Physiological Basis of Fatigue

ABSTRACT

This work summarizes our knowledge of the physiological basis of fatigue and the effects of exercise and pharmacological interventions on fatigue. Fatigue may be defined as physical and/or mental weariness resulting from exertion, that is, an inability to continue exercise at the same intensity with a resultant deterioration in performance. The concept of deconditioning in patients is discussed as well as the implications for their rehabilitation and exercise. Because fatigue may result from a number of causes, including loss of muscle mass, deconditioning, nutritional deficiencies, oxygen delivery, and anemia, it should be treated comprehensively. Antifatigue therapy should be the standard of care for most chronic conditions associated with fatigue.

Key Words: Fatigue, Exercise, Physiology, Pharmacology, Rehabilitation

A broad array of clinical conditions is associated with extreme levels of fatigue. Chronic renal failure, congestive heart failure, cancer, musculoskeletal diseases, chronic fatigue syndrome, chronic obstructive pulmonary disease, human immunodeficiency syndrome/acquired immunodeficiency syndrome, (HIV/AIDS) and more are associated with mild-to-often debilitating fatigue. Aging is also associated with fatigue, which may lead to frailty and disability. Perhaps the chronic condition most associated the fatigue is cancer. Cancer and its treatment are associated with a broad range of physiological and metabolic adaptations, including cachexia, muscle wasting, anemia, and inflammation. One of the most commonly reported symptoms of cancer is a reported lack of energy or fatigue. Fatigue is highly prevalent (between 80 and 99%) among cancer patients who undergo treatment with chemotherapy, radiotherapy, or both.

A patient’s perception of fatigue results from many factors related to physiological, psychological, or cognitive changes. Fatigue also may result from a lack of sleep. The purpose of this review is to describe the physiological basis of fatigue and how these factors may be related to fatigue related to chronic disease or its treatment. There is a large body of literature on fatigue associated with cancer and its treatment. However, few studies have examined the physiological or biological basis of this fatigue. It is very likely that many aspects of cancer-related fatigue are quite different from fatigue related to physical exertion. However, it is also likely that the underlying causes of fatigue related to exertion share common mechanisms with fatigue related to chronic illness. A
recent National Institutes of Health conference issued a "state of the science statement on symptom management in cancer, specifically related to pain, depression, and fatigue."明智

Among the conclusions of this conference were the following:

1. Too many cancer patients with pain, depression, and fatigue receive inadequate treatment for their symptoms.
2. Clinicians should use brief assessment tools routinely to ask patients about pain, depression, and fatigue and to initiate evidence-based treatments.
3. Research is needed on the definition, occurrence, assessment, and treatment of pain, depression, and fatigue alone and together through adequately funded prospective studies.

For the purpose of this review, we will define fatigue as physical and/or mental weariness resulting from exertion, that is, an inability to continue exercise at the same intensity with a resultant deterioration in performance. The term "fatigue" appears often in the medical literature but rarely is an operational definition included. Fatigue associated with cancer also may include tiredness or lack of sleep. However, we will use the term "fatigue" as it relates to exertion (such as walking, climbing stairs, or participating in normal activities of daily living).

Because activities of daily living require muscular effort and increased levels of physical activity, an understanding of the causes of fatigue during exertion is helpful in describing the causes of the fatigue associated with other diseases (including cancer), aging, or severe deconditioning (from immobilization or prolonged bed rest). Fatigue resulting from increased physical activity may result from a number of metabolic adjustments to increased muscular activity. Physical activity varies with respect to intensity and duration for any individual. It is important to note that physical conditioning of an individual determines the type of exertion and its intensity. For example, walking at a pace of 2–3 miles per hour would be considered a low-intensity aerobic exercise for a healthy, normally active young man or woman, whereas the same walking pace would be considered high intensity, anaerobic exercise for a severely deconditioned patient with heart failure.

Aerobic Capacity

Physical function may be measured in a great many ways; however, one of the most fundamental measures is maximal aerobic capacity or \( VO_{2\text{max}} \). \( VO_{2\text{max}} \) (volume of oxygen consumed during maximal aerobic exercise or the maximal rate of oxygen consumption) is defined by the Fick equation \((VO_2 = \text{cardiac output} \times \text{arteriovenous oxygen difference})\). \( VO_{2\text{max}} \) is expressed as either milliliters of \( O_2 \) consumed \( \cdot \) kg\(^{-1}\) body weight \( \cdot \) min\(^{-1}\) or liters of \( O_2 \) consumed \( \cdot \) min\(^{-1}\). \( VO_{2\text{max}} \) is a total integrated measurement that is determined by the following: the capacity to inhale sufficient quantities of oxygen, extract oxygen by the lung, carry oxygen by the red blood cells, deliver oxygen (blood) by cardiac output, diffuse oxygen through capillaries, diffusion into muscle cells and binding to myoglobin, and oxidative phosphorylation in muscle mitochondria for ATP production. This equation demonstrates that there are two important determiners of \( VO_{2\text{max}} \), central factors that control the delivery of oxygen to skeletal muscle and the capacity of skeletal muscle to extract and use oxygen for ATP during exercise. Regularly performed aerobic exercise increases \( VO_{2\text{max}} \) through a number of mechanisms: (1) increased cardiac output resulting from a plasma volume expansion (approximately 15%) and increased stroke volume as a result of cardiac hypertrophy and (2) improved capacity to extract and use oxygen by skeletal muscle. This enhanced oxidative capacity of muscle is caused by increased capillarization, mitochondrial density, and myoglobin content.

Few individuals actually exercise or work at an intensity that is equal to their \( VO_{2\text{max}} \) during the normal course of a day. However, a diminished maximal aerobic capacity can greatly limit the performance of activities of daily living. For example, the oxygen cost of walking at a pace of 2 miles per hour (a relatively slow pace) for a 60-kg individual is almost 0.8 liters of oxygen per minute. If an individual has a \( VO_{2\text{max}} \) of 15 mL/kg per minute, he or she can only consume a maximum of 0.9 liter of oxygen per minute. For people who are functionally intact with no impairment in oxygen delivery or use, virtually all activities of daily living are performed at a low to moderate exercise intensity. Most individuals pace themselves as an intensity of about 50% of \( VO_{2\text{max}} \) when asked to perform work over a sustained period of time (walking, for example). For men and women with very low levels of \( VO_{2\text{max}} \), one can see that self-paced activities at 50–60% of maximal capacity is significantly lower than the oxygen costs of most activities of daily living.

Anemia and Aerobic Capacity

Under most conditions, the delivery of oxygen (cardiac output) limits \( VO_{2\text{max}} \). That is, the capacity to extract and use oxygen by skeletal muscle is greater than the capacity to deliver oxygen. Because of this, a number of investigators have demonstrated a remarkably close relationship between hemoglobin and \( VO_{2\text{max}} \). Increasing blood hemoglobin concentration (from anemic to normal or normal
from normal to supernormal) has been demonstrated to increase \( VO_{2\text{max}} \) and submaximal exercise performance.\(^{6-8} \) Anemia caused by malnutrition has been demonstrated to limit functional status and work capacity.\(^{9} \) On the other hand, aerobic exercise performance in athletes can be substantially improved by increasing hemoglobin levels above normal through the use of recombinant human erythropoietin.\(^{10} \)

Muscular activity may be generally classified as anaerobic or aerobic. Aerobic activities are performed at intensities that require oxygen consumption lower than an individual's \( VO_{2\text{max}} \) whereas anaerobic activities are performed at intensities that are greater than \( VO_{2\text{max}} \). Exercise intensities above \( VO_{2\text{max}} \) must rely on a combination of aerobic and anaerobic metabolism and will result in fatigue when sustained over an extended period of time.

**Types of Exertion and Causes of Fatigue**

**Submaximal Activities**

During exercise of any intensity, skeletal muscle produces and consumes lactic acid as a fuel for energy production. During low-intensity exercise, the use of lactic acid as a fuel prevents its accumulation. However, as exercise intensity (and oxygen consumption) increases, the production of lactic acid increases and, at some intensity, production becomes greater than oxidation and intracellular lactic acid accumulation occurs. The exercise intensity at which lactic acid accumulation occurs has been referred to as the anaerobic threshold or the lactate threshold. This increasing blood (and muscle) lactic acid level results in muscle fatigue as well as an increased respiration and heart rate,\(^{11,12} \) and an overall feeling of fatigue. The exercise intensity that generally corresponds to the anaerobic threshold in sedentary individuals is approximately 60% of \( VO_{2\text{max}} \). This means that for a cancer patient with an already low \( VO_{2\text{max}} \), performing most activities of daily living requires an intensity that is greater than the anaerobic threshold. Therefore, it is easy to see why most physical activity performed by this person will lead to an overwhelming feeling of fatigue.

**Glycogen Depletion**

A number of early studies demonstrated that depletion of skeletal muscle glycogen stores coincided with fatigue during submaximal exercise.\(^{13-15} \) Bergstrom et al.\(^{13} \) reported that a high-carbohydrate diet prolonged time to exhaustion by 220% compared with a high-protein, high-fat diet and by 50% when compared with a mixed diet. They showed that consumption of a high-carbohydrate diet resulted in the highest muscle glycogen concentration compared with a mixed diet and a high-protein, high-fat diet. These results have been confirmed by a number of studies; however, the mechanism for this effect is not clear. That is, despite an abundant source of fuel in the form of fatty acids, the depletion of muscle glycogen results in fatigue. Glycogen provides a carbon source for the tricarboxylic acid cycle (TCA) provides NADH, FADH\(_2\), which then is converted into ATP by the electron transport system. ATP and GTP are also directly produced by the TCA cycle. Thus, the glycogen ultimately leads to increased ATP production both anaerobically (glycogenolysis) and through the TCA cycle (aerobic metabolism), and thus results in improved performance. However, Baldwin et al.\(^{16} \) recently reported that glycogen availability had no effect on maintaining the concentration of TCA cycle intermediates or the total adenine nucleotide pool (ATP + ADP + AMP), suggesting that the mechanism for the improvement in performance with high muscle glycogen levels may not be as simple as previously believed. A study in situ in rodents suggests that a decrease in sarcoplasmic reticulum glycogen and sarcoplasmic reticulum glycogen phosphorylase occurring with a reduction in whole muscle glycogen and tetanic force resulted in a significant reduction in sarcoplasmic reticulum Ca\(^{2+}\) uptake.\(^{17} \) Thus, this is a potential mechanism for the fatigue that occurs with a reduction in intramuscular glycogen concentrations. This possibility awaits further scientific inquiry.

**Dehydration**

Dehydration will impair physical performance. As little as a 2% reduction in body weight will impair endurance exercise performance.\(^{18} \) Further, Montain et al.\(^{19} \) reported that a 4% reduction in body weight is adequate to reduce short-term (exhaustion reached in approximately 4 mins) exercise capacity. However the mechanism(s) for this reduced performance, which includes impaired metabolism and/or hyperthermia, has not been adequately answered until recently. Gonzalez-Alonso et al.\(^{20} \) examined the effect of the reduced blood flow associated with dehydration on substrate delivery, metabolite, and heat removal to and from the active skeletal muscles as well as fuel utilization across the leg. These investigators concluded that fatigue was the result of hyperthermia and not the result of altered muscle metabolism.

**Nutritional Deficiencies**

Loss of appetite often is associated with chronic diseases and/or aging. Decreased food intake can result in involuntary weight loss and specific nutritional deficiencies. Vitamin D deficiency
is associated with muscle weakness, type II fiber atrophy, and accelerated sarcopenia. Bischoff et al. found that among elderly women in a long-term care facility, vitamin D deficiency is associated with an increased rate of falling and that a single intervention with vitamin D reduced the risk of falling by 45% compared with a calcium-only-supplemented group. They concluded that the "impact of vitamin D on falls might be explained by the observed improvement in musculoskeletal function." In an older (>65 yrs) population of community-dwelling men and women, vitamin D supplementation (single intramuscular injection of 600,000 IU 25(OH)D) improved functional capacity but did not have any effect on rate of falls. These and other studies demonstrate a strong effect of vitamin D on muscle function. Treatment for weakness or fatigue that may be associated with chronic disease, particularly in elderly people, should include assessment of vitamin D status or the use of a vitamin D supplement.

Protein energy malnutrition (PEM) impairs muscle function. PEM results in a decrease in high energy phosphate levels in skeletal muscle as well as a number of components of contractile function. Refeeding elderly, malnourished patients (15 g of protein and 836 kJ, twice daily) increased muscle strength and function compared with a well-nourished age-matched control group strongly indicating that intracellular energy metabolism is affected by PEM refeeding can have a rapid and powerful effect on muscle function, functional capacity, and the feeling of fatigue. In addition, long-term PEM will greatly reduce muscle size, ultimately diminishing strength.

Central Fatigue

Central fatigue is impaired muscular performance that arises from the central nervous system. There are two general ways to study central fatigue. The first way and likely the best way is by using a technique where "added force" is determined. This occurs by superimposing a supramaximal electrical stimulus of a muscle onto a maximal voluntary contraction for that muscle. Any "added force" generated in addition to that produced by the maximal voluntary contraction is indicative of an impairment from the central nervous system down to the level proximal to the neuromuscular junction. Thus, this is a fairly direct way to determine central fatigue. This can be done after exercise and/or after an intervention thought to induce central fatigue. A second way is to exogenously provide a substance thought to induce central fatigue and look at its effect on exercise capacity. However, this is indirect because you do not know if the substance had peripheral and/or central effects. Further, this technique is usually undertaken in animal models.

Recent data suggest that prolonged exercise in a thermoneutral or hot environment and exhaustive short-term exercise (30–45 mins) results in a significant level of central activation failure or central fatigue. Lepers et al. reported that 2–5 hrs of cycling at 55% of VO_{2max} resulted in an 8% reduction in the ability to activate the quadriceps in trained endurance athletes. Further, Millet et al. reported that maximal voluntary activation was reduced by 30.2% in the knee extensors and by 27.7% in the plantar flexors after an ultramarathon. Nybo reported that 3 hrs of cycling at 60% of VO_{2max} resulted in a significant reduction in muscle activation in trained endurance athletes when placebo was ingested but not when glucose was ingested suggesting that central fatigue can be induced by exercise induced hypoglycemia. Nybo and Nielsen reported that central activation was 34% lower in individuals who exercised for 50 mins at 60% of VO_{2max} in a hot (40°C) environment than in those same individuals exercising for 60 mins in a thermoneural (18°C) environment. The subjects in that study were trained endurance cyclists. Bentley et al. reported that 30 mins of exercise at 80% of VO_{2max} followed by 4 × 60 secs at 120% of VO_{2max} in trained cyclists led to an approximately 6% deficit in muscle activation.

Effects of Aerobic Exercise on Brain Dopamine

Drugs such as methylphenidate and pemoline act to increase brain dopamine concentrations and reduce fatigue in individuals with cancer. Other interventions that have been shown to beneficially alter dopamine metabolism in the brain are an acute bout of aerobic exercise and chronic aerobic exercise training. Gilliam et al. reported that chronic exercise training (1 hr/day, 6 days/wk for 12 wks) increased the number of dopamine receptors in the striatum of rats by 48%. Meeneus et al. reported that 60 mins of acute exercise significantly increased the dopamine concentration of the striatum during exercise and for 2 hrs after exercise. Heyes et al. reported that exhaustive running in rats increased dopamine concentrations in the striatum significantly by 10%. Hattori et al. reported that extracellular dopamine in the striatum of rats was increased by approximately 25% as a result of treadmill running for only 20 mins. Wilson and Marsden reported a approximately 89% increase in dopamine in the extracellular fluid of the nucleus accumens in response to 20 mins of treadmill exercise in rats. In contrast, in the only human study examining the effects of exercise on striatal dopamine release, Wang et al. found no significant effect of intense aerobic exercise. One possible explanation for this negative result is methodological. The dopamine concentration only
increases 80% in response to exercise in rats but administration of methylphenidate can increase dopamine by approximately 600%. Thus, the increase in brain dopamine concentration in humans (it has been shown to be an 80% increase in rats using the microdialysis approach) may not be large enough to be detectable by using the positron emission tomography scan. In an open labeled pilot study using 10–30 mg/day of methylphenidate in advanced cancer, Sarhill et al. reported that 9 of 11 patients had reduced fatigue after 7 days of treatment. The most prominent side effect of this therapy was insomnia in 5 of the 11 patients.

**Short-Term High-Intensity Exercise**

During very short-term, high intensity exercise (5–10 secs), maximal power output declines and correlates well with the decline in phosphocreatine (PCr). At the same time, the [H+] concentration is decreasing, likely as the result of the consumption of protons when PCr + ADP + H+ gets converted to Cr + ATP. Early in vitro investigations at temperatures much lower than physiology suggested the [H+] is a major contributor to fatigue; however, more recent investigations suggest that at near physiological temperature the [H+] has little effect on the contractile processes. Also, in some instances, force recovers more rapidly than pH during recovery from fatiguing contractions. There seems to be a large amount of data suggesting that an increase in the Pi concentration is a major contributor to fatigue during intense contractions. Additionally, Degroot et al. reported a better correlation between Pi and H2PO4− concentrations and the decline in maximal force generating capacity than for the H+ concentration and the decline in maximal force generating capacity. However, creatine monohydrate ingestion, which raises the intramuscular PCr concentration, results in improved exercise performance despite an increase in Pi released as a result of the greater amount of PCr. This argues against a role for Pi in fatigue.

**Factors Limiting Strength**

Factors that limit the strength of muscle force generation can be broadly classified into factors that deal with the muscle itself and factors within the nervous system. Generally speaking the more muscle mass an individual has the greater the ability to produce force. However, type II (fast twitch) muscle fibers exert more force than type I muscle fibers thus the fiber type composition and size of type II and type I fibers also play a major role. With regard to the nervous system and muscle force generation many factors are involved. First, an inability to recruit all available motor units (motor neuron and all of the muscle fibers it innervates) may limit performance. Second, motor unit firing rates may be sub optimal. The faster the motor unit firing rates the greater the muscle force that can be generated. For movements involving more than one muscle group the ability to synchronize the activation of motor units from different muscle groups is of paramount importance. Coactivation of antagonist muscle groups can also limit muscle force generating capacity of agonists. Resistance training acts to reduce the coactivation of antagonists. Further, inhibition of force generation resulting from activation of the Golgi tendon organ, referred to as neural inhibition, can also limit force generating capacity and resistance training seems to reduce this neural inhibition.

Cross-sectional area may be the most important determinant of strength (maximal force production). Akima et al. reported a correlation of 0.827 between muscle cross-sectional area and maximum knee extensor torque in men and a correlation of 0.657 in women. In that study, 164 individuals were studied and were grouped into five age group spanning from ages 20 to 84. However, in a group of frail elderly subjects, muscle cross sectional area explained approximately 6% (after controlling for gender, $r^2 = 0.06, P < 0.05$) of the variability in muscle strength. Loss of muscle mass with advancing age (sarcopenia) is associated with age-associated loss of strength; however, it may not be the most important variable among extremely inactive people. As mentioned previously, factors affecting strength that are considered neurological in origin are motor unit recruitment, motor unit firing rates, and antagonist muscle cocontraction. It is clear that in some disease states such as multiple sclerosis and chronic fatigue syndrome, there is a reduction in the ability of muscle activation (motor unit recruitment and/or motor unit firing rates), which leads to a reduction in muscle strength.

**Fatigue in Chronic Conditions**

**Multiple Sclerosis**

Increased fatigability and reduced muscle strength are observed in individuals with multiple sclerosis when compared with control subjects. Reduced muscle oxidative capacity results in increased fatigability when muscles are electrically stimulated, but during voluntary contractions it seems that fatigue is a result of impaired muscle activation possibly at the level of excitation–contraction coupling. At least part of the reduced force generating capacity in individuals with multiple sclerosis may be attributable to the inability to activate the muscle mass that they have. However, another major factor resulting in reduced muscle strength is reduced muscle fiber size. Muscle fiber
size is 25% smaller in individuals with multiple sclerosis compared with control subjects.55

**Chronic Heart Failure**

Increased skeletal muscle fatigability is evident in chronic heart failure (CHF),57 which may at least in part the result of reduced muscle blood flow to the working muscle and is definitely attributable to metabolic abnormalities intrinsic to skeletal muscle.57-61 The changes in skeletal muscle that result in increased fatigability are most likely related to reduced muscle oxidative capacity,62,63 in addition to reduced type I muscle fibers and increased type II B muscle fibers.63 These changes may be the result of disuse and/or the direct effects of the disease.

CHF also results in reduced muscle mass and muscle strength64 in this patient population. Muscle cross-sectional area significantly correlates with peak VO2, suggesting that, in patients with CHF and in the elderly,65 muscle mass is a significant predictor of peak aerobic capacity. Elevated levels of the proinflammatory cytokines interleukin-6 and tumor necrosis factor alpha have been reported in individuals with CHF, and high levels of these cytokines have been implicated in muscle wasting in elderly individuals.66 Hambrecht et al.67 reported that individuals with CHF have reduced muscle insulin-like growth factor-I mRNA and protein and that this is significantly correlated with muscle cross-sectional area. Resistance upregulates muscle IGF-I mRNA and protein,68,69 resulting in muscle hypertrophy.

van den Berg-Emons et al.70 examined the effects of aerobic exercise training on levels of physical activity and quality of life. They found that although the exercise training increased aerobic power (17%), 6-min walk distance (10%), and strength (13-15%), no changes in physical activity or quality of life were seen compared with a control group of patients receiving standard therapy but no exercise. On the other hand, in a similar group of patients with CHF,71 exercise training decreased perceived dyspnea during submaximal exercise and improved Minnesota Living with Heart Failure Score. Six-minute walk time was improved by 65% with exercise training (compared with activity restriction) in patients with severe chronic heart failure (ejection fraction 21 ± 1%). Although the number of well-controlled, randomized trials examining the effects of exercise in people with chronic heart failure is few, they have all demonstrated positive results. Differences in improvements in functional capacity may be the result of inherent differences in baseline functional status, severity of disease, and the intensity, frequency, and duration of the exercise intervention.

**Chronic Renal Failure**

This condition leads to a reduction in hemoglobin concentration,72 a decrease in muscle mass,73 and a reduction in muscle quality termed “uremic myopathy.”74 All of these manifestations can lead to increased fatigability. Correction of the reduced hemoglobin concentration via the administration of recombinant erythropoietin does not improve maximal oxygen consumption proportionally. Marrades et al.75 reported that erythropoietin therapy resulted in increased hemoglobin 69% and a 33% increase in maximal oxygen uptake. The impaired O2 extraction is the result of reduced O2 conductance from the muscle capillary to the mitochondria.74,75,77 Impaired oxidative metabolism intrinsic to the muscle does not seem to be a source of fatigability in chronic renal failure.74,78 The major factor that seems to contribute to the reduced O2 conductance from muscle capillary to mitochondria in chronic renal failure is a low number of capillaries per muscle fiber.78,79

The reduction in muscle strength in individuals receiving hemodialysis is the result of a reduction in muscle contractile tissue and not the result of an inability to activate the available muscle.72 In addition, muscle quality as measured by force generating capacity per unit contractile tissue was not reduced in individuals on hemodialysis.73 The reduction of muscle mass in chronic renal failure seems to be attributable to increased protein degradation80 and reduced protein synthesis.81 The increased muscle protein degradation is the result of activation of the ATP-dependent ubiquitin–proteasome pathway which is further activated by acidosis present in uncontrolled chronic renal failure.82

Although anabolic steroids have been used frequently for the treatment of anemia associated with chronic renal failure, their effects on body composition and function have not been determined in this population. The potential for anabolic steroids/testosterone to be beneficial is likely given the fact that these patients suffer from malnutrition, reduced muscle mass, and fatigue.82 Johansen et al.83 reported that in patients undergoing dialysis for at least 3 mos, 100 mg of nandrolone decanoate given weekly for 6 mos increased lean body mass by 4.5 kg and time to complete a walking/stair climbing test improved significantly by 11.5% whereas it became slower by 8.8% in the control group. Those receiving nandrolone also reported less fatigue than control patients after the intervention period. Thus, anabolic therapies would seem to be beneficial in this population of patients. This patient population also should be a target for active exercise and rehabilitation therapies. The reduced muscle capillary density, decreased muscle protein synthesis, and fa-
tigue are likely to be strongly influenced by increased levels of physical activity.

In patients with end-stage renal disease on hemodialysis, 6 mos of aerobic exercise training resulted in substantial increases peak VO_{2}, and exercise time to exhaustion. The exercise training was more effective in subjects performing their exercise on nondialysis days compared with those exercising on the days that they received dialysis.

**Chronic Fatigue Syndrome**

The causes of fatigue in this disease seem to be proximal to impaired muscle metabolism. In addition, there seems to be minor morphological abnormalities of skeletal muscle in this disease. Byrne and Trounce reported that carnitine, glycolytic enzymes, and mitochondrial enzymes were normal in individuals with chronic fatigue and those with fibromyalgia syndrome, suggesting that impaired muscle metabolism is not the reason for the increased fatigability of these conditions. Kent-Braun et al. reported greatly reduced central activation of muscles during sustained contraction in individuals with chronic fatigue syndrome (CFS), implicating central factors in fatigue during exercise. McCully and Natelson examined oxygen delivery to skeletal muscle in CFS using continuous-wavelength near-infrared spectroscopy and found that the time constant for oxygen delivery was 36.8% longer in individuals with the disease than control subjects. However, in a subsequent study the same investigators observed that blood flow was not impaired in patients with CFS relative to controls. A frequent finding in CFS is impaired recovery of force generating capacity after fatiguing exercise. Indeed, Paul et al. reported that force-generating capacity was impaired in CFS patients for as long as 24 hrs after fatiguing isometric contractions but not in controls. There is a fair amount of evidence suggesting that there is physical and cardiovascular deconditioning in CFS, which may be reversible with exercise training. However, muscle wasting or atrophy does not seem to be a universal or major problem in CFS as Lane et al. reported that muscle fiber atrophy was only present in 10.4% of the cases of CFS.

**Aging**

Normal aging is associated with a decline in muscle strength and mass and a reduction in VO_{2max}. After the age of 30, the decline in VO_{2max} seems to be about 10% per decade, whereas the loss in muscle strength is approximately 12–14% per decade. This decrease in maximal aerobic capacity results from sarcopenia, reduced maximal heart rate, and reduced overall levels of physical activity. Fleg and Lakatta demonstrated that muscle mass accounts for most of the variability in VO_{2max} among people older than the age of 60 yrs. The decrease in strength means that a given load (e.g., carrying a bag of groceries) is a greater percentage of maximal force production. The greater the percentage of maximal force production, the fewer number of repetitions possible and the slower the speed of contraction. Thus, the decline in strength ultimately leads to greater fatigue or shorter endurance or both. Further, the age-associated decrease in maximal aerobic capacity results in a greater relative intensity at any given submaximal energy expenditure. The greater the relative intensity (%VO_{2max}), the shorter the exercise duration that is possible because of fatigue. It is clear that maximal force generating capacity decreases with age. What is less clear is the relationship between fatigue or endurance at a given percentage of maximal force generating capacity and age. Studies report that fatigue is less or similar or greater for older individuals than young individuals at a given percentage of maximal force generating capacity. Of interest from a practical standpoint is that older women classified as fallers (unexplained contact with the ground during the previous 18 mos) had reduced endurance time during isokinetic knee extensions and prolonged recovery time after the knee extensions than older women who were not classified as fallers and than younger women indicating that muscle endurance may be related increased risk of falls in elderly women.

**Testosterone and Sarcopenia**

Morley et al. studied 37 men ages 69–89 yrs old, 26 of whom had a mean total testosterone level of less than 272 ng/dl. They were administered 200 mg of testosterone enantate every 2 wks for 3 mos. They reported a ninefold increase in bioavailable testosterone and significant increase in right hand muscle strength. Sih et al. reported that 12 mos of testosterone replacement (biweekly injections of 200 mg) in hypogonadal elderly men resulted in a significant increase in bilateral grip strength. Bhasin et al. examined the effects of 10 wks of testosterone replacement (100 mg/wk) on body composition and strength in seven hypogonadal men ages 19–47. By day 15, serum testosterone had increased from 71.9 to 509 ng/ml. There was an 8.8% increase in fat-free mass, an 11% increase in triceps cross-sectional area, and a 7% increase in thigh cross-sectional area. This group has also demonstrated that both older and young subjects demonstrate similar responses to testosterone injections. Strength on the bench press increased by 22% and on the squat exercise increased by 45%. Urban et al. administered 100 mg of testosterone enanthate week to six elderly men (mean age 67) for 4 wks and observed significant increases in muscle strength of the ham-

January 2007

Physiological Basis of Fatigue

S35

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
patients with cancer complain of chronic fatigue. Winningham\(^{[152]}\) wrote that the manifestations of fatigue are better appreciated "if fatigue is conceptualized as a syndrome, namely, cancer-related fatigue syndrome." Patients and practitioners often mistake lack of sleep as a cause of cancer-related fatigue syndrome and often advise rest or increased sleep to alleviate this syndrome. Increased rest paradoxically can result in further deconditioning and exacerbate cancer-related fatigue syndrome. Lee and coworkers\(^{[153]}\) demonstrated that, compared with age- and gender-matched subjects, patients with lymphoma scored significantly lower on a variety of functional tasks, including a 6-min walk, a 50-ft walk, and forward reach. They also found a significant relationship between performance on these functional tests and score on a brief fatigue inventory, indicating that physical functional capacity is strongly linked to fatigue in these patients. Interestingly, even among breast cancer survivors, 5 yrs after treatment, reduced functional status is highly prevalent compared with age-matched controls.\(^{[154]}\) Patients with cancer who are most severely fatigued during treatment for their cancer remain fatigued well after treatment and even after resolution of their disease.\(^{[155]}\) Because of the persistence of cancer-related fatigue even after treatment and often after resolution of the tumor, metabolic and physiological adaptations such as deconditioning and cachexia may play a large role in this problem. Therefore, strategies to increase physical activity and decrease loss of skeletal muscle during treatment for cancer should be strongly considered.

Kurzrock\(^{[156]}\) speculated that cytokines may play a role in cancer-related fatigue. Cachexia is present in almost 50% of patients with cancer and is characterized by loss of body mass and, in particular, skeletal muscle. This loss of muscle and body mass is not explained by reduced food intake alone, and has been associated with increased levels of cytokines such as interleukin 1 (IL-1), IL-6, IL-8, and tumor necrosis factor alpha.\(^{[157],[158]}\) Elevated cytokines have been implicated directly in the etiology of fatigue. However, the accelerated loss of skeletal muscle is likely the primary mechanism by which elevated cytokines result in increased fatigue in patients with cancer.

As discussed previously causes of cancer-related fatigue likely fall into the following general categories: anemia, deconditioning, and weakness that may be secondary to cachexia or loss of skeletal muscle. It is quite likely that fatigue associated with cancer and its treatment involves each of these problems as well as anorexia/malnutrition, which also may lead to muscle dysfunction.\(^{[159]}\) Unfortunately, there have been no systematic examinations of the potential causes of cancer-related fatigue. The most frequent interventions to reduce cancer-related fatigue have been increasing hemoglobin levels through the use of rhEPO and/or exercise.

Anemia

Anemia is a frequent consequence of cancer and the use of chemotherapy as well as hemodilution. These causes of anemia respond to the use of rhEPO, with a number of studies demonstrating significant improvements in Hb levels.\(^{[159],[160]}\) The development of anemia in cancer patients and its subsequent treatment with rhEPO is strongly associated with quality of life. Two large, multicenter trials demonstrated that increasing Hb levels were associated with a significant improvement in "energy" level, activity level, functional status, and overall quality of life.\(^{[161],[162]}\) These studies show a clear benefit of the treatment of anemia in enhancing quality of life and decreasing symptoms of fatigue. A recent review of literature\(^{[163],[164]}\) shows a consistent effect of the use of epoetin alfa on improving quality of life in patients with a wide range of different tumor types. However, these studies used qualitative endpoints (questionnaire, self-reported fatigue) and no direct measure of functional status.

Although there are very few studies examining effects of both correcting anemia and exercise training in patients with cancer, there is evidence of improvements in functional capacity by increasing Hb levels in hemodialysis patients. Lundin\(^{[165]}\) demonstrated a 50 ± 0.9% increase in VO\(_{2}\)\(_{\text{max}}\) when rhEPO was used to increase Hb levels from an average of 7.1 ± 1.4 to 9.8 ± 2.1 g/dl in men and women undergoing hemodialysis. Metra\(^{[166]}\) also demonstrated a significant improvement in VO\(_{2}\)\(_{\text{max}}\) in severely anemic hemodialysis patient after use of rhEPO. Akiba\(^{[167]}\) described such a study in patients receiving hemodialysis. VO\(_{2}\)\(_{\text{max}}\) was first measured in anemic dialysis patients before and following treatment with rhEPO. The patients experienced a significant increase in aerobic capacity (approximately 20% improvement). The patients were then divided into a 3-mo aerobic exercise training and sedentary control group. Those patients assigned randomly to the control group demonstrated a decrease in VO\(_{2}\)\(_{\text{max}}\) (despite unchanged Hb levels), whereas those participating in exercise showed a significant and substantial increase in exercise capacity. These results demonstrated that the use of rhEPO can result in improved function, but some of the decreased VO\(_{2}\)\(_{\text{max}}\) and functional capacity seen in these patients was the result of inactivity.

In one of the few studies examining the effects of anemia and cancer on exercise capacity, Daneryd\(^{[168]}\) examined 108 selected cancer patients experiencing involuntary weight loss. They randomly assigned these patients to rhEPO or indomethacin.
strings and quadriceps. These investigators also observed that the fractional synthetic rate of muscle protein was increased by 200% as a result of testosterone administration. Brodsky et al.\textsuperscript{109} administered 3 mg/kg of testosterone biweekly to hypogonadal men (no age given) for 6 mos and reported a 15% increase in fat-free mass and a 56% increase in the muscle fractional protein synthetic rate. Snyder et al.\textsuperscript{107} reported that administration of a testosterone patch to men older than 65 yrs of age for 9 mos, resulted in a significant 1.9 kg increase in lean mass. However, it did not improve the strength of leg extension or flexion. Schroeder et al.\textsuperscript{108} reported that oxandrolone administration (20 mg/day) for 12 wks to elderly men mean age 72 resulted in a 6.3% improvement in the leg press and a 6.3% improvement for the leg flexion. Recently, Steidle et al.\textsuperscript{109} reported that the application 100 mg/day of a testosterone gel over the course of 90 days resulted in an improvement in lean body mass of 1.7 kg and a reduction in body fat of 1.2%. Thus, all but one of the studies cited found increases in strength with testosterone administration and all of the studies that examined the effects of testosterone on body composition found an increase in fat-free mass and/or muscle mass.

Megestrol acetate (MA) is a powerful appetite stimulant that is commonly used to treat involuntary weight loss in elderly people, patients with HIV-associated wasting, and cancer. MA is a synthetic progestin and its use is associated with suppressed testosterone and ACTH secretion.\textsuperscript{110} Lambert and coworkers\textsuperscript{111} examined the combined effects of MA (800 mg/day), testosterone replacement (weekly injections of 100 mg), and progressive resistance exercise training (80% one-repetition maximum (1RM), three sets of eight repetitions, 3 days/wk) in a group of underweight elderly men (n = 30, 67 ± 5.8 yrs) during a 12-wk period. The administration of MA resulted in an average 3.8-kg weight gain in all subjects with a decrease in muscle mass that was not affected by testosterone. Men receiving MA + exercise showed no loss in muscle and MA + testosterone + exercise resulted in an increase in both body weight and muscle size. Recently, Sullivan et al.\textsuperscript{112} examined the combined interaction of testosterone administration and strength training (low or high intensity, 20 or 80% of 1RM, respectively) in extremely frail, hypogonadal, old men (78.2 ± 6.4 yrs), all of whom were inpatient recuperative care patients. They saw no significant interaction between exercise and testosterone for body composition, strength, or functional capacity. High-intensity exercise produced a greater gain in strength and testosterone administration produced a greater increase in muscle size than did exercise alone.

Potential Side Effects of Testosterone Replacement in Older Hypogonadal Men

Sih et al.\textsuperscript{102} reported that 4 of 17 older hypogonadal men withdrew as a result of an abnormal elevation in hematocrit (>52%) during a 12-mo study where 200 mg of testosterone was administered biweekly. Hajjjar et al.\textsuperscript{113} retrospectively assessed 45 elderly hypogonadal men receiving testosterone replacement. The treatment dose was 200 mg of testosterone enanthate or cypionate every 2 wks. They reported that 24% of the testosterone treated subjects developed polycythemia sufficient enough to require phlebotomy or temporary withholding of testosterone injections. In one third of the individuals in whom this problem occurred it occurred less than 1 yr into treatment.

Some studies support the notion that hypogonadism may negatively alter blood lipids and that testosterone replacement may improve blood lipids in these individuals.\textsuperscript{114-118} However, the administration of testosterone to individuals who already have “normal” testosterone concentrations may have adverse effects on blood lipids. Thus, the effect of testosterone replacement on blood lipids in hypogonadal men requires close scrutiny. Berg et al.\textsuperscript{117} reported that the restoration of normal testosterone levels in hypogonadal men did not adversely affect the total cholesteryl/high-density lipoprotein or the low-density lipoprotein cholesterol/apoprotein B ratios, both of which are reflective of atherogenesis. Whitsel et al.\textsuperscript{118} performed a meta-analysis on the effects of testosterone on plasma lipids in hypogonadal men. They reported that the administration of testosterone esters to hypogonadal men resulted in a small, dosage-dependent decrease in high-density lipoprotein cholesterol but also resulted in concomitant declines in total cholesterol and low-density lipoprotein cholesterol. Thus, it seems from their conclusions that testosterone replacement may have little effect on atherogenesis as reflected by the changes in blood lipids.

As summarized by Morales et al.\textsuperscript{119} it seems that in placebo-controlled studies of hypogonadal men receiving androgen replacement that there is not a significant effect of such replacement on prostate specific antigen or prostate volume when compared with the placebo group. As discussed by these authors, there is controversy regarding the relationship between serum testosterone concentrations and the prostate gland. It seems firmly established that testosterone promotes the growth of an established adenocarcinoma, but it is unknown whether testosterone promotes the new development of prostate cancer. A recent meta-analysis\textsuperscript{120} of placebo-controlled interventions using testosterone in elderly men described the incidence of adverse events. These authors examined 19 studi...
ies of 651 men treated with testosterone and 433 with placebo. They found that rates of prostate cancer, prostate-specific antibody >4 ng/ml, and prostate biopsies were numerically high, but no statistical differences in any of these event between groups. Increase in hematocrit was the most frequent adverse event with testosterone treatment. Although, testosterone replacement therapy seems to be beneficial with regard to the restoration of muscle mass and strength, there remain questions concerning its safety that must be resolved before widespread use of androgens in the hypogonadal elderly.

Exercise

A large number of exercise trials have demonstrated that both aerobic exercise and progressive resistance exercise training results in significant and, often, quite substantial improvements even in very old and frail subjects. Meredith et al.121 demonstrated that when the frequency (3 days/wk), intensity (70% \( VO_{2\text{max}} \)) and duration (50 min/day) were controlled aerobic exercise results in the same absolute gains in \( VO_{2\text{max}} \) in older (60–70 yrs) as young men and women (20–30 yrs). In addition, in older people aerobic exercise increases insulin sensitivity, improves tolerance to heat, slows the loss of bone, and increases life expectancy. Progressive resistance exercise training results in large number of positive adaptations in elderly people. Frontera et al.122 showed that high-intensity progressive resistance exercise program of the knee extensors and flexors (80% of 1RM, 3 days/wk, for 12 wks) resulted in a 2- to 3-fold increase in strength, almost 15% increase in muscle size, and a concomitant increase in leg, but not arm, \( VO_{2\text{max}} \).123 in a group of older, previously sedentary men. Progressive resistance exercise training enhances nitrogen retention,124 bone health,125 balance,126 increased energy requirements,127,128 and levels of physical activity129 in elderly people. Piattone et al.127,128 have demonstrated that extremely old and frail nursing home residents show similar, substantial increases in strength. Along with increased strength, improved functional capacity and spontaneous physical activity was demonstrated. The overwhelming consensus130 is that regularly performed exercise training is both safe and effective at any age. Because a regular exercise program has an effect on the two most important causes of fatigue in older people (sarcopenia, deconditioning), an exercise prescription should be the standard of care for all elderly people.131

HIV/AIDS

Fatigue is a common problem in individuals with HIV/AIDS. In additional, muscle wasting is a prominent feature of this disease state. As described previously, a reduction in muscle mass will increase the percentage of maximal voluntary contraction that an individual has to exert for a given standard load (e.g., bag of groceries). Thus, fatigue and/or endurance time will be earlier as a result. Grinspoon et al.132 reported that the 6-min walk time (maximal distance walked in 6 mins) was best predicted by lower body muscle cross-sectional area. Anemia is an additional factor contributing to fatigue in individuals with HIV/AIDS.133 Patient reported fatigue is far more common134 in HIV-positive patients with anemia.

A number of studies have been conducted examining the effects of testosterone and anabolic steroid administration in individuals with HIV and AIDS. AIDS wasting syndrome is characterized by a 30–50% decline in circulating testosterone.135 Therefore, the administration of androgen would seem to be particularly efficacious in this population. A substantial majority of studies published on androgen administration in HIV/AIDS have a significant effect on accrual of fat-free mass. A few studies have examined muscle mass135,136 and have reported positive results. The typical dosage of testosterone is 100 mg/wk. Nandrolone decanoate and oxandrolone have been the anabolic steroids used, and the dosage range for nandrolone decanoate was fairly large (100–600 mg); however, the fat-free mass gains were similar (3.5–3.9 kg) when 100 or 600 mg were administered. A large increase in lean body mass (6.9 kg) and greatly increased nitrogen retention was observed when 20 mg/day of oxandrolone was combined with progressive resistance training.137 The combination of progressive resistance training with androgen administration may be more beneficial with regard to increases in lean body mass than the administration of androgen alone. In the positive study of Sattler et al., a high dose of androgen (600 mg/wk of nandrolone decanoate) was administered whereas in the negative studies testosterone was administered at 100 mg/wk135 and 200 mg/wk. Testosterone at a rate of 100 mg/wk is considered a replacement dose and, thus, the differences in dosages may be the reason for the divergent results. The combination of androgen and resistance training seems to be more efficacious than resistance training alone.133,136,137

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is the presence of an airflow obstruction attributable to either chronic bronchitis or emphysema. Chronic bronchitis occurs when an individual has a chronic cough and sputum production. Emphysema is characterized by abnormal permanent enlargement of the respiratory bronchioles and the alveoli; the airspaces distal to the terminal bron-
chioles. This is accompanied by destruction of lung parenchyma without obvious fibrosis. Patients with COPD have a problem with respiratory mechanics and fatigue of the diaphragm and/or intercostals muscles that may cause them to stop exercising before the exercising limb reaches functional limits. These individuals have reductions in oxidative enzyme activity, conversions to a faster fiber type within muscle, and reduced muscle capillarity. Mador et al. reported that most individuals with moderate to severe COPD do not develop contractile fatigue of the diaphragm after intense exercise to the limits of tolerance. Mador et al. reported that quadriceps maximum voluntary contraction force was reduced by 16% when comparing healthy older adults to individuals with moderate COPD and by 24% when comparing the healthy older individuals to the individuals with severe COPD. Further, it seems that the decrement in muscle strength is greater for the lower limbs than the upper limbs. Differences in muscle strength were proportional to the reduction in thigh cross-sectional area, suggesting a quantity is a greater determinant than is quality. This group also examined the effects of combining strength and aerobic exercise (compared with aerobic exercise alone) on quality of life, 6-min walk distance, endurance time, and strength. They found that although the combined effects of strengthening exercises and aerobic exercise produced substantial gains in muscle strength, both modes of exercise training produced similar increases in quality of life and exercise tolerance. In other words, the increased strength seen with both forms of exercise did not translate to a greater improvement in functional status. These data point to the fact that oxygen delivery and utilization may be more important for quality of life than muscle strength in patients with COPD.

Growth Hormone

Similar increases in muscle strength and muscle size as those attained with testosterone replacement have been observed in older subjects receiving growth hormone therapy. In addition, growth hormone seems to be more effective on reducing fat mass than testosterone replacement. However, the side effects associated with the use of growth hormone include headaches, lethargy, joint swelling, pain, edema, arthralgia, carpal tunnel syndrome, glucose intolerance, and diabetes.

Growth hormone combined with strength training has not been demonstrated to have an additive or synergistic effect. Hennessy et al. demonstrated that 6 mos of rhGH + progressive resistance training and placebo injections + exercise resulted in a 55.6 and 47.8% increase in strength, respectively, with no differences between the two interventions. Yarasheski and colleagues showed similar results with regards to increased strength with a combined intervention of rhGH + strength training in older men and also showed that progressive resistance exercise resulted in an increase in muscle protein synthesis that was not augmented by rhGH.

These studies demonstrate an effect of rhGH on fat free mass but a greatly increased risk of undesirable adverse effects. Because testosterone seems to produce similar result with regards to muscle and strength, growth hormone use to treat sarcopenia, and muscle fatigue should be discouraged. This is particularly true because growth hormone produces no additional effects compared strength training alone.

Albutelor

Albutelor (salbutemol) is a β2 adrenergic receptor agonist with anabolic effects although its effects have not been evaluated in many patient groups. Caruso et al. examined 9 wks of resistance exercise training and the use of albutelor (16 mg/day) or a placebo in healthy young subjects. Albutelor combined with resistance training improved strength to a greater extent than resistance training alone. Kissel et al. administered albutelor at 16 and 32 mg/day to patients with facioscapulohumeral dystrophy for 52 wks. They observed an increase in lean body mass of 1.57 kg as well as an increase in strength for the 32-mg/day group vs. 0.25 kg for the control group. Kinali et al. administered albutelor to children with spinal muscular atrophy for 6 mos and reported a 21.6% improvement in strength and a 20% increase in forced vital capacity as well as a 4.2% increase in lean body mass with few side effects. Uc et al. administered albutelor to overweight Parkinson’s disease patients at 16 mg/day for 14 wks. Symptoms of the disease were significantly improved by the intervention. Further, lean body mass was increased by 9.5% and thigh-muscle cross-sectional area was increased by 5.3%. One of the eight subjects receiving albutelor withdrew after 2 wks because of headache, jitteriness, and anxiety. Further, resting heart rate in the seven patients who completed the trial went from 78.3 to 85.6 beats/min. Thus, albutelor seems to be effective in increasing lean body mass, muscle mass, and strength in various patient groups. Further study of this agent in other patient populations is warranted, particularly when combined with strength training.

Cancer Fatigue

Although fatigue is an almost universal symptom of cancer, there are few studies that have examined its causes or treatment. A number of studies have shown that a large percentage of pa-
hensive battery of therapies designed to reduce fatigue and increase functional status and quality of life.

REFERENCES


22. Visser M, Deeg DJ, Lips P: Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia). The Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab 2003;88:5766–72


42. Sarhill N, Walsh D, Nelson KA, et al: Methylphenidate for...
treatment. Although there was no difference in the rates of mortality between the two groups, the patients treated with rhEPO did not become anemic and preserved their exercise capacity. The patients who did not receive rhEPO demonstrated a significant decrease in Hb and a concomitant decrease in VO$_2$max and functional capacity. These investigators concluded that “the institution of early and prophylactic rhEPO treatment to patients with progressive cancer prevents development of tumor-induced anemia. This achievement was associated with a better preserved exercise capacity, which is explained in part by improved whole-body metabolic and energy efficiency during work load.” This study demonstrates the importance of maintaining or improving Hb levels to prevent a decrease in functional capacity in men and women with cancer.

Central Fatigue in Cancer Can Be Successfully Treated Using Psychostimulants

Fatigue in cancer patients can be treated effectively using psychostimulants such as methylphenidate. This drug increases brain dopamine concentrations. Thus, the possibility exists that brain dopamine concentrations are reduced in individuals with cancer. Regardless, increasing brain dopamine concentrations has a beneficial effect on cancer-related fatigue. In a pilot study, Schwartz et al. reported that in cancer patients receiving interferon-α therapy who ingested 20 mg of sustained release methylphenidate and followed and exercise program 4 days/wk for (15–30 min/day) for 4 mos had a reduction in subjective fatigue and had better cognitive function than those individuals who exercised only and than a historical control group that received interferon-α therapy. Obviously, a weakness of this study is the use of a historical control group rather than a control group randomized and going through the interventions at the same period of time. Breithart et al. reported that the treatment of patients with HIV who had fatigue with 60 mg of methylphenidate or 150 mg of pemoline another dopaminergic agent resulted in reduced fatigue severity, improved quality of life, and reduced depression levels. Thus, based on these data in from patient populations with fatigue, the use of psychostimulants could have a beneficial effect in treating fatigue in individuals with cancer.

Anabolic Hormones

Few studies have examined the effects of androgens on body composition in cancer. Chlebowinski et al. administered nandrolone decanoate (200 mg/wk for 4 wks) to individuals on chemotherapy who had advanced nonsmall cell lung cancer. They reported that half as many patients had weight loss on the anabolic hormone therapy compared with those patients not treated.

Aerobic Exercise Training in Patients With Cancer

Decreased levels of physical activity result in deconditioning, characterized by a decreased VO$_2$max. Complete bed rest results in a rapid and profound decrease in aerobic capacity. Because one cause of cancer-related fatigue may be deconditioning and reduced levels of physical activity, there have been a few studies examining the effects of regularly performed exercise on functional status in cancer patients.

Dimeo and his colleagues examined the effects of aerobic exercise in hospitalized cancer patients. They recruited patients receiving chemotherapy treated on an ambulatory basis by autologous peripheral blood stem cell transplantation. Thirty-three patients were randomly assigned to a training program that consisted of interval type of training on a cycle ergometer while supine (30 min/day, 15 1-min bouts at 50% of maximal heart rate reserve with 1-min rest periods) and a control group of patients who performed no exercise. These investigators saw a 27% greater loss in performance on a treadmill in controls compared with the exercised patients. Interestingly, the investigators observed significant decreases in duration of neutropenia and thrombocytopenia, severity of diarrhea, severity of pain, and duration of hospitalization in the exercise group compared with control. Schwartz et al., examined the effects of regular exercise on self-reported fatigue in women (n = 72) with breast cancer receiving chemotherapy. They examined the effects of a home-based exercise over the first three cycles of chemotherapy and observed a significant reduction in fatigue that was related to compliance to the exercise recommendations. Segal et al. examined a large group of breast cancer patients (n = 123) and demonstrated that when compared with control (no exercise) and self directed and a supervised exercise program produced a significant increase in functional capacity and decrease in weight and fatigue.

Dimeo and coworkers examined a small number of cancer patients (n = 5); however, all of the patients who were studied reported suffering from severe fatigue for a time ranging between 5 wks and 18 mos and because of this fatigue they were hindered from performing normal daily activities. All of the patients trained on a motorized treadmill at an intensity that had been determined to correspond with a circulating lactate level of 3 mmol for six consecutive weeks. This value roughly corresponds to the anaerobic threshold. As they
became better conditioned, their blood lactate levels began to fall during the training, the speed of the treadmill was increased. In this way the training intensity remained constant. The results were very instructive about the capacity of cancer patients to respond to aerobic exercise training. The training speed increased by 23% ($P = 0.06$) and the distance walked per session increased by 100% ($P < 0.05$). Maximal exercise performance was also significantly increased. The authors concluded that cancer patients suffering from primary fatigue should not be advised to increase the amount of daily rest. Rather they should be counseled to carry out aerobic exercise ...." These studies demonstrated the regularly performed aerobic exercise training is both safe and effective in patients with cancer whether they are receiving chemotherapy. Increasing the amount of time that a patient is in bed resting will very likely cause a further deterioration of $V_{O_{2max}}$, anaerobic threshold and functional capacity, leading to an even greater feeling of fatigue. Windsor and coworkers randomly assigned men with prostate cancer receiving "radical radiotherapy" to a control group who were given the advice to rest when they were tired compared with a group who were advised to participate in an home-based walking program (3 days/week, 30 min/day, 60-70% of calculated heart rate maximum) and measured treatment related fatigue. They found a significant increase in the ratings of fatigue after only 4 weeks of treatment in the control group with no change in fatigue in those men participating in the exercise. They noted that "improved physical functioning may be necessary to combat radiation fatigue."

Aerobic capacity is a strong predictor of the level of fatigue in patients with cancer. In patients with nonsmall cell lung cancer, $V_{O_{2max}}$ is an independent predictor of postoperative complication following lung resection surgery. Six of seven patients with a $V_{O_{2max}}$/kilogram body weight less than 60% of predicted, but only 8 of 65 with values >90% of predicted, exhibited postoperative complications. Anaerobic threshold (exercise tolerance) was found to be an independent predictor of postoperative mortality in patients with lung cancer.

Kolden and coworkers examined the effects of a group exercise program consisting of flexibility training and approximately 20 mins of aerobic exercise 3 days per week for a total of 16 weeks in women (mean age of 55.3 ± 8.4 yrs) who had been surgically treated for stage I, II, or III breast cancer. They observed an increase in quality-of-life perception as well as $V_{O_{2max}}$ and strength.

Summary

As stated previously, fatigue is physical and/or mental weariness resulting from exertion, that is, an inability to continue exercise at the same intensity with a resultant deterioration in performance. The physiological mechanisms for this fatigue may be related to a number of physiological and metabolic parameters. An understanding of these parameters is essential if fatigue is to be addressed in a systematic way. Fatigue from exertion may be related to deconditioning (decreased maximal cardiac output and/or reduced muscle perfusion or oxidative capacity), reduced muscle mass or muscle quality, anemia, poor oxygen extraction, poor nutrition or malnutrition, or any combination of these factors.

Aerobic exercise and strength training regimens have been used to improve functional status and reduce fatigue that has been associated with advancing age and/or an existing chronic disease or condition. CHF, COPD, and end-stage renal disease are associated with accelerated loss of muscle and fatigue. Both cancer-related fatigue and cancer-associated pain have physiological causes and are treatable. Pain management in the treatment of cancer is a standard component of cancer therapy, while management of fatigue is not considered the standard of therapy. Despite an overwhelming body of literature that demonstrates improved quality of life and decreased fatigue after treatment for anemia, the treatment of anemia in cancer is less a therapy for fatigue and quality of life than a prophylaxis against transfusion. Fatigue and cachexia related to cancer and its treatment results in long-lasting, persistent fatigue. Comprehensive therapy for cancer related fatigue should included exercise along with nutritional and pharmacological therapy. It is unlikely, for example, that any patient will be able to participate in even a low intensity exercise program if he is anemic.

It also should be recognized that regular aerobic exercise and progressive resistance exercise have different effects. Loss of muscle mass in response to cachexia or inactivity should be treated with resistance exercise training along with any anticachexia therapy. On the other hand, decreased $V_{O_{2max}}$ that is secondary to anemia and deconditioning should include regular aerobic exercise such as walking. There is not a single published study examining the effects of exercise in patients with cancer that has reported a negative result. "Cancer rehabilitation" programs to comprehensively treat fatigue should be the standard of care. Just as the common advice to those who had suffered a myocardial infarction who had been bed rest has now changed to early and vigorous cardiac rehabilitation in these same patients, exercise may have a powerful effect on fatigue and fatigue related symptoms in those with cancer. Additional cachectic conditions resulting from heart failure, COPD, and hemodialysis should be treated with a compre-


64. Harrington D, Coats A: Skeletal muscle abnormalities and evidence for their role in symptom generation in chronic heart failure. Eur Heart J 1997;18:865–72


January 2007

Physiological Basis of Fatigue  S43


164. Jones M, Schenkel B, Just J, et al: Epoetin alfa improves...


Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.