a third may experience worse disease, with risk of relapse after delivery requiring careful monitoring.

PH in pregnancy is a particular challenge, and many medical societies regard PH as a contraindication to pregnancy.[70,71] The increased pulmonary blood flow that occurs in normal pregnancy is not tolerated owing to PH-related loss of pulmonary vascular compliance, raising the risk of right ventricular failure. Hormonal changes causing vasodilation and reduced blood pressure activate the renin-angiotensin-aldosterone system, and perpetuate a cycle of fluid overload. In particular, the acute haemodynamic changes during delivery, including autotransfusion of blood between the placenta and systemic circulation with labour contractions, as well as exertion-related changes in HR and blood pressure,[72] may critically compromise right ventricular function further. PH management requires careful pre-pregnancy counselling with discussion of oestrogen-sparing contraceptive methods, and in the event of pregnancy, holistic multidisciplinary management in a specialist centre, with consideration for prostaglandin and/or calcium channel blocker therapy, and careful monitoring during the peri- and postpartum periods.[70,71]

Exercise, competitive sport and medication restrictions

Most patients with significant respiratory conditions may not have the physical capacity to participate in competitive sports, where formal anti-doping drug testing is performed. Asthma is the exception, however, and the area where most care should be taken to comply with anti-doping regulations. This is especially true in younger athletes, where asthma may develop over time, and competition may extend to national, international or even Olympic level, requiring exceptional asthma control and awareness of anti-doping regulations.

The World Anti-Doping Agency (WADA) publishes an annual list of prohibited medications, including modes of delivery. These are grouped into those prohibited: (*i*) at all times; (*ii*) in competitions only; or (*iii*) only in certain sporting codes. The current list is available online (https://www.wada-ama.org/en/prohibited-list).

Respiratory-specific medications: Short- and long-acting beta-2-agonists (SABAs/LABAs)

Although all formulations and isomers of beta-agonists are included on the banned list (including salbutamol, fenoterol, terbutaline, salmeterol, formoterol, indacaterol, oladaterol and vilanterol), specific beta-agonists, in an inhaled formalation, are permitted within strict dosing parameters. Urinary threshold limits, as influenced by the athlete's metabolic profile (fast or slow metaboliser), are also defined. If higher than permitted levels are detected, the results are considered an adverse analytical finding. The threshold-permitted beta-agonists are shown in Table 1.

Long-acting muscarinic antagonists (LAMAs)

These bronchodilators, including glycopyrronium, tiotropium and

Table 1. Exceptions to prohibited LABAs

LABAs (all inhaled)	Maximum permitted dose	Urine threshold limit*
Salbutamol	1 600 µg over 24 hours in divided doses, not to exceed 600 µg over 8 hours starting from any dose	1 000 ng/mL
Formoterol	54 µg over 24 hours in divided doses, not to exceed 36 µg over 12 hours starting from any dose	40 ng/mL
Salmeterol	200 µg over 24 hours; not to exceed 100 mcg in any 8 hours	-
Vilanterol	25 µg over 24 hours	-

LABA = long-acting beta-2-agonist; AAF = adverse analytical finding; TUE = therapeutic use exemption.
*Indicates the threshold above which the presence of the substance will be considered an AAF. The presence of these substances, at any level, will be considered an AAF in the presence of a diuretic or other masking agent, unless the athlete has a TUE for that substance as well as the diuretic or masking agent. Note: Indacaterol/olodaterol are not on the permitted list and formally require a TUE (see under 'Respiratory-specific medications: Short- and long-acting beta-2-agonists (SABAs/LABAs)') if prescribed.

umeclidinium, while predominantly used in COPD, can be used in asthma, and are not included on the WADA prohibited list. However, asthmatics requiring these medications and competing at elite level should be managed by a sports physician or pulmonologist.

Glucocorticoids

All glucocorticoids administered via the injectable (intravenous or intramuscular), oral, mucosal or rectal route are prohibited in competition. Inhaled and intranasal corticosteroids are permitted when used within licensed doses and therapeutic indications.

Therapeutic use exemption application

If prohibited medications are required, the athlete needs to apply to their national anti-doping organisation for a therapeutic use exemption (TUE), with the following supportive information: (*i*) complete medical history and clinical examination, with specific focus on the respiratory system; (*ii*) exact name, specialty and contact details of examining physician; (*iii*) spirometry report with flow-volume loop (and if spirometry indicates airway obstruction, it should be repeated after inhalation of a SABA to document bronchodilator responsiveness); and (*iv*) documentation of a bronchial provocation test to establish the presence of bronchial hyper-responsiveness if reversibility is not shown on routine spirometry. Provocation testing should be conducted in an experienced laboratory with full resuscitation equipment available. Most commonly, an exercise provocation test is employed, where a fall of ≥10% in forced expiratory volume in 1 second and 200 mL over two consecutive timepoints is considered a positive test. Other provocation tests include histamine, methacholine aerosol or hypertonic saline aerosol challenge.

If an athlete is on chronic medication for asthma but does not require a TUE, it is advised that they have the requisite information supporting their diagnosis available. In the event of a life-threatening asthma attack during competition, where higher doses of salbutamol or glucocorticoids are required, the patient should be treated appropriately, followed by a retrospective application for TUE.

Conclusion

Exercise is an essential part of life and wellbeing and can be severely limited by respiratory illness. For patients with known respiratory diseases as outlined, optimal treatment of the condition is imperative to restoring as much functional ability as possible. However, in many situations, limits on functional capacity will remain. Understanding the basic pathophysiology and impact on exercise of a disease can assist clinicians and affected patients to tailor their exercise plans as well as their exercise expectations. When patients with respiratory disease engage in specific situations that directly influence respiratory function, including pregnancy and high-altitude travel, careful planning, optimisation and pre-emptive decision-making are essential to avoid potentially life-threatening destabilisation. Finally, for those engaging in competitive sports, awareness of and adherence to anti-doping regulations will prevent violation of formal restrictions and unwanted adverse analytical findings. These frequently stem from a lack of knowledge around the prohibitions on medications prescribed to treat common conditions such as asthma.

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