



Pulmonary disorders and exercise

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Exercise is rarely limited by pulmonary causes in the normal subject. Normal individuals, despite steep minute rises in ventilation during exercise, maintain a substantial breathing reserve. Exercise can indeed be limited by a number of pulmonary disorders, however. Acute pulmonary causes such as exercise-induced bronchospasm (EIB), vocal cord dysfunction (VCD), exercise-induced anaphylaxis, and exercise-induced urticaria or chronic obstructive and restrictive lung disorders may all reduce exercise tolerance. Exercise testing has proven to be the mainstay for diagnosis and treatment of these disorders.

Pulmonary response to exercise

Healthy individuals augment their minute ventilation (V_E) to exercise loads in large part as a response to increased carbon dioxide production (VCO_2). Increments in V_E and VCO_2 are linear to increments in O_2 consumption (VO_2), up to 50% to 60% of maximal oxygen consumption (VO_{2max}). Beyond this threshold, the rise in V_E is more closely linked to rises in VCO_2 [1]. In an attempt to maintain homeostasis with regard to arterial carbon dioxide and pH, minute ventilation is initially increased by tidal volume augmentation. When plotted against minute ventilation, increments in tidal volume follow a hyperbolic curve and plateau at 60% to 70% of vital capacity [2]. The shape of the curve is determined by the hyperbolic relationship between transpulmonary pressure and lung volume. Increments in minute ventilation are also paralleled by rises in breathing frequency.

The maximum minute ventilation (MVV) that can be sustained voluntarily for 4 minutes can be mathematically expressed as a function of the expired volume in the first second of exhalation of a forced maneuver from full inspiration (FEV_1). An approximation commonly used is $MVV = 35 \times FEV_1$ [3]. Healthy subjects

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generally reach 70% of their MVV at VO_2max . Hence their breathing reserve (BR) is 30% of MVV.

Patients respond to increased load by increasing minute ventilation. Their response pattern and capabilities are governed by their disease states, however. Patients with chronic obstructive lung disease will respond to exercise by increasing their tidal volumes, despite their reduced FEV_1 values [4–6]. The energy expense of maintaining these relatively high tidal volumes is quite high, however, and patients with airflow obstruction will be forced to a more energy-conserving mode by reducing their tidal volumes. These patients may achieve minute ventilations equivalent to MVV and have minimal BR available. In this case, it is likely that exercise limitation is pulmonary in origin. Patients with restrictive lung disease will respond to the stimulus of exercise by increasing breathing frequency, because increments in tidal volume are far too energy expensive [7].

Minute ventilation can be divided into two components: alveolar ventilation (V_A), and wasted ventilation (dead space ventilation). Alveolar ventilation parallels VCO_2 closely, as PaCO_2 changes little until normal subjects reach 75% of their VO_2max [8]. At this point, PaCO_2 falls as alveolar ventilation increases more rapidly than VCO_2 , perhaps in response to rising blood lactate levels and resultant falls in arterial pH. Reduced PaCO_2 values may be seen in patients with interstitial lung disease, because hypoxia stimulates minute ventilation as well as VCO_2 [1]. Patients with cardiac limitations to exercise are likely to have elevated alveolar minute ventilations as lactate levels rise. Those with pulmonary hypertension also demonstrate reduced PaCO_2 values during exercise [9]. Conversely, PaCO_2 commonly rises during exercise in patients with obstructive lung disease [10]. These elevations likely result from increased production from the work of breathing and reduced responsiveness to carbon dioxide. The latter should not be confused with a decreased drive, but is a blunted rise in drive for changes in PaCO_2 .

During exercise the normal dead space to tidal volume ratio (V_D/V_T) of 0.25 to 0.35 at rest falls by 5% to 20% [11]. This fall results from augmented tidal volumes, but is partially negated by increases in anatomic dead space associated with larger airway diameter. Reduction in the V_D/V_T ratio also results from recruited perfusion to the apical portions of the lung, thus minimizing alveolar dead space [12]. The efficiency of ventilation is directly related to the V_D/V_T ratio, and reductions seen during increased minute ventilation minimize the impact of increasing carbon dioxide production seen with exercise. Patients with lung disease often have an elevated V_D/V_T ratio, however. Those with interstitial lung diseases breathe with reduced tidal volumes and have regions of high ventilation but low perfusion, resulting in elevated V_D/V_T ratios [1]. These patients exhibit greater minute ventilations for the same VCO_2 . This is not the case for patients with chronic obstructive pulmonary disease (COPD), even though they have an increased V_D/V_T ratio. Their blunted alveolar ventilation responses parallel increasing VCO_2 , and hence minute ventilation may be normal, yet PaCO_2 elevated [13].

Impact of training on cardiopulmonary response to exercise

Training can be primarily for strength or endurance. Endurance training results in an increase in VO_2max by 8% to 15%, primarily by enhancing maximal cardiac output and secondarily to an increased arterial-venous gradient [14]. The value of training is not at maximal exercise but at submaximal exercise, however. Training results in increased capacity for aerobic exercise as oxygen delivery and skeletal muscle utilization are enhanced [15–19]. Furthermore, the onset of anaerobic metabolism is delayed, and thus the rise in minute ventilation and VCO_2 out of proportion to VO_2 is delayed. In fact, for a given level of exercise lactate levels, minute ventilation and VCO_2 are reduced after training [15,20,187]. Patients also report reduced perception of dyspnea with training.

The level of training intensity appears critical if benefit is to be obtained. Duration is also an important factor [188]. Assessing intensity is best done by measuring VO_2max and then training at a level greater or equal to 50% of VO_2max [21]. Alternatively, normal subjects can achieve similar results by performing exercise at 60% to 70% of their predicted maximal heart rate or 50% of their heart rate reserve [21]. To calculate heart rate reserve, resting heart rate is subtracted from predicted maximal heart rate (HRmax). VO_2max is a more reliable measure for exercise intensity, however. Some have also advocated exercising at the point of lactate accumulation, which approximates 50% VO_2max or 50% of heart rate reserve [20,22–24]. Other studies have demonstrated training benefits even when exercise is at levels below those established by lactate accumulation [25].

Training sessions should range between 30 and 60 minutes [14,26]; however, benefit is achieved with higher intensity exercise for durations of at least 20 minutes [27]. Frequency should be at least twice weekly; still greater benefits are associated with more frequent exercise. Recommendations for frequency generally range between three to five times per week [14,19,21]. Training benefit reaches its maximum in 3 to 4 weeks if training work is initiated at 50% VO_2max [25,28,29]. Because patients and many normal subjects rarely start at these levels of training intensity, an 8-week program is advisable [27]. The mode of training depends on the goals, as only those muscles trained will benefit [14]. Training programs anchored on running, rapid walking, or bicycling can achieve equal increases in VO_2max [30]. Others may choose to focus on swimming or arm cranking exercises. Age is not a contraindication to exercise programs, because geriatric patients benefit as well. Exercise prescriptions for the elderly need to be tailored even in normal subjects, however, as VO_2max and predicted maximal heart rates are reduced and anaerobic threshold is elevated [31]. Exercise prescription in these patients should be based on a higher percentage of the reduced VO_2max value [32].

Impact of age on pulmonary response to exercise

Aerobic capacity declines by 6% to 10% per decade of life [33–37]. The respiratory system in the young adult responds to exercise by several mech-

anisms: reducing end-expiratory lung volume, increasing tidal volume, enhancing breathing frequency by fourfold, improving perfusion to all regions of the lung, and reducing dead space ventilation [38–41]. As we age, however, structural changes occur that impede the ventilatory response. A loss of elastic recoil is noted, which results in reduced lung compliance [42–50]. In addition, the chest wall becomes stiffer, which further affects compliance [51]. Mechanical efficiency is also impaired through a change in chest wall configuration as a result of reduced intervertebral space and resultant increased anterior-posterior diameter [52]. These changes result in reduced vital capacity, increased functional residual capacity, and significant reductions in maximal expiratory airflow. Muscle mass is reduced as well, and this results in reduced strength of the diaphragm [53,54]. Oxygen transfer from air to blood is impeded by loss of alveoli, reduced arterial compliance, and increased airway diameter [40,55–58]. Resting measurements of dead space increase 6% to 8% per decade, and diffusing capacity of carbon monoxide falls 4% to 8% per decade [56,57,59–61]. Pulmonary capillary blood volume is also reduced with age [59,62]. In spite of these changes, the respiratory system in the elderly permits significant exercise capacity and does allow for achievement of each individual's VO_2max .

Training goals in healthy elderly subjects are similar to those of their younger counterparts. Elderly subjects should achieve 50% to 80% of VO_2max and perform continuous or rhythmic aerobic exercise for 30 to 60 minutes [63–67]. Exercising at 70% of VO_2max may be preferred, as the anaerobic threshold is elevated in the elderly subject. Target heart rates of 70% to 90% predicted maximum roughly correlate with VO_2max levels of 50% to 75% [68].

Exercise-induced arterial hypoxia

Elite athletes may exhibit exercise induced arterial hypoxia (EIAH) during moderate or high intensities. Highly trained young athletes demonstrate a drop in arterial oxygen tension (PaO_2) after achieving 50% to 60% of VO_2max [69]. Young, highly trained female athletes and masters male athletes (aged 60 to 70) may demonstrate a fall in PaO_2 at 40% VO_2max [69,70]. Fifty percent of young male endurance athletes will have EIAH when VO_2max exceeds 55 ml/min/kg [70–75]. The drop in PaO_2 among these athletes ranged between 8 mm to 35 mm Hg. Prevalence rates of EIAH in masters athletes are as high as 70% to 100% [70,76].

Although the mechanisms are not clearly elucidated, it appears that when EIAH occurs during moderate exercise in highly trained athletes a relative hypoventilation and higher arterial carbon dioxide tensions (PaCO_2) are reported [70,71,77]. Variables reflective of relative hypoventilation include $V_E/V\text{CO}_2$, $V_E/V\text{O}_2$, and $P_{A\text{O}_2}$, and are all lower in trained athletes as compared with untrained subjects at maximal exercise [77,78]. Although some have associated the degree of hypoxia with the degree of lactic acidosis generated during exercise, others have correlated the relative hypoventilation with a decrease in carbohydrate oxidation [76,79,80].

During higher intensity exercise, the alveolar-arterial oxygen gradient [(A-a)DO₂], increases [70]. In an effort to preserve oxygen tension in the alveolus, P_ACO₂ is reduced. The maximal ventilation needed to overcome increased (A-a)DO₂ may not be achievable in young female athletes or highly trained masters athletes, however [77,81]. Thus these two groups are more likely to develop EIAH. Increases in (A-a)DO₂ result from alterations in ventilation perfusion matching (V/Q) as well as alveolar-capillary diffusion limitations [82–94]. The alveolar-arterial oxygen gradient increase for exercise intensities below 65% VO₂max appears to be related primarily to V/Q inequalities [83]. Above this level of exercise intensity, alveolar-capillary diffusion limitations account for two thirds of the increase in (A-a)DO₂ and V/Q mismatch for one third [89]. Diffusion limitations may result from the fast capillary transit time seen in elite athletes but not untrained individuals, or from the development of mild interstitial edema from increased hydrostatic pressures.

Acute pulmonary disorders and exercise

Exercise in the normal subject is not limited by the respiratory system; however, acute pulmonary disorders are not uncommon in the competitive athlete or in an athletic individual. Exercise-induced asthma or bronchospasm (EIA) and vocal cord dysfunction (VCD) are perhaps the two most common and disabling acute pulmonary disorders in the competitive athlete. Rare pulmonary disorders that may prevent or limit an individual's participation in sports include exercise-induced anaphylaxis and urticaria.

Exercise-induced asthma

Exercise-induced asthma or bronchospasm is a common disorder in the general population. EIA has been reported to occur in 50% to 80% of asthmatics, in up to 40% of patients with allergic rhinitis, and in up to 10% of normal subjects [95,96]. Some believe that all asthmatics will develop EIA given a sufficient exercise load. Competitive athletes appear to have a high prevalence of asthma and EIA, particularly those athletes participating in winter endurance sports [97–109]. The prevalence of asthma among US Olympians in the 1984 summer games has been reported at 11% [106]. The prevalence in the US Olympians in the 1996 summer and 1998 winter games has been reported at 16.7% and 22.4% respectively [107,108]. Concurrent use of asthma medications was 10.4% and 17.4% respectively.

Active asthma in summer athletes was highest in those competing in cycling and mountain biking events (45%), whereas the lowest prevalence was seen in weight lifters and divers (0%) [107]. The prevalence of active asthma in those athletes competing in water sports ranged between 13.8% and 25.9%. Track and field athletes had a prevalence of 12.6%; gymnasts and fencers had a rate of 2.8%. The prevalence of active asthma in winter athletes was also activity related,

with Nordic combined, cross-country, and short track athletes having the highest rate (57.1%), followed by a rate of 16% in alpine, long track, figure skating, snowboarding, and curling competitors [108]. A Finnish study compared the prevalence of asthma as diagnosed by a physician in elite athletes on the Finnish national teams with asthma prevalence in 124 control subjects [110]. Athletes were separated into two groups: 107 long distance runners and 106 speed and power athletes. The odds ratio of having asthma compared with controls was 6.7 (95% CI 2.1–22.1) for long distance runners and 3.2 (95% CI 0.90–11.4) for speed and power athletes.

Exercise-induced asthma is airway obstruction induced by exercise. Symptoms may include wheezing, cough, and shortness of breath or chest pain. Wheezing is commonly absent and postexercise cough may be the only symptom [111,112]. Generally it takes 5 to 8 minutes of strenuous exercise to invoke EIA, and symptoms peak 5 to 10 minutes after cessation of exercise before dissipating at 30 minutes [113]. The diagnosis of EIA can be established with an exercise study demonstrating a rise in peak flow or FEV₁ during exercise, or a fall in either after cessation of exercise [113,114]. Strenuous exercise should be limited to 6 to 10 minutes, as the extent of fall in FEV₁ post-test is blunted with longer activity [115,116]. The severity of airway obstruction is related to the minute ventilation achieved during exercise, temperature and humidity of the inspired air, and the baseline airway reactivity prior to exercise initiation [115,117]. Cold, dry air is more likely to induce EIA, as both heat and water losses appear to induce bronchospasm. The cold temperature appears to impact local blood flow to the bronchus, and water loss impacts the mucosal osmolarity, leading to alterations in blood flow and smooth muscle contraction. The role of inflammatory mediators leading to exercise-induced asthma is poorly understood. Inconsistent results have been reported. It does appear, however, that the 5-lipoxygenase pathways play a significant role in the pathogenesis of EIA, as does underlying pulmonary eosinophilic inflammation [118,119]. Asthmatics commonly demonstrate a one-hour partial refractory period to recurrent EIA after experiencing EIA. Although the mechanism is poorly understood, the knowledge that it occurs in 40% to 50% of asthmatics is useful when employing a nonpharmacologic approach to prevention [111].

As previously noted, diagnosing EIA can be accomplished by means of exercise testing. Alternatively, one could opt to perform a methacholine or histamine challenge test [120]. Methacholine is preferred over histamine because it has fewer systemic side effects. Both tests are less specific than exercise testing for EIA, and bronchial hyper-responsiveness is more likely to be detected, even for those without exercise-induced bronchospasm [121]. Hence, the preferred test is exercise. Although a cycle ergometer is more suited for sophisticated measurements, the treadmill may be more likely to induce bronchospasm, due to increased minute ventilations for the same level of workload. Well-designed computer programs are now in use to control the test and apply workloads in a standard fashion. The objective is to achieve 6 minutes of exercise at 80% to 85% of predicted HR_{max} in a dry, air-conditioned environment [115]. Serial spiro-

metry measurements are taken after exercise cessation and a 15% drop in FEV₁ is diagnostic for EIA. Care should be taken to assure that short acting bronchodilators have been withheld for 12 hours and long-acting bronchodilators for 24 hours. Caution in performing the test should be exercised when the pretest FEV₁ is below 70% or 80% of the subject's personal best [117].

Prevention of EIA requires successful treatment of chronic asthma if present, as effective therapy for EIA is unlikely to succeed if airway obstruction is present before exercise. Nonpharmacologic options include induction of a relative refractory period prior to the exercise event and controlling the climatic conditions. The former is generally performed 45 to 60 minutes before the exercise event [112,122]. Sufficient pre-event exercise loading is required to provoke EIA. The degree of refractoriness appears to be correlated with the extent of bronchospasm induced by the pre-event exercise [123]. As noted above, cool air and dry air impact the extent of bronchospasm associated with EIA. Nasal breathing or use of a surgical mask or scarf reduces water loss and warms inspired air [124–126]. Avoidance of winter sports and choosing to exercise indoors under climate-controlled conditions minimizes the occurrence of EIA [117]. Recent studies have demonstrated that low-sodium diets improve post-exercise pulmonary function and that both sodium and chloride are determinants of EIA [127]. Hence, dietary intervention may be useful in asthmatics and in those with EIA as well.

Primary pharmacologic options include use of inhaled beta₂-adrenergic agonists or inhaled cromolyn sodium or nedocromil sodium 15 minutes before exercise [111,112]. Inhaled beta₂-adrenergic agents are effective in ameliorating or attenuating EIA in 90% of patients. Furthermore, they are the agents of choice as rescue medicines should EIA develop. Cromolyn sodium is not as effective in preventing EIA when compared with beta₂-adrenergic agents, yet it is a viable option. Up to 40% of patients will not develop EIA after inhaling 1600 µg (µg = mcg) of cromolyn sodium and 73% will experience some degree of protection [128]. Optimal dosing of cromolyn is 1600 µg (2 puffs) four times daily, with an additional dose 15 minutes before exercise.

For patients with chronic asthma and EIA, care should be primarily directed toward the chronic asthma. Routine usage of inhaled corticosteroids improves pre-exercise FEV₁ and reduces the propensity to develop EIA [117]. Additional agents include leukotriene modifiers and long-acting beta₂-adrenergic agents. Montelukast (10 mg po qhs), a leukotriene receptor antagonist, has been shown to be superior to salmeterol (42 mcg inhaled BID), a long-acting beta₂-adrenergic agonist, in preventing EIA in patients with chronic asthma over an eight-week trial [118,119].

Training goals in the athlete with EIA are no different than for normal subjects as outlined above. Clark and Cochrane have outlined a method to help asthmatics define the exercise level needed to achieve 75% HR_{max} but maintain their V_E/MVV (also termed dyspnea index) below 60%. When V_E/MVV exceeds 60% it is unlikely that exercise will be maintained for greater than 15 minutes. Asthmatics undergo incremental exercise testing to the point of exhaustion and a

plot of %HRmax against dyspnea index (V_E/MVV) is generated. Exercise intensity for training is chosen at a level where the patient achieves 70% HRmax with a V_E/MVV ratio less than 60% [129]. Repeat testing is recommended because training effects and the status of the underlying asthma will impact the plot.

Asthmatics should choose their exercise and training activities carefully, realizing that cold, dry air exacerbates asthma and is a major factor in inducing EIA. Activities that do not generate high minute ventilations (tennis, handball, racquetball, karate, wrestling, boxing, golf, sprinting, isometrics, downhill skiing, football, baseball) are preferred, as are water activities (swimming, diving, water polo). High minute-ventilation activities (long distance running, cycling, basketball, soccer, rugby) or those taking place in a cool and dry climate (ice hockey, ice skating, and cross-country snow skiing) are more likely to induce EIA [100,107,108,110,117].

Vocal cord dysfunction

Vocal cord dysfunction (VCD) is a syndrome of inappropriate vocal cord adduction during the respiratory cycle, resulting in wheezing and shortness of breath [130]. Patients may complain of inability to get air in. They often point to their upper trachea as the region of concern. Audible upper airway wheezing is appreciated and lack of responsiveness to bronchodilators is the rule. It is more commonly seen in young female athletes. Frequently patients are identified by their coaches as not keeping up during training exercises and in game competition.

Between 1984 and 1991, National Jewish Hospital identified 95 patients referred with refractory asthma to have VCD (44% with VCD alone and 56% with VCD and asthma) [130]. Patients with VCD alone were more likely to have ED visits in the year preceding referral (9.7 versus 5.5). Hospital admissions and intubation rates in the preceding year were similar between the two groups.

On physical examination, rapid breathing is noted at or near residual volume. Wheezing is localized to the larynx and not well transmitted to the thorax. Hyperinflation is generally not appreciated. One fourth of patients will have evidence of a truncated inspiratory limb on flow-volume loops [130]. Pulmonary function testing is variable and often not reproducible. Furthermore, pulmonary function testing will not respond to β_2 -adrenergic agonists. Arterial blood sample analysis is usually normal. Laryngoscopy is the mainstay of diagnosis but is only 60% sensitive during an asymptomatic period. Its sensitivity approaches 100% during an attack of VCD. Laryngoscopy may reveal vocal cord adduction during inspiration or early expiration [130–132]. The adduction is more prominent in the anterior portion of the cords, creating a diamond-shaped passage. Psychiatric diagnoses are common in patients with vocal cord dysfunction. Of those with psychiatric diagnoses, 73% have an Axis I diagnosis, whereas 37% have an Axis II diagnosis [130,132,133]. Physical, sexual, or emotional abuses are more common in patients with VCD than in asthmatics.

Because many of these patients are referred for EIA, pulmonary function testing and exercise testing can be quite useful to distinguish. Evidence of upper

airway obstruction is often elucidated during an exercise test [133]. Laryngoscopy can be performed once signs of vocal cord dysfunction are triggered from exercise. Newer exercise test equipment permits real time flow-loop display, thus allowing detection of the variable extrathoracic upper airway obstruction.

Treatment is effective both for immediate relief and prevention. In an effort to abort an attack, the patient may pant or cough. Additional interventions include administration of a short-acting sedative or inhalation of heliox (a mixture of helium and oxygen). The latter option reduces flow resistance because the heliox is a less dense gas. More chronic interventions can include speech pathology consultation to teach diaphragmatic breathing and oral airway relaxation during an attack [130]. Chronic use of sedatives or antidepressants has been useful in preventing or reducing the incidence of attacks. We have found bupropion to be quite useful at doses ranging from 5 mg twice daily to 7.5 mg three times a day. The side effect profile is favorable with a minimum of sedation or enhanced appetite.

Cough or chest pain

Cough and chest pain are common symptoms in athletic individuals. As noted above, EIA must be considered. Other diagnoses must be entertained as well, however. In the young healthy individual, noncardiac etiologies dominate, but as the subject ages, cardiac chest pain becomes more prominent [134–144].

Common noncardiac etiologies include: pleuritis, pleurodynia, bronchitis, pneumonia, costochondritis, intercostal muscle strains, and chest wall trauma. Less common etiologies one should consider include pneumothorax, pleural effusion, pulmonary embolism, esophageal reflux or spasm, cervical disk disease, arthritis, breast disorders, herpes zoster, panic attacks, and performance anxiety. Cardiac etiologies include angina, ventricular and supraventricular arrhythmias, pericarditis, Wolff-Parkinson-White syndrome, hypertrophic cardiomyopathy, mitral valve prolapse, aortic stenosis, aortic dissection, and cocaine usage.

Common causes of cough include bronchitis, postnasal drip, sinusitis, pneumonia, postviral bronchospasm, tonsillitis, laryngitis, and EIA. Less common causes include infectious etiologies (tuberculosis, fungal, *Pneumocystis carinii pneumonia*), drug-induced (ACE-inhibitors, beta blockers), gastroesophageal reflux (GERD), aspiration, foreign body aspiration, tumors (bronchogenic, mediastinal, laryngeal), interstitial lung diseases, congenital anomalies, local irritants, and post-traumatic effects.

Exercise-induced anaphylaxis and urticaria

Some individuals are susceptible to anaphylaxis and urticaria during exercise. Exercise-induced anaphylaxis (EIA) is uncommon, and death resulting from an episode is rare. Most patients with this disorder either have mild symptoms or recognize life-threatening symptoms early and discontinue exercise. The mast cell seems to be integral to the development of EIA, as increased levels of

histamine, tryptase, and leukotrienes are demonstrated. Manifestations of exercise-induced urticarial disease are: (1) cholinergic urticaria, (2) classic exercise-induced anaphylaxis, and (3) variant exercise-induced anaphylaxis.

Patients with cholinergic urticaria generally develop papules (2 mm–5 mm) surrounded by an erythematous halo. A large (10 cm–20 cm) macular erythematous and pruritic lesion may be the sole manifestation, however [145]. Lesions appear on upper thorax or neck but may spread [146]. They appear in response to exercise, passive warming, and emotional stress [147,148]. Pulmonary symptoms commonly occur, yet changes in pulmonary function tests are inconsistent.

Classic exercise-induced anaphylaxis manifests with urticaria or angioedema, upper airway obstruction, and hypotension from vascular collapse. Patients complain of itching, choking sensation, wheezing, gastrointestinal spasms, nausea, and headache [145]. A variety of activities have been implicated, although jogging and running have been primarily reported. Symptoms last 30 minutes to 4 hours after termination of exercise [149]. Patients with variant exercise-induced anaphylaxis present with small erythematous papules, much like those with cholinergic urticaria. The variant form accounts for 10% of EIA, and unlike cholinergic urticaria the papules are only provoked by exercise and may progress to anaphylaxis [146,148].

The diagnosis of exercise-induced urticaria or anaphylaxis is based primarily on history [145]. With exercise-induced urticaria, patients complain of exercise-induced cutaneous warmth, pruritis, and erythema. If symptoms progress to dyspnea, wheezing, dizziness, or syncope, then the diagnosis becomes exercise-induced anaphylaxis. As noted above, patients may complain of gastrointestinal symptoms and headache. A history of atopy is also supportive. If patients develop lesions during passive rewarming, they likely have cholinergic urticaria and not variant exercise-induced anaphylaxis. For patients suspected of having EIA, an exercise test (with emergency equipment readily available) can be performed to elucidate symptoms. A negative test does not exclude the diagnosis, however, as the presentation is variable.

Some patients have food-dependent, exercise-induced anaphylaxis (FDEIA), in which exercise following ingestion of a specific food leads to anaphylaxis. A recent study from Italy evaluated 54 patients with FDEIA and found that tomatoes, cereals, and peanuts were the most common triggers [150]. Fifty-two patients had more than 1 food allergy and 22 had more than 20 food allergies. Patients exercising more than 4 hours after ingestion of identified foods did not develop FDEIA.

Treatment should be directed at modifying behaviors and activities [151–154]. Patients should not exercise alone and should have epinephrine available at all times. They should not exercise within 4 to 6 hours after eating. Women should not exercise in the perimenstrual time frame. Patients who develop symptoms should stop exercising and administer epinephrine immediately. Antihistamines are also effective in preventing EIA [146,151,152,155]. Variable success has been seen with cromolyn [155,156]. The role of leukotriene antagonists in the prevention of exercise-induced anaphylaxis remains undefined [118,157].

Exercise in patients with chronic obstructive pulmonary disease (COPD)

In comparison with normal subjects, patients with COPD have increased dead space ventilation at rest and during exercise. To maintain homeostasis, increases in minute ventilation with exercise need to accommodate not only increasing $\dot{V}CO_2$ but also increasing dead space ventilation. In an effort to conserve energy, however, patients with COPD accept somewhat elevated $PaCO_2$ levels and minimize the increases in minute ventilation associated with exercise [10,158,159]. These patients also demonstrate a reduced MVV and quickly achieve V_E/MVV levels exceeding 0.75, which is distinctly unusual for normal subjects [31]. Such levels cannot be sustained.

Patients with COPD assume a breathing pattern similar to normal subjects, with tidal volume and frequency increasing in response to demand until tidal volume reaches 50% to 60% of vital capacity. At that point, additional increments in V_E are primarily achieved through changes in respiratory frequency [160,161]. At any given level of minute ventilation, patients with COPD exhibit smaller tidal volumes and higher respiratory rates. Due to alterations in respiratory mechanics, primarily hyperinflation, patients with COPD will generate higher inspiratory pressures than normal subjects at similar work rates [31]. As patients with COPD have reduced inspiratory muscle strength, these increased pressure requirements will result in fatigue more rapidly.

Patients with severe COPD, as indicated by spirometry, will likely exhibit oxygen desaturation during exercise [162,163]. This results from a fall in mixed venous blood oxygen tension flowing to low ventilation-perfusion areas of the lung, as well as relative hypoventilation (see above) [164,165]. Unlike patients with mild COPD, these patients cannot improve their overall ventilation-perfusion ratios with exercise. The resulting hypoxia can serve to stimulate ventilation and limit exercise even more rapidly [31]. Oxygen therapy can ameliorate this problem. Oxygen therapy may also reduce the extent of right ventricular dysfunction that is seen in patients with moderate to severe COPD as a result of pulmonary hypertension and increasing pulmonary artery pressures during exercise.

Exercise in patients with COPD is limited by a variety of factors: V_E/MVV , respiratory muscle inspiratory pressure/strength, dyspnea, deconditioning, acidosis associated with lactate, respiratory acidosis, cardiac dysfunction, limb muscle dysfunction, and motivation. Exercise endurance can be extended when achieving intensities equal to 60% of $\dot{V}O_{2max}$ at least three times per week, however. Patients with COPD exercising at levels equal to 30% of $\dot{V}O_{2max}$ do not derive any benefit of training. An exercise study permits determination of $\dot{V}O_{2max}$ as well as a workload at 60% $\dot{V}O_{2max}$ [166,167].

A common alternative to a formal exercise study is to determine the level of exercise at which a subject achieves 70% of his or her maximal heart rate. A recent study, however, has shown that in patients with COPD the relationship between percent maximum heart rate and percent $\dot{V}O_{2max}$ are different from that suggested by the American College of Sports Medicine [168]. Thus a formal exercise test affords more accurate data.

Exercise training is only one aspect of a complete pulmonary rehabilitation program. Patients not only benefit in exercise capacity and endurance but also quality of life when participating in pulmonary rehabilitation programs [166]. In addition to exercise training, they receive upper and lower extremity endurance training, strength training, respiratory muscle training, education, and training in energy conservation techniques and control of breathing techniques, as well as psychosocial and behavioral intervention.

Exercise in patients with interstitial lung disease (ILD)

Patients with interstitial lung disease also have increased dead space ventilation at rest and during exercise, and hence an increased ventilatory response at each level of exercise in comparison with normal subjects [169–172]. Additional stimuli to enhance minute ventilation may include afferent signals from mechanoreceptors, chemoreceptors, respiratory muscles, and mediators of lung inflammation. Patients with ILD have reduced MVV values and thus an increased V_E/MVV value for any level of exercise. Their breathing pattern response to exercise is similar to normal subjects, but they achieve tidal volumes equal to 50% to 60% of their vital capacity quickly, as vital capacity is markedly reduced [7,173,174]. Thus the patient with restrictive lung disease is very dependent on respiratory rate to increase minute ventilation. Patients with ILD often are hypoxic at rest and most will exhibit oxygen desaturation during exercise [170,171,175]. An increased (A-a)DO₂ results from greater ventilation-perfusion mismatch and shunting. Diffusion limitations and low mixed venous blood oxygen tension also contribute to exercise induced hypoxia, however. Although resting PaO₂ does not correlate with disease severity, the degree of oxygen desaturation is related to the diffusing capacity of carbon monoxide (DLCO) as measured at rest [176,177]. The right ventricular response to exercise appears to be normal in patients with ILD [178]. These patients also have reduced respiratory muscle strength and yet must generate high pleural pressures [179–183] because of their poorly compliant lungs.

Exercise in patients with ILD is limited by: V_E/MVV , the ratio of respiratory muscle pressure to respiratory muscle strength, arterial desaturation, dyspnea, and poor conditioning and motivation [184]. Oxygen therapy has not resulted in improved incremental exercise performance [185]. Oxygen therapy has been shown to improve endurance exercise performance as well as reduce dyspnea and minute ventilation, however [185,186].

Insufficient data exist to recommend an exercise prescription for patients with ILD. Exercise testing can determine the amount of oxygen required for given exercise intensities. In clinical practice, the recommendations for patients with COPD are applied to patients with ILD.

Summary

The respiratory system rarely limits exercise in the normal subject. In patients with chronic pulmonary processes or in the elite athlete, however, the respiratory

system may indeed be the limiting factor. Common respiratory disorders include chest pain syndromes, cough, exercise-induced asthma, and vocal cord dysfunction. Chronic lung diseases such as asthma, COPD, and interstitial lung disease impact exercise capacity and endurance. Exercise testing can be useful to distinguish acute and chronic pulmonary causes of dyspnea during exercise, as well as to differentiate between cardiac and pulmonary causes.

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