American Thoracic Society/European Respiratory Society

Skeletal Muscle Dysfunction in Chronic Obstructive Pulmonary Disease

A Statement of the American Thoracic Society and European Respiratory Society

Introduction

Chronic obstructive pulmonary disease (COPD) is almost always caused by cigarette smoking. Although medical science has developed no cures (1), several forms of treatment are of symptomatic benefit. Smoking cessation can slow the rate of deterioration of lung function. Bronchodilator and anti-inflammatory agents are of appreciable help to many patients, but the reduction in airway obstruction is generally modest. Oxygen supplementation prolongs survival and improves quality of life in severely hypoxemic patients (2, 3). Lung transplantation (4) and lung volume reduction surgery (5) may have a role in a highly selected minority of patients.

COPD frequently leads to significant debilitation. Patients often come to medical attention only after severe damage to the lung's function has been induced. The most frequent complaint of these unfortunate patients is exercise intolerance (6). Patients often become homebound, isolated, and depressed as they seek to avoid the dyspnea that everyday activities produce.

Pulmonary rehabilitation has been touted by some as the standard of care for patients chronically disabled by their lung disease (7), and it is commonly prescribed. However, a skeptic might view it as a therapy without a clearly established rationale in the context of improving exercise tolerance. Current concepts involving the pathophysiologic mechanisms of exercise intolerance focus on the lung, where abnormal lung mechanics (leading to mechanical disadvantage of the respiratory musculature), impaired gas exchange, and destruction of the pulmonary vascular bed directly impact the ability to sustain exercise. Clearly, pulmonary rehabilitation does nothing to improve lung function. Nevertheless, there are many reports of improvements in exercise tolerance after a program of rehabilitation (6, 8). This has been ascribed to psychological factors, including improved motivation and decreased sensitivity to dyspnea (9); these factors are undoubtedly important.

There is a growing realization that COPD is a multi-organ-system disease. In particular, there is accumulating evidence that the skeletal muscles do not function normally and that this contributes to exercise intolerance. This is important because skeletal muscle dysfunction may well be a ***remediable*** source of exercise intolerance. Moreover, programs of pulmonary rehabilitation are a natural setting to attempt to apply remediation. It may, therefore, be appropriate to reorient pulmonary rehabilitation to focus on strategies to improve skeletal muscle function. Pulmonary rehabilitation might be established as a modality that treats (and perhaps cures) skeletal muscle dysfunction.

To further this end a workshop group was established under the auspices of the Respiratory Structure and Function Assembly of the American Thoracic Society. Sponsorship of both the American Thoracic Society and the European Respiratory Society was obtained. An international group of 16 scientists was recruited. Included in this group were experts in the basic science of muscle biology, exercise physiologists, and rehabilitation specialists. This group met twice in Miami, Florida, in December 1997 and in Chicago, Illinois, in April 1998. Each participant composed a section of the manuscript; all members reviewed and commented on the resulting document. Among the group's earliest decisions was to restrict this document to discussion of the limb musculature. Respiratory muscle abnormalities are undoubtedly present; this topic has been thoroughly reviewed (e.g., 10). However, the group felt that fundamental differences between these two types of skeletal muscles were present (among them that, in most patients with COPD, the respiratory muscles are chronically overworked and the limb muscles are chronically underworked) and justified the division. Another decision was to compare and contrast the role of strength versus endurance characteristics of the limb muscles. To date, the COPD literature has almost exclusively focused on endurance activities; recent literature has stressed the importance of muscle strength in elderly subjects (11).

This position paper is divided into three sections. The first is a primer on muscle biology in which the characteristics of skeletal muscle that dictate the ability to perform both strength and endurance activities are discussed. The second section summarizes the state of current knowledge concerning the mechanisms of skeletal muscle dysfunction in COPD. The third section describes strategies for treating skeletal muscle abnormalities. Finally, a short section concerns possible directions for future research.

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I. Normal Muscle Function

A. OVERVIEW OF MOTOR CONTROL

Early in this century, Sherrington (12) recognized that motoneurons constitute the final common pathway for the central nervous system control of muscles. The motor unit, comprising a motoneuron and the muscle fibers it innervates, was identified as the basic functional element (or quantum) of neural control of muscles (13). Sherrington also introduced the concept of an orderly recruitment of motor units to accomplish different motor behaviors (13, 14). Accordingly, in this model, the total force generated by a muscle depends on the numbers of motor units activated and the quantal amount of force contributed by each motor unit. Because the force generated by each motor unit depends on the rate of neural activation (i.e., the force/frequency relationship), the central nervous system has two levels of control of the force generated by the muscle: (*1*) the number of activated motor units (i.e., recruitment), and (2) the action potential discharge frequency of motoneurons (frequency modulation). This simple model assumes that all muscle fibers within a motor unit are activated by the motoneuron in an all-or-none fashion, and that each muscle fiber belongs to only one motor unit. These assumptions have been shown to be essentially correct in normal healthy adults.

Within a muscle, motor units can vary considerably in their mechanical, histochemical, and biochemical properties (15–24), and it is this variety that provides the basis for a range of motor control via the selective recruitment of different motor unit types. In the early 1970s, Burke and colleagues (15, 16) introduced standardized criteria for the classification of different motor unit types based on mechanical and fatigue properties. Accordingly, motor units were classified as (I) slow-twitch, fatigue resistant (S), (2) fast-twitch, fatigue resistant (FR), (3) fast-twitch, fatigue intermediate (FInt), and (4) fast-twitch, fatigable (FF). With few exceptions, it has been shown that each motor unit type comprises muscle fibers of a single histochemical type, regardless of the classification scheme used (Table 1) (15, 16, 24–26).

In one histochemical technique, muscle fibers were classified as slow-twitch oxidative (SO), fast-twitch oxidative, glycolytic (FOG), or fast-twitch glycolytic (FG) based on differences in staining for myofibrillar ATPase and subjective differences in staining for glycolytic and oxidative enzymes (27). In another histochemical classification scheme, differences in the pH lability of staining for myofibrillar ATPase were used to classify fibers as type I, IIa, IIb, or 11x (28, 29). Finally, in most recent studies, fiber types have been classified based on differences in immunoreactivity for antibodies specific to different myosin heavy chain (MHC) isoforms (30-34). Several studies have confirmed a general correspondence between the histochemical classification of fibers as type I, IIa, IIb, and 11x and immunoreactivity for MHC_{Slow}, MHC_{2A}, MHC_{2B}, and MHC_{2X} isoforms, respectively (31-34). Indeed, this relationship formed the basis for the identification of these MHC isoforms in skeletal muscle. In contrast, it has been shown that there is only a very poor correspondence between the classification of SO, FOG, and FG fiber types and the classification of type I, IIa, IIb, and 11x fibers (35-37). Thus, there is general agreement that the classification of S, FR, FInt, and FF motor unit types corresponds with the expression of MHC_{Slow}, MHC_{2A}, MHC_{2X}, and MHC_{2B} isoforms in muscle fibers and the histochemical classification of type I, IIa, IIx, and IIb fibers (24-26).

TABLE 1

MUSCLE FIBER TYPE COMPOSITION OF MOTOR UNITS

Fiber Type Classification Scheme	Motor Unit Type S	FR	FInt	FF
Metabolic enzyme staining	SO	FOG	?	FG
pH Lability of myofibrillar ATPase staining	I	IIa	IIx	IIb
MHC immunoreactivity	MHC_{Slow}	MHC_{2A}	MHC_{2X}	MHC_{2B}

Definition of abbreviations: FF = fast-twitch, fatigable; FInt = fast-witch, fatigue intermediate; FR = fast-twitch, fatigue resistant; MHC = myosin heavy chain isoforms; S = slow-twitch, fatigue-resistant.

Four decades ago, Henneman (38) suggested- that motoneuron size was the major determinant of motoneuron excitability and susceptibility to discharge. He demonstrated that motoneurons with slower conduction velocities, a correlate of motoneuron size, were recruited first during most motor behaviors. This "size principle" predicted that the orderly recruitment of motor units was related to the intrinsic membrane properties of motoneurons (38, 39). Smaller motoneurons, with smaller axonal diameters and conduction velocities, have high input resistance, providing them with a more negative threshold for discharge. In contrast, larger motoneurons, with larger axons and faster conduction velocities, have lower input resistance and, thus, a less negative recruitment threshold. Based on a comparison of axonal conduction velocities and motor unit recruitment thresholds, the size principle has been confirmed in a number of mammalian motor systems (17,394).

Models have also been proposed based on an orderly recruitment of different motor unit types, with S units recruited first followed by FR, FInt, and FF units (e.g., 23, 45). Based on the average force contributed by each motor unit type and the proportion of each type within a muscle, the recruitment requirements to accomplish different motor behaviors can be predicted. For example, in the cat medial gastrocnemius muscle, it has been estimated that only type S motor units need to be recruited during standing, that additional recruitment of type FR motor units is required during walking and running, and that FInt and FF motor units are recruited only during behaviors such as jumping, which require maximal efforts for short durations (45). Similarly in the cat diaphragm muscle, eupneic breathing can be achieved by the recruitment of only type S motor units, whereas more forceful ventilatory behaviors (e.g., during hypoxia and hypercapnia) would require the recruitment of FR and some FInt units (23). Recruitment of the more fatigable FInt and FF motor units in the diaphragm muscle would be required only during more forceful nonventilatory behaviors (23). These motor unit recruitment predictions hold even assuming submaximal motoneuron discharge rates in the range of 10 to 30 Hz (e.g., 46). It should be noted that motor unit activation rates represent the steepest portion of motor unit force/frequency curves, and thus allow for optimal frequency coding of motor units for rapid adjustments in force generation (46).

B. MUSCLE STRENGTH

1. Determinants of Muscle Strength

As mentioned above, the force generated by a muscle is determined by the number and type of motor units recruited (17, 23). In most muscles, it has been generally reported that FInt and FF motor units generate greater forces than do S and FR units (17, 19, 23, 47, 48). The force generated by a motor unit

depends on three interrelated factors: (*1*) the innervation ratio of the unit, i.e., the number of muscle fibers innervated by a motoneuron; (2) total functional cross-sectional area of all muscle fibers within the unit; and (3) specific force of the muscle fibers, i.e., the force per cross-sectional area (17). In 1968, Edstrom and Kugelberg (49) introduced the method of glycogen depletion by which muscle fibers making up a single motor unit can be identified. Subsequently, a number of studies have characterized the importance of these three factors in the forces generated by different motor unit types. Generally, the greater force generated by FInt and FF motor units has been attributed to a combination of all three factors (17, 19, 47, 48).

The force generated by single skeletal muscle fibers is determined primarily by the level of activation (e.g., intracellular Ca^{2+} concentration, $[Ca^{2+}]_i$) and the force per cross-sectional area of muscle (specific force). As the frequency of neural activation increases, the force generated by muscle fibers increases in a sigmoidal fashion. In motor unit studies, it has been shown that the force/frequency relationship of slow-twitch motor units is shifted leftward compared with fast-twitch motor units (23). Thus, at a given frequency of submaximal neural activation, slow-twitch motor units generate a greater percentage of their maximal force. This difference in the force/frequency relationship of motor units could relate either to the amount of Ca^{2+} released from the sarcoplasmic reticulum at a given frequency of activation (differences in excitation-contraction coupling) (50–53), differences in sarcoplasmic reticulum Ca^{2+} reuptake (54), or differences in the Ca^{2+} sensitivity of myofibrillar proteins (55-59).

A number of studies have examined the force/Ca^{2+} relationship in single permeabilized skeletal muscle fibers, where $[Ca^{2+}]_i$ can be clamped at different levels. Generally, it has been reported that muscle fibers expressing the MHC_{Slow} isoform have greater Ca^{2+} sensitivity than do fibers expressing fast MHC isoforms, so that slow fibers generate a greater fraction of their maximal force for a given $[Ca^{2+}]_i$. Accordingly, the force/Ca^{2+} relationship of slow muscle fibers is shifted leftward compared with fast fibers (57-61).

Fiber type differences in specific force have been reported (60–64), but such differences remain controversial (65). Differences in mitochondrial volume densities may contribute, at least in part, to fiber type differences in specific force. Generally, fibers expressing the MHC_{Slow} and MHC_{2A} isoforms have significantly higher mitochondrial volume densities and oxidative capacities than do fibers expressing the MHC_{2X} and MHC_{2B} isoforms (33). Indeed, it is likely that the higher oxidative capacities of fibers expressing the MHC_{Slow} and MHC_{2A} isoforms may at least partially account for the greater fatigue resistance of these fibers as compared with fibers expressing the MHC_{2X} and MHC_{2B} isoforms (18, 66). The higher mitochondrial volume densities of fibers expressing the MHC_{Slow} and MHC_{2A} isoforms would presumably be at the expense of a corresponding lower myofibrillar volume density, lower MHC content, and, thus, fewer cross-bridges in parallel for a given fiber cross-sectional area.

2. Protein Turnover

Protein turnover refers to a continuous and dynamic flux in protein metabolism whereby all proteins are constantly being synthesized and degraded (Figure 1) (67). Although this process incurs a significant metabolic cost, it permits the ability to finely regulate specific protein pools (68, 69). Thus, turnover rates for specific proteins may differ considerably depending on function and need (69). Amino acids, the building blocks of proteins, are derived from an active metabolic pool, 40% of which originates from endogenous protein breakdown, with the remainder being derived from dietary protein sources (69). The regulation of protein turnover in skeletal muscle is of considerable importance in view of the fact that skeletal muscle mass makes up about 40 to 45% of body weight and about 60 to 80% of body cell mass. As such, skeletal muscle serves as an important reserve system that, in conditions of need, maintains supplies of essential amino acids for protein synthesis and energy metabolism (70).

a. ***Muscle Protein Degradation.*** Although numerous cellular proteolytic systems have been described, degradation of muscle contractile proteins, particularly in catabolic states, is likely mediated via the ubiquitin-proteasome pathway (Figure 1) (71, 72). This involves activation of small peptide cofactors (ubiquitin) and their transfer and covalent linkage to the specific target proteins to be degraded. The ubiquitin-protein conjugate binds to an activating protein complex, which releases the ubiquitin chain, catalyzes conformational change in the protein, and promotes entry into the 26S proteasome (a barrel-shaped protein structure composed of several rings and subunits surrounding a central cavity), where the protein is degraded by multiple proteolytic sites within the inner rings of the proteosome. The degraded products (i.e., peptides) are subsequently released into the cytoplasm, where they can be rapidly metabolized to amino acids (71, 72). The ubiquitin pathway has been implicated in mediating enhanced proteolysis in a number of different catabolic states, in both animal models and in humans. For example, varying increments in messenger RNA (mRNA) for ubiquitin, proteasome subunits, and/or key pathway enzymes have been reported in a variety of models. These include fasting (73), acidosis (74), denervation (75), sepsis/endotoxemia (76, 77), tumor necrosis factor (TNF) administration (78), diabetes mellitus (79), and neopla-

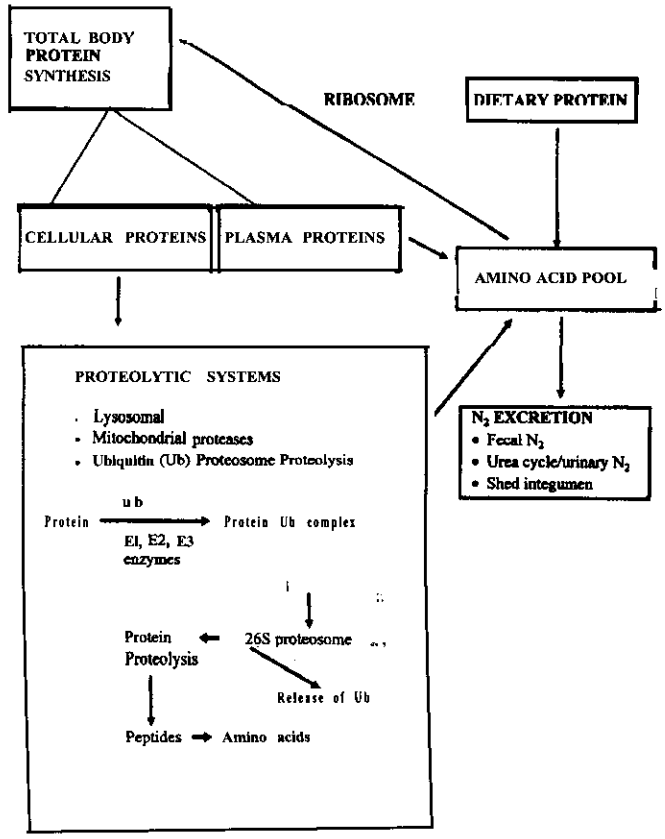

figure 1. Pathways mediating protein turnover (see text).

sia (80). There is also evidence for activation of the ubiquitin pathway in rat limb muscles with the use of high dose corticosteroids (81). By contrast, insulin and insulinlike growth factor-I (IGF-1) have been shown to suppress E2 (a ubiquitin conjugating enzyme) in muscle cell cultures, and thus could in part suppress proteolysis via influences on the ubiquitin pathways (82, 83).

b. ***Hormonal and Mediator Influences on Muscle Protein Turnover.***

(1) **Anabolic influences.** The growth-promoting and anabolic actions of growth hormone (GH) are thought to be mediated via polypeptide growth factors (somatomedins) produced in the liver and in other tissues, including skeletal muscle (84). IGF-1 is the principal somatomedin, and it can exert both hormonal and local effects via the IGF-1 receptor (85). The actions of IGF-1 in either the bloodstream or within specific tissues can be modulated by various binding proteins (IGFBP). In animal and ***in vitro*** studies, IGF-1 produces increments in protein synthesis and usually diminishes protein degradation (86). In humans, both GH and IGF-1 enhance local skeletal muscle protein synthesis when administered directly (87, 88). GH administered systematically or locally has no impact on protein degradation, whereas IGF-1 at high dosages suppresses protein breakdown, possibly via effects on the ubiquitin pathways (82, 87, 88). In skeletal muscle, the anabolic effects of IGF-1 on muscle fibers may be mediated in part by stimulatory effects on satellite cells (89). The latter are myogenic cells that retain mitotic activity and serve as a source of myonuclei to growing, enlarging, and regenerating fibers (90). Testosterone, an anabolic/androgenic steroid, has distinct influences on skeletal muscle protein turnover in animals as well as in humans (91-93). In humans, testosterone administered in replacement or pharmacologic doses increases muscle protein synthesis (93-95). It is likely that the anabolic effects of testosterone may be mediated at least in part by increased intracellular production of IGF-1. For example, after administration of testosterone to elderly men, several changes were found in vastus lateralis muscle biopsy specimens (95). IGF-1 mRNA was increased and IGFBP4 was decreased, presumably leading to decreased IGF-1 binding. In cell cultures, ***in vitro*** muscle preparations and in animals, insulin promotes anabolism by promoting amino acid uptake with increment in protein synthesis and inhibition of protein degradation (96). Studies in humans, however, indicate that the predominant anabolic action of insulin is mediated primarily by a reduction in protein breakdown (97-100). It is postulated that the reduction in serum levels of amino acids induced by insulin may limit enhanced protein synthesis.

(2) Catabolic influences. In animal studies, corticosteroids have demonstrated catabolic influences mediated predominantly by inhibition of protein synthesis, with or without enhanced protein degradation (96). The latter effect may in part be due to activation of ubiquitin-mediated proteolysis (81). Insufficient data on protein turnover in skeletal muscle are available in human studies to draw parallel conclusions to those in animal models (101). Studies in patients with rheumatoid arthritis treated with corticosteroids, however, suggest reduced skeletal muscle protein synthesis (102). Although release of stress hormones (corticosteroids, catecholamines, glucagon) may result in protein catabolism, glucagon has not been shown to effect protein metabolism in human skeletal muscle (103). In addition, variable results have been reported for the influences of epinephrine on skeletal muscle in humans (104). Excess thyroid hormone may produce a negative protein balance by influences on both protein degradation (enhanced) and protein synthesis (suppressed) in skeletal muscle (105). A variety of cytokines, including tumor necrosis factor (TNF) and interleukins (e.g., IL-l) have been reported to produce muscle wasting, mediated in part by activation of ubiquitin pathways with enhanced proteolysis (78). Furthermore, various prostaglandins (PG) may also exert positive (e.g., PG F2α, El) or negative (e.g., PG E2) influences on protein turnover in skeletal muscle (106,107).

c. Nutrient Influences on Muscle Protein Turnover. Malnutrition is an important clinical state exerting a negative influence on protein balance, particularly within muscle. Significant degrees of malnutrition may complicate clinical illness in unstressed or stressed conditions. The main difference between unstressed and stressed states of malnutrition (e.g., associated with sepsis, major trauma, etc.) is the inability to suppress amino acid release from muscle with stress despite nutritional supplementation (70). Furthermore, much greater urinary losses of nitrogen are observed with states of stressed starvation (e.g., 15 to 50 g/d) compared with the unstressed state (3 to 12 g/d). Most of the nitrogen lost during acute stress derives from skeletal muscle sources and, in particular, contractile proteins (108, 109). Among the amino acids mobilized during stress are substrates for synthesis of essential proteins, those involved in gluconeogenesis, and fuel substrates such as branched chain amino acids (70). Malnutrition with or without associated stress is associated with a biochemical milieu that favors a negative protein balance. This includes reduced serum levels of IGF-1 and insulin, coupled with elevated levels of stress hormones and other mediators (e.g., TNF).

d. *Influence of Aging on Muscle Protein Turnover.* With advancing age, reductions in skeletal muscle mass parallel loss of total muscle force (11, 110). In both elderly animals and humans, reductions in muscle protein synthesis have been documented. For example, Welle and colleagues (111) reported a significant (~ 28%) reduction in the rate of myofibrillar protein synthesis in elderly subjects compared with that in young subjects. Hormonal changes noted with aging may be partly responsible. For example, in the elderly, GH is less responsive to GHRH while levels of the inhibitory somatostatin increase (112). The above events result in a decrease in circulatory and possibly tissue levels of IGF-1. In addition, in elderly male subjects, significant reductions in total and free testosterone are noted (113, 114). It is currently unclear to what extent reduced estrogen levels in postmenopausal women contribute to reduced muscle bulk and protein turnover. Finally, age-related changes in cytokine production may also produce altered protein turnover in the elderly (e.g., enhanced IL-1J production ***in vitro*** in blood cells from elderly subjects compared with those from young subjects) (115).

e. Measurement of Muscle Protein Turnover. A variety of indirect and direct measures may be employed in humans to evaluate aspects of protein turnover. These include urinary creatinine excretion (116), urinary 3-methylhistidine measurement (derived from actin and myosin proteolysis) (117), muscle protein analysis, amino acid balance studies (e.g., across forearm) (99), and estimates of protein turnover using amino acid incorporation techniques (118, 119) or arteriovenous amino acid balance techniques. As myofibrillar proteins comprise several different constituent proteins (e.g., myosin, actin, mitochrodrial proteins, and sarcoplasmic reticulum proteins), new techniques have been developed to determine myosin heavy chain synthesis rates in skeletal muscle samples using incremental enrichment of both radiolabeled (120, 121) and stable isotope labeled (122) leucine into myosin heavy chains. Using these techniques, it has been shown that the synthesis rate of slow myosin isoenzyme is faster than that of the fast myosin isoenzyme (121). Recently, techniques have been de-

veloped aimed at determining the fractional synthesis rate of individual myosin heavy chain isoforms extracted from single skeletal muscle fibers (G. C. Sieck, K. S. Nair, P. Balagopal, unpublished data).

3. Measurements of Muscle Strength

a. ***Morphologic.*** The overall mass of functioning muscle tissue and the size and type of its constituent muscle fibers provide an index of predicted muscle force. A number of direct and indirect approaches have been used to assess muscle mass (123). These include measurements of total body potassium and nitrogen (124–126), estimates of fat-free mass, e.g., anthropometry such as four-site skinfold thickness (127, 128), deuterium dilution (129), underwater weighing (130), bioelectrical impedance (129, 130), biochemical estimates of total skeletal muscle mass, e.g., creatinine height index (116), measures of regional limb skeletal muscle mass, e.g., dual energy X-ray absorptometry (DEXA) scanning (131) and ultrasonography (132), and anatomic delineation of the mass of specific muscles, e.g., magnetic resonance imaging (MRI) (133), computed tomography (CT) (134).

Although these methods offer noninvasive approaches to the estimation of muscle mass, a number of important limitations should be highlighted. First, most of these methodologies provide only gross whole-body or regional estimates and are not specific for individual muscles or muscle groups. Anthropometric indices may be more prone to error in the elderly because of alterations in the distribution of body fat (135). In addition, an increase in the extravascular fluid compartment can be mistaken for an increase in muscle mass. More recently, comparisons between anthropometric estimates of limb muscle mass in the elderly with either CT or MRI have revealed significant inconsistencies (133, 136). Similarly, total body potassium and nitrogen assays were reported to underestimate skeletal muscle mass using CT as the "gold standard" (137). Bioelectrical impedance has not been fully validated in the elderly and its interpretation may be limited by the presence of edema and skin changes that affect impedance (138). Although total body skeletal muscle mass determined by DEXA scanning has correlated well with estimates obtained by CT, the former tended to overestimate muscle mass (137). Lastly, although CT and MRI appear to be emerging as reference measurements, they are expensive tests. Furthermore, logistic and cost considerations may preclude the performance of multiple serial studies.

Muscle biopsy is an extremely valuable tool as it affords a detailed assessment of morphologic and biochemical indices at molecular, cellular, or tissue levels (e.g., 139). Among the main indices that pertain to the determination of muscle strength, the most important include: (I) determination of fiber type proportions using myofibrillar ATPase histochemical staining techniques (28) or antibodies against myosin heavy chain (MHC) isoforms (32), (2) quantitative assessment of individual fiber cross-sectional areas, and (3) gel electrophoresis of muscle homogenates from whole biopsy specimens or single muscle fibers dissected from the biopsy to determihe MHC proportions and/or their mRNA transcripts (55).

Despite the useful information obtained from muscle biopsy analyses, several limitations of the method should be highlighted. Although the needle biopsy technique is generally regarded as a minor procedure, potential complications include pain and discomfort, bleeding, infection, and scarring. A major limitation is the presence of sampling error as the biopsy represents only a tiny fraction of the whole muscle. The coefficient of variation for duplicate biopsies is in the region of 10 to 20% for fiber-type proportions and 15 to 20% for cross-sectional areas (140, 141). Errors relating to cross-sectional areas may also originate from fiber contraction, with sectioning or delays in freezing (142) and nonperpendicular orientation of the muscle fibers. In humans, considerable genetic variation in fiber types exists among subjects, thus mandating a larger number of subjects to account for this. Although the vastus lateralis represents the most commonly studied limb muscle, the choice of muscle for biopsy should take into account the intervention administered to the study group. In addition, recent molecular studies have demonstrated that human skeletal muscle fibers traditionally classified as type IIb fibers express MHC mRNA transcripts for the 2X isoform (143). Because there is no evidence that true type IIb fibers exist in human skeletal muscle, this may have implications for both accurate fiber typing and physiologic correlates of specific force.

b. ***Functional.*** Four different devices/methods have been employed in the measurement of limb muscle strength: cable tensiometer, dynamometer, motorized dynamometer, and repetition maximum (RM) tests. All these tests may be limited by volitional factors, learning effect, and non-muscle factors (e.g., arthritis in the elderly). The cable tensiometer can reliably measure isometric force only (144). Hand grip dynamometry evaluates a limited muscle group and there are few reference data applicable to the elderly (145). In addition, upper limb strength is better preserved than lower limb strength in the elderly (146). The Cybex II isokinetic motorized dynamometer is commonly used to assess limb muscle strength (e.g., quadriceps/knee extension). Artifacts caused by excess acceleration of the lever arm of the machine and problems incurred by gravitational effects with flexion testing can result in significant errors (147, 148). RM tests with free weights or exercise machines assess the maximum resistance that can be moved across a range of motion and correlate better with normal dynamic functional tasks (149), but they may require a greater learning period than other tests.

C. MUSCLE ENDURANCE

1. Oxygen Transport to Mitochondria

In contrast to strength performance, endurance exercise depends on O_2 transport from the air to the muscle mitochondria. The O_2 transport pathway (150) begins with ventilation delivering air to the alveolar surface, principally by convection. Without adequate ventilation, in relation to metabolic rate, arterial P_{O_2} will fall and arterial P_{CO_2} will rise. O_2 crosses into pulmonary capillary blood by diffusion. Whether diffusion equilibration (equalization of alveolar and end-capillary P_{O_2}) occurs or not depends on three factors: (I) the diffusing capacity of the lungs (D_L), (2) blood flow ($\dot{Q}$), and (3) the capacitance of blood for O_2 (β, which is defined by the slope of the O_2Hb dissociation curve between arterial and venous P_{O_2} values and is thus equivalent to effective solubility of O_2). In fact, it is the ratio $D_L/(\beta\dot{Q})$ that determines degree of equilibration (151) and to the extent that D_L is reduced and/or $\beta\dot{Q}$ increased, arterial P_{O_2} may be less than alveolar P_{O_2}.

In addition to potential diffusion limitation, nonuniform distribution of inspired air and of pulmonary capillary blood occurs even in normal lungs, for a number of reasons. In pulmonary disease, such ventilation/perfusion inequality is usually exaggerated and may further lead to significant reduction in arterial P_{O_2} (152). The fourth factor that can reduce arterial P_{O_2} is the presence of right-to-left shunts. In health, these are negligible (on the order of 4%), but shunts can cause severe hypoxemia in certain diseases. Abnormalities in pulmonary gas exchange from inadequate ventilation, diffusion limita-

tion, ventilation/perfusion inequality, or shunt may limit endurance performance by impairing O_2 transport to the muscles and by impairing CO_2 transport from the muscles to the lungs. Reduced O_2 and CO_2 transport in turn may contribute to uncomfortable leg and/or respiratory symptoms during exercise.

Blood containing O_2 combined with Hb as a result of the pulmonary gas exchange process is pumped to the muscles, and this requires adequate cardiovascular function. Cardiac output during exercise is very tightly coupled to O_2 consumption, even in COPD, both rising linearly with heart rate along approximately the same relationship as in healthy subjects (153). Although the mechanisms responsible for this coupling remain incompletely understood, the autonomic nervous system is centrally involved. Parasympathetic withdrawal and sympathetic activation are seen with exercise, increasing both heart rate and stroke volume (154). Venous return is enhanced by skeletal muscle contractions and by increased venous tone, and these appear to contribute to increasing cardiac output via the Starling effect (154).

Preferential distribution of blood flow to the contracting muscles is an important adjustment to exercise and requires vasodilatation in the active muscles (and vasoconstriction in other vascular beds). This occurs through a number of parallel mechanisms involving the autonomic nervous system as well as a host of local metabolic and neurologic factors. The end result is (at least in health and during submaximal exercise), appropriate delivery of O_2 for the metabolic needs of the muscle. O_2 delivery ($\dot{Q}o_2$) to the muscle microcirculation is defined as:

$$\dot{Q}o_2 = (1.39 \times [Hb] \times Sa_{O_2} + 0.003 \times Pa_{O_2}) \times \dot{Q}_M \quad (1)$$

where [Hb] is hemoglobin concentration, Sa_{O_2} is fractional arterial O_2 saturation, Pa_{O_2} is arterial P_{O_2} and $\dot{Q}_M$ is muscle blood flow. Except in extraordinary circumstances such as severe anemia and hyperbaric environments, the amount contributed by physically dissolved O_2 ($0.003 \times Pa_{O_2}$) can be neglected for simplicity since it accounts for less than 2% of the O_2 present in blood. Therefore, the implications of this equation are paramount to understanding the basis for endurance exercise: O_2 supply to the muscles depends on the blood ([Hb]), the lungs (Sa_{O_2}), and the cardiovascular system ($\dot{Q}_M$). The latter factor encompasses not only adequate cardiac function but also peripheral vascular structure and function to assure proper distribution of cardiac output to active muscle. Reduction in any one of these three variables ([Hb], Sa_{O_2}, or $\dot{Q}_M$) will reduce convective muscle oxygen transport and, consequently, endurance performance.

It is important to note that this discussion focuses on muscle blood flow, $\dot{Q}_M$, and not on cardiac output. This is for two practical reasons. First, attempting to infer muscle blood flow from cardiac output is likely to produce significant errors in assessment of muscle O_2 delivery. Second, using cardiac output and $\dot{V}o_2$ at the mouth to calculate arteriovenous $[O_2]$ difference and from this to estimate muscle O_2 extraction is equally uncertain when a significant proportion of cardiac output and $\dot{V}o_2$ is distributed to tissues other than actively contracting muscle. Thus, experimental methods should focus directly on the active muscle groups.

O_2 delivery to muscle (*Equation* 1) is by no means the end of the O_2 transport story. O_2 must be unloaded from Hb in the muscle microcirculation and diffuse through the red cell wall, plasma, and the capillary wall. It then must diffuse into the myocyte where it binds to myoglobin, which is believed to greatly facilitate its transport to the mitochondria for use in ATP generation (155). The intramuscular diffusion pathway is unique because of myoglobin. Although the distance O_2 must diffuse between Hb and the sarcolemma is just a few microns, and the distance O_2 must travel to the mitochondria may be some 50 microns, almost all of the impedance to O_2 diffusion is in the initial short distance from Hb to sarcolemma. This is shown by the large difference between mean capillary P_{O_2} (generally $\sim$ 40 mm Hg) and average intracellular P_{O_2} (about 3 mm Hg) during exercise in humans (156). Several lines of evidence point to the critical importance of muscle capillary surface area in determining the impedance to O_2 unloading in muscle; diffusion distance may well be relatively unimportant (156158). Thus, from a morphometric standpoint, the ability to move O_2 from Hb to the mitochondria is a function of how many capillaries surround each muscle fiber. Fiber cross-sectional area on the other hand appears unimportant (159). If in a given disease state there is a reduction in the number of capillaries around each fiber, one would expect impaired O_2 unloading; fiber size changes without alterations in capillary number would not be expected to reduce O_2 availability.

Just as described above for the lungs, the diffusive process of O_2 unloading depends on the muscle diffusing capacity for O_2 (D_M), the capacity of blood to hold O_2 (β), and muscle blood flow ($\dot{Q}_M$). Again, completeness of unloading depends on the ratio $D_M/(\beta\dot{Q}_M)$ (153). Intuitively, the greater the D_M, the higher the rate of transport of O_2 between Hb and mitochondria. However, completeness of unloading will be reduced if there is a large amount of O_2 to be unloaded from the blood (large value for β) or if perfusion ($\dot{Q}_M$) is high. When β is high, it simply takes longer to unload O_2 because there are more O_2 molecules in the blood; when $\dot{Q}_M$ is high relative to the muscle capillary volume, transit time is reduced and there is less time available for O_2 unloading.

Extraction is thus dependent on $D_M/(\beta\dot{Q}_M)$. If one assumes that the relevant portion of the O_2Hb dissociation curve is linear, then muscle venous P_{O_2} (Pv_{O_2}) is a simple exponential function of $D_M/(\beta\dot{Q}_M)$:

$$Pv_{O_2} = Pa_{O_2} \cdot \exp[-D_M/(\beta\dot{Q}_M)] \quad (2)$$

where Pa_{O_2} is arterial P_{O_2}. Assuming a linear O_2Hb dissociation curve (approximately correct at low P_{O_2}), fractional O_2 extraction, E (which is the ratio of arteriovenous $[O_2]$ to arterial $[O_2]$) becomes:

$$E = 1 - \exp[-D_M/(\beta\dot{Q}_M)]. \quad (3)$$

The critical message of *Equation* 3 is the following: whereas D_M is reasonably considered as a "peripheral" factor in that it is mostly determined by muscle structure, both β and $\dot{Q}_M$ are largely determined by factors unrelated to muscle. They are functions of the heart and blood. Extraction of O_2 is thus *not* simply an index of peripheral (muscle) function but a complex end-product of the interaction between the peripheral factor D_M and the "central" factors β and $\dot{Q}_M$. These concepts remain valid even if the O_2 dissociation curve is not linear. Quantitative but not qualitative differences in predictions from *Equations* 2 and 3 will be seen for the case of the real O_2 dissociation curve (160,161).

Equally important is another concept: just as in the lungs, where O_2 diffusing capacity increases with pulmonary blood flow, so too will muscle diffusing capacity increase with increasing muscle blood flow: as exercise intensity increases, more muscle fibers and capillaries are recruited. Consequently, if overall exercise intensity in COPD is governed mostly by a low ceiling on ventilation, which in turn results in a limited increase in cardiac output and hence in $\dot{Q}_M$, so too will muscle O_2 diffusing capacity not reach its potential maximal value during exercise.

An inference may be drawn: attempting to study the skeletal muscles during exercise using large enough muscle groups

to force the patient to have reached his low ventilation ceiling will not provide the answer to a basic question: are the skeletal muscles normal or not in COPD? To answer this question, it can be predicted that a helpful strategy will be to activate a relatively small muscle mass. Ideally, the amount of muscle involved should be small enough to permit it to reach this muscle's maximal O_2 utilization without the patient having reached his ventilatory limit. However, the muscle would need to ideally be large enough to allow measurement of muscle O_2 delivery (Q_{O_2}) (*Equation* I). O_2 delivery to the contracting muscle is a key measurement. If O_2 delivery is reduced, the immediate biochemical consequences might be interpreted as evidence of intrinsic muscle dysfunction instead of actually reflecting inadequate O_2 supply to otherwise normal muscle. The increase in arterial lactate concentration ([La]) with increasing V_{O_2} is a case in point. Patients with COPD or congestive heart failure often exhibit an early rise in [La] that may be due to inadequate O_2 delivery. Enhancing O_2 delivery (and thereby normalizing [La] response) would indicate that the problem lay with O_2 delivery rather than with skeletal muscle dysfunction. The same holds for indices of bioenergic state measured by magnetic resonance spectroscopy such as phosphocreatine/inorganic phosphate ratios and intracellular pH. Unless O_2 delivery to the active muscle can be measured and matched to that of appropriate control subjects, differences in such indices of muscle function may well be incorrectly attributed to an intrinsic myopathy when all that they reflect is reduced O_2 delivery.

2. Mitochondrial Function and Cellular Energetics

a. ***Cellular Energetics.*** Skeletal muscle is capable of large changes in metabolic activity (162); relative to the basal rate, metabolism can be increased 20- to 500-fold (163). Several strategies are available to the muscle fiber for generating adenosine triphosphate (ATP), which is the common energetic currency of the cell. ATP provides the energy for cross-bridge cycling and for active transport. At the onset of contractile activity, muscle fibers initially draw on a small pool of existing high-energy phosphates (164). However, ATP levels do not change significantly because phosphocreatine provides the substrate for rapid resynthesis catalyzed by creatine kinase. Inorganic phosphate and creatine are the net products of this overall reaction; both metabolites accumulate within the tissue during the early phase of exercise and can contribute to fatigue (see below). Skeletal muscle contains high levels of phosphocreatine relative to other tissues (165), but these stores can supply cellular needs for only a few seconds of strenuous contractions. During this time, glycogenolysis accelerates and the rate of glycolysis increases to provide a more sustainable energy source. Cytosolic pathways metabolize glucose to pyruvate. Pyruvate is either reduced to lactic acid via lactate dehydrogenase, an anaerobic mechanism, or is transported into the mitochondrion. Within the inner mitochondrial matrix, pyruvate is converted to acetyl CoA and metabolized aerobically via the tricarboxylic acid cycle to yield CO_2 and water.

Compared to anaerobic glycolysis, aerobic metabolism requires longer to activate. Energy utilization during the first 2 to 3 min of exercise requires more ATP than can be synthesized from oxygen stores in the muscle; the time required for blood flow and oxygen delivery to increase to steady-state levels causes an "oxygen debt" to develop within the muscle (166) that must be repaid after exercise. Nevertheless, aerobic metabolism has two important advantages to working muscle fibers. It produces more energy, 38 ATP per mole of glucose versus 2 ATP from anaerobic glycolysis, and it enables the cell to utilize stored lipid as a fuel via fatty acid metabolism (167). These properties are critical for muscle endurance, and mitochondrial content is a major determinant of muscle performance during prolonged exercise.

b. ***Mitochondrial Metabolism.*** Mitochondria are syncytial organelles that are located in interfibrillar or subsarcolemmal regions of the muscle fiber (168). Muscle fibers differ profoundly in their mitochondrial content both within and among muscles. Within a given individual, mitochondrial content of muscle fibers is not tightly linked to myosin ATPase activity (i.e., fiber type) but is strongly influenced by the pattern of muscle use. Muscles that undergo chronic endurance activity have the highest mitochondrial content; these include the heart, diaphragm, and soleus muscles (169).

Mitochondrial respiration requires dehydrogenases within the mitochondrial matrix that metabolize pyruvate or free fatty acids to produce reducing equivalents, i.e., reduced nicotinamide adenine dinucleotide (NADH). In the presence of molecular oxygen, NADH functions as a substrate for oxidative phosphorylation with the following overall reaction:

$$NADH + H^+ + \frac{1}{2}O_2 + 3ADP + 3Pi \rightarrow 3ATP + NAD+ + H_2O. \quad (4)$$

Three factors determine the maximum rate of this reaction at the cellular level (170). First is the capacity of respiratory chain enzymes to process oxygen and NADH via oxidative phosphorylation. In the absence of pathology, this capacity is determined by the quantity of respiratory chain enzymes that is proportional to mitochondrial volume: more mitochondria equals a higher oxidative capacity. Second is the amount of NADH available to the respiratory chain. This is influenced by the activity of mitochondrial dehydrogenases and by enzymes of the metabolic pathways that supply substrate for these dehydrogenases. These are primarily located within the mitochondrial matrix and, like the respiratory enzymes, are increased in proportion to mitochondrial volume density. Third is delivery of oxygen to the mitochondria. As noted in the previous section, oxygen delivery depends on a complex array of factors, including arterial oxygenation, hemoglobin content, muscle blood flow, vascular regulation, capillary number, fiber size, and myoglobin content.

c. ***Metabolic Adaptation.*** The metabolic properties of skeletal muscle are highly adaptive (171). Endurance training stimulates an integrated response within the tissue that increases the overall capacity for oxidative metabolism. Each of the three factors listed above—oxidative capacity, availability of reducing equivalents, and oxygen delivery-is affected by training. Proliferation of mitochondria in endurance-trained muscle simultaneously increase the capacity of the respiratory chain, the dehydrogenases that generate reducing equivalents, and the activities of metabolic pathways that supply the dehydrogenases. Oxygen delivery is increased by a pleiotropic response at the local and systemic levels: muscle adapts by increasing capillary number and myoglobin content. This is complemented by an increase in cardiac function that improves the peak capacity for blood flow and oxygen delivery to the muscle. The opposite changes are produced by chronic reductions in muscle activity, e.g., by denervation or inactivity, and aerobic capacity falls accordingly.

3. Determinants of Fatigue

Muscle fatigue can been defined as a loss in contractile function-force, velocity, power, or work-that is caused by prolonged exercise and is reversible by rest (10). Studies of iso-

lated muscle preparations have shown that fatigue directly compromises intracellular processes. Prolonged contraction at near-maximal activation frequencies causes fatigue because of electrical failure of the sarcolemma, so-called "high-frequency fatigue." Repetitive contraction using lower, quasi-physiologic activation frequencies causes loss of calcium homeostasis in muscle fibers, diminishes the calcium sensitivity of myofilaments, and can cause cross-bridge dysfunction. In contrast to isolated muscle preparations, human subjects may experience fatigue during volitional exercise because of cardiovascular limitations or central neural mechanisms. Thus, a variety of factors can limit endurance performance, and the actual cause(s) of fatigue depends on exercise conditions. This section provides an overview of the mechanisms that are most likely to contribute to fatigue in intact humans under physiologic conditions. Readers desiring more detail are referred to reviews by Westerblad and colleagues (167) and by Fitts (165).

a. *Events Within the Muscle Fiber.* Fatigue is generally associated with a metabolic imbalance in which metabolite concentrations change in order to maintain energetic supply. Such imbalance leads to- depletion of intracellular energy stores such as glycogen, glucose, and phosphocreatine and accumulation of metabolic by-products within the cell. Under most conditions, muscle function declines prior to depletion of high-energy phosphate stores; ATP availability generally is not rate-limiting (172). In contrast, metabolic by-products directly inhibit contractile function and are thought to be primary mediators of fatigue. First among these are the hydrogen ions generated by glycolytic metabolism. Lactate production by muscle sharply increases when energetic demand exceeds 50 to 60% of maximal aerobic capacity (165). Lactate release from muscle has long been correlated with muscle fatigue (173), but lactate itself is unlikely to cause dysfunction (174). Lactate-derived hydrogen ions have been implicated; acidosis directly compromises myofilament function, decreasing both force and the velocity of shortening (175); however, the magnitude of this effect is small at physiologic temperatures (176). A second factor contributing to fatigue is the inorganic phosphate produced by ATP hydrolysis. When phosphorylation potential falls, as occurs in heavy exercise, inorganic phosphate accumulates in the muscle and decreases calcium sensitivity of the myofilaments. Force production falls as a result (177). A third factor is the magnesium produced by MgATP hydrolysis. During periods of heavy MgATP utilization, intracellular magnesium concentration rises (178). Elevated magnesium levels may contribute to fatigue by inhibiting calcium release from the sarcoplasmic reticulum and thereby depressing myofilament activation (179). Fourth, reactive oxygen species are produced at accelerated rates by heavily exercising muscle. Accumulation of reactive oxygen species causes oxidative stress, inhibiting the function of both myofilaments and the sarcoplasmic reticulum (180, 181) and contributing to loss of muscle function in fatigue (182).

Electrolyte shifts may disrupt sarcolemmal function during fatiguing exercise. Muscle activation causes potassium release and sodium influx with each action potential. During periods of intense activation, electrolyte flux rates can exceed the regulatory capacity of sarcolemmal pumps such that intracellular potassium concentration falls and intracellular sodium levels rise (183). Resting membrane potential therefore becomes less negative and the charge movement produced by action potentials is diminished. During intense activation, potassium accumulation within t-tubules can prevent action potential conduction and inhibit voltage-dependent calcium release (184). This phenomenon is the putative basis for high-frequency fatigue (167).

b. *Mechanisms Beyond the Muscle Fiber.* In intact humans, fatigue of exercising muscle may be influenced by other physiologic mechanisms. Blood flow to working muscle determines the rate of oxygen delivery and governs the clearance of deleterious metabolites (185). The process of exercise hyperemia is regulated by local mediators released from the working muscle (186), by vasoactive mediators produced locally (187), and by autonomic control (188). Loss of vascular control or peripheral vascular disease can accelerate fatigue by decreasing total blood flow to the muscle or, more subtly, by causing maldistribution of flow within the tissue. A global determinant is cardiac function. Insufficient cardiac output can limit blood flow to working muscle, especially in whole-body exercise tasks that involve a large muscle mass (189).

Neural mechanisms also are important. During volitional exercise, fatigue is most commonly reflected by "task failure," which is defined at the whole-body level as the inability to sustain a desired level of exercise. Task failure usually reflects two concurrent processes: contractile failure of the fatiguing muscle leading to loss of neural activation (190). Conscious activation of exercising muscle requires coordinated neural output from motor and premotor regions of the cerebral cortex; this is automatically accompanied by neural adjustments to cardiovascular function (191) and to respiration (192). Task failure may be caused by peripheral mechanisms. For example, neuromuscular transmission failure can be demonstrated in electrically stimulated neuromuscular preparations and is known to mediate fatigue in persons with neuromuscular disease such as myasthenia gravis; however, the physiologic importance of neuromuscular transmission failure during normal motor activity remains controversial (193). Task failure also may be accelerated by inhibitory spinal reflexes that are stimulated by afferent nerve endings in the working muscle (194). Alternatively, the subject may consciously decide to quit exercising because the task has become uncomfortable. Both neural mechanisms depend on afferent signals that can be used by the central nervous system to monitor changes in exercising muscle. The free nerve endings of group III and group IV afferents probably serve this purpose; they are sensitive to a variety of physiologic stimuli and can mediate either reflex or conscious adjustments to motor output (194). During day-to-day activities, the primary cause of task failure is that people quit when exercise becomes unpleasant. Highly motivated subjects and well-trained athletes can sustain motor output despite considerable discomfort. In these persons, it is controversial whether task failure directly reflects muscle fatigue or whether inhibitory reflexes accelerate task failure.

4. Measurements of Muscle Endurance

Endurance reflects the ability of muscle to sustain mechanical output during loaded contraction, i.e., resist fatigue. Measurement of endurance requires that a muscle or muscle group contract against a load, producing a time-dependent loss of mechanical function. The slower the loss, the greater the endurance. For detailed accounts of the techniques used to measure muscle endurance in humans, readers are referred to recent reviews of the field (195, 196). To briefly outline the concepts, measurements of muscle endurance have three basic components that can vary according to experimental design.

First is the strategy of muscle activation: volitional effort versus exogenous stimulation. Volitional activation is used for stereotypical exercise tasks performed using specific muscle groups, e.g., hand grip or knee extension. This strategy may be complicated by variations in motor output caused by dyscoordination, distraction, or lack of motivation, which cause the intensity of muscle activation to vary. Thus, it can be difficult to

discriminate between decrements caused by muscle fatigue and decrements caused by a drop in motor output. In studies of individual muscles, the classic twitch interpolation technique (197) can be used to assess muscle activation; an electrical pulse is applied to the motor nerve while measuring the force of a volitional contraction; an abrupt increase in force upon stimulation demonstrates that volitional activation was submaximal. An alternative approach is to bypass the central nervous system altogether. Exogenous electrical stimulation can be used to induce fatigue of limb muscles from which mechanical output can be measured such as adductor pollicis or tibialis anterior. A limitation of electrical stimulation is that activation of the motor nerve is usually submaximal, recruiting only a subset of the motor units in the muscle.

Second is the exercise condition: isometric versus isokinetic. Under isometric conditions, muscle length is fixed and endurance is measured as the ability to maintain force or torque. During isokinetic exercise, the muscle undergoes loaded shortening; endurance is measured as the ability to maintain velocity, work, or power. Note that exercise condition is largely independent of activation strategy.

Third is the exercise pattern: timing and intensity. The exercise task may involve either a single prolonged contraction or a series of repetitive contractions. During volitional exercise, the subject usually is asked to maintain a submaximal exercise level. Endurance then is measured as the time over which the task is maintained, i.e., time to task failure. During electrical activation, exercise intensity is determined by the stimulus characteristics, which usually remain fixed during the exercise bout; endurance is assessed by the rate at which muscle function declines during continued stimulation.

II. Skeletal Muscle Abnormalities in COPD

A. PATHOPHYSIOLOGY OF SKELETAL MUSCLE DYSFUNCTION IN COPD

1. Structural Alterations of Skeletal Muscle in COPD

a. **Muscle *Mass.*** There are no quantitative data available concerning the mass of specific limb muscles in patients with COPD. However, indirect estimates of a reduced muscle mass in patients with COPD have been reported. These have included findings of a decreased fat-free mass assessed by bioelectrical impedance analysis (129, 198-199) and a significantly smaller (13%) cross-sectional area of the calf muscle evaluated by magnetic resonance imaging (MRI) compared with matched control subjects (200). Assessment of more specific regional bone, fat, and lean body mass by dual emission X-ray absorptometry (DEXA) scanning has recently been used in conjunction with limb muscle size measurement by MRI in a longitudinal study in patients with COPD (201). However, a matched healthy control group was not included in the study.

b. ***Muscle Fiber Types and Sizes.*** More direct evidence of structural alterations of skeletal muscle in patients with COPD comes from studies at the cellular level. Biopsy analyses from the quadriceps femoris of patients with moderate COPD revealed no change in fiber-type proportions but significant atrophy of type II fibers, with the degree of atrophy correlated to the amount of weight loss (202). Others reported a reduced proportion of type I fibers in the vastus lateralis of patients with advanced COPD compared with unmatched control subjects (203, 204). Compared with matched control subjects, this reduction in the proportion of type I fibers in patients with COPD was recently found to be accompanied by an increase in the proportion of type IIb fibers (205). Furthermore, atrophy of both types I and IIa fibers was reported for these patients (205). It has been suggested that hypoxemia (204) and long-term disuse (205) may contribute to the high proportion of type II fibers found in patients with COPD. In contrast to the lower limb, the proportion of type I fibers in the biceps of patients with severe COPD was found to be similar to that of age-matched control subjects (206). The diameter of type I and (to a greater degree) type II fibers were smaller than those of control subjects and correlated with amount of weight loss and reduction in percent predicted FEV_1 (206). Another study in patients with COPD reported fiber-type analysis by quantifying myosin heavy-chain (MHC) and myosin light-chain (MLC) isoforms determined by gel electrophoresis (207). A significantly greater proportion of MHC-2B was found in the vastus lateralis of patients with COPD than in control patients. Moreover, the pattern of distribution of MLC isoforms in patients with COPD was also significantly shifted towards fast isoforms (207). Diffusion indices, VC and FEV_1 were all positively correlated with the content of slow MHC. As reported above (204,205) it was hypothesized that both reduced oxygen availability and muscle disuse probably determine muscle alterations in COPD (208). In this study, however, control patients were not age-matched.

c. ***Capillarity.*** An electron microscopic study reported that the number of capillaries per unit surface area in the vastus lateralis of patients with COPD was 53% lower than in age-matched normal subjects (209). Because the number of mitochondria per unit surface was unchanged in patients with COPD, their capillary/mitochondria ratio was also decreased by 59% compared with that in normal control subjects. Whereas the capillary/fiber ratio in the vastus lateralis of patients with COPD was not significantly lower than in control subjects, the number of capillary contacts for types I and IIa fibers were significantly lower in the patients with COPD (205). However, when normalized for fiber cross-sectional areas, the number of capillary contacts for each type of fibers were similar between patients with COPD and control subjects (205). This lower number of capillary contacts, along with a 25% lower myoglobin level found in the vastus lateralis of patients with COPD (209), may contribute to reduced oxygen delivery within muscle in these patients.

d. ***Metabolic Enzymes.*** Analyses from homogenates of muscle biopsy specimens from patients with severe COPD have demonstrated lower oxidative enzyme (citrate synthase, succinate dehydrogenase, and 3-hydroxyacyl-CoA dehydrogenase) capacities in the vastus lateralis compared with age- and height-matched healthy subjects (210,211). No significant differences in glycolytic enzyme (phosphofructokinase, lactate dehydrogenase, and hexokinase) activities were detected between these two groups (210,211) with the exception of phosphofructokinase activity, which was higher in the patients with COPD (210). It was suggested that both inactivity and hypoxemia contribute to these metabolic alterations in the COPD group. However, there were no reversal in the activities of any enzyme after 7 mo of long-term oxygen therapy (210). No studies have been performed to analyze enzyme activities within individual muscle fibers of identified type in limb muscles of patients with COPD.

2. Skeletal Muscle Function in COPD

a. ***Muscle Strength.*** Peripheral muscle weakness is common in patients with COPD (212,213). In a large study, Hamilton and colleagues (213) found that approximately 70% of patients with chronic lung disease, some of them with restrictive disorders, had lower quadriceps strength than the mean value obtained in normal subjects of similar age. The reduction in muscle mass certainly contributes to peripheral muscle weakness in patients with COPD (199, 214), but it is still unclear if muscle weakness can be attributed entirely to muscle atrophy (215,216).

Compared with normal subjects of similar age, the reduction in quadriceps strength averaged 20 to 30% in patients with severe to moderate disease (212, 213, 215), but, in general, their upper limb strength was relatively preserved compared to that of the lower limbs (212, 214, 217). The uneven distribution of muscle weakness between upper and lower limbs could be related to differences in accustomed level of activity between the different muscle groups. Compared with lower limb muscles, the upper limb muscles are probably more normally involved in activities of daily living. Furthermore, in COPD, the pectoralis major and the latissimus dorsi muscles may also act as accessory inspiratory muscles, another potential source of stimulation (218,219).

b. ***Muscle Endurance.*** The information on limb muscle endurance in patients with COPD is conflicting. Endurance of the vastus lateralis muscle has been reported to be normal in hypoxemic patients with COPD (220). This finding is surprising when taking into account the morphologic and enzymatic deficiencies found in the vastus lateralis muscle of these patients (203-205, 211). In contrast, other investigators found a 50% reduction in the endurance of the vastus lateralis muscle in 17 patients with COPD when compared with age-matched normal control subjects (221). The effects of COPD on the endurance of the upper limb muscles is also unclear; both normal endurance of the elbow flexors (217) and reduced endurance of the adductor pollicis muscle have been reported (220). Discrepant results between studies may be related in part to

differences in the methodology used to measure peripheral muscle endurance; further studies are required to resolve to what extent limb muscle endurance is altered in patients with COPD.

3. Muscle Bioenergetics

a. ***Oxygen Delivery and Utilization.*** Patients with COPD characteristically show poor exercise performance indicated by a marked reduction in both peak pulmonary O_2 uptake and work rate at peak exercise. However, the relationship between whole-body O_2 uptake and work rate is normal and the O_2 uptake for a given submaximal work rate in these patients is similar to that seen in healthy sedentary subjects (222-224).

Central pulmonary factors such as inability to adequately increase total ventilation because of the elevated work of breathing and disturbances of arterial respiratory blood gases (Pa_{O_2} and Pa_{CO_2}) have been historically invoked as principal determinants of exercise intolerance in these patients (222, 225). Recently, other evidence (211, 212, 226-229) suggests that skeletal muscle dysfunction should also be considered as playing a role in the limitation of exercise tolerance in COPD.

At peak exercise, systemic O_2 delivery is clearly below normal levels (222). Pulmonary dysfunction is not the sole cause because V_A/Q inequality does not lead to a large fall in O_2 content ***(Equation*** I) in most patients (225). Because the linear relationship between cardiac output and V_{O_2} is about the same in patients with COPD and in normal subjects, cardiac output at a given submaximal O_2 uptake is close to the expected normal value (153, 230-233). The principal difference is that the rise in cardiac output with exercise is usually achieved through a higher heart rate and lower stroke volume than in healthy subjects.

Because total ventilation, cardiac output, and exercise intensity remain closely coupled in COPD, the inability to raise ventilation appears to be the principal governor of the O_2 transport process: a low ceiling on ventilation means a low ceiling on cardiac output and thus on systemic O_2 delivery. It should be mentioned that the mechanisms that couple ventilation to cardiac output during exercise are still not well understood. Montes de Oca and colleagues (234) proposed that the large pleural pressure swings observed during exercise can constrain left ventricular function, thus limiting both peak cardiac output and exercise tolerance in patients with very severe COPD.

The coupling between whole-body O_2 uptake and cardiac output during exercise implies that the O_2 difference between arterial and mixed venous blood and the fractional O_2 extraction at a given work rate are normal or near normal (234-236). However, there is also evidence that whole-body fractional O_2 extraction may be less than normal in some patients with COPD (235,237) indicating either impaired O_2 uptake by exercising muscles and/or abnormal redistribution of blood flow during exercise. This type of result (235, 238) prompts the need for regional measurements of O_2 **transport/O_2** utilization during exercise. However, at the present time, an analysis of the relationships between skeletal muscle O_2 supply and cellular bioenergetics is incomplete since a complete picture of limb muscle O_2 **transport/O_2** utilization in an appreciable number of patients with COPD encompassing the spectrum of the disease is not available yet.

Femoral venous blood flow ($\dot{Q}leg$) measurements by thermodilution in patients with moderate to severe airflow limitation have recently shown a marked reduction in peak Qleg (236,237). Leg blood flow (and leg O_2 delivery) at a given submaximal whole-body O_2 uptake is normal in these patients (237, 239). This indicates that regional O_2 transport response in patients with COPD, as in healthy subjects, is proportional to the energetic requirements of the exercising muscle. In athletes during extreme exercise, there is competitive redistribution of blood flow away from the leg muscles to the respiratory muscles (240). This was hypothesized to occur in COPD because the work of breathing is so high, but the finding of normal leg blood flow during submaximal exercise (236, 237) appears to rule this out.

Mixed venous P_{O_2} is lower at rest in patients with COPD than in young healthy subjects (241). During exercise, patients with COPD show a peak limb muscle fractional O_2 extraction similar to that seen in untrained subjects (236, 237) since as much as 70% of arterial O_2 content is extracted by tissues at peak exercise. However, although healthy sedentary subjects manifest a steady increase in O_2 extraction ratio as work rate progresses, patients with COPD reach their peak limb fractional O_2 extraction at very low work levels relative to their peak work rate and they display a plateau in fractional O_2 extraction ratio thereafter. The abnormal profile of muscle O_2 extraction ratio observed in these patients during light exercise is consistent with an earlier and more intense recruitment of muscle capillaries than in the control subjects. The subsequent plateau in fractional O_2 extraction ratio observed in the patients while their muscle O_2 delivery is still increasing is compatible with a similar increase in both peripheral O_2 transfer and leg O_2 delivery, so that the ratio between these two components of O_2 transport, and consequently the fractional O_2 extraction ratio, remains unchanged across a range of exercise intensities. The profile of the O_2 extraction ratio in COPD can be interpreted as a functional adaptation of limb muscles to fulfill cellular O_2 requirements during submaximal exercise in the face of a rather low number of capillaries per muscle fiber compared with normal subjects (203,242).

Several studies have shown early increases of blood lactate levels during submaximal exercise in patients with moderate to severe COPD (211, 236, 243). Because leg blood flow during submaximal exercise is preserved, this finding indicates an increased net lactate output across the leg (236,237). The increased lactate production is responsible for the fall in muscle pH, which in turn may play a role in determining exercise intolerance in these patients (237). Premature lactic acidosis during exercise in patients with COPD has been associated with reduced oxidative enzyme concentrations in the lower limb muscles (211,226) that can be at least partly reversed by physical training. Recent evidence demonstrates that an early increase in femoral venous blood lactate levels during exercise is not correlated with reduced O_2 delivery to the lower limb (237). This provides further support for a biochemical abnormality that may be considered a hallmark of muscle dysfunction in COPD.

In summary, regional studies of O_2 **transport/O_2** utilization in patients with COPD indicate that both leg oxygen delivery and leg O_2 uptake at peak exercise are markedly limited likely because of complex interactions involving central and peripheral (impaired mitochondrial oxidative capacity) factors. In contrast, leg blood flow (and leg O_2 delivery) during submaximal exercise are apparently preserved and not different from those seen in untrained healthy subjects.

Analysis of intrinsic skeletal muscle dysfunction and quantitation of the relative contribution of peripheral factors in the limitation of peak O_2 uptake requires further studies assessing: (I) the impact of potential factors impairing O_2 uptake, physical detraining being one of the chief suspects, and (2) exercise of small muscle groups, which, at least partly, avoids central limiting factors. It should be recognized that reduced mitochondrial capacity in these patients does not necessarily

imply intrinsic muscle dysfunction caused by COPD. For example, muscle detraining plays an important role in the disturbances of skeletal muscle bioenergetics in COPD (236).

Finally, studies of the relationships between muscle O_2 transport and direct measurements of cellular oxygenation deserve attention to adequately assess the effects of high FI_{O_2} breathing on skeletal muscle performance. These types of studies are also needed to gain further insight into the relationships between tissue hypoxia and the phenomenon of weight loss (244–246).

b. ***Energy Metabolism.*** ^{31}P magnetic resonance spectroscopy (^{31}P-MRS) has rapidly become an important tool for ***in vivo*** assessment of tissue energy metabolism and pH (247). The ratio of intracellular phosphocreatine (PCr) to inorganic phosphate (Pi) is closely related to that of ATP to ADP and is, therefore, a useful measure of mitochondrial phosphorylation potential (248,249). In conjunction with intracellular pH measurements, which can also be obtained from ^{31}P-MRS, flux of ATP from oxidative phosphorylation, anaerobic glycolysis, and the creatine kinase reaction can be calculated (250).

Using ^{31}P-MRS, Kutsuzawa and colleagues (228) compared forearm muscle energy metabolism during exercise in 18 patients with COPD to that in normal control subjects. During repetitive handgrips performed against a load, the ratio of PCr/(PCr + Pi) for a normalized work rate was consistently lower in patients with COPD than in control subjects and could not be accounted for by mean forearm circumference, triceps skin fold, or percentage of ideal body weight (228). Likewise, Tada and colleagues (251) measured forearm PCr/Pi ratio and pHi during and after exercise in 11 patients with COPD, nine patients with congestive heart failure (CHF), and eight healthy control subjects; pHi and PCr/Pi were reduced in COPD and CHF during exercise and recovery, and nutritional parameters were not different among the three groups. These results suggest limb skeletal muscle oxidative capacity is reduced in COPD and that nutritional status is not the mechanism.

Thompson and coworkers (252) measured ^{31}P-MRS indices of skeletal muscle mitochondrial function in patients with severe COPD with resting hypoxemia. As in the study of Kutsuzawa and colleagues (228), more rapid PCr depletion was observed during exercise. Payen and coworkers (253) also found abnormal PCr/Pi ratio at end-exercise in patients with hypoxemic COPD. Wuyam and coworkers (200) examined calf muscle energy metabolism of eight stable, mildly hypoxemic patients with COPD (Pao, = 58 ± SE 3 mm Hg at rest) by ^{31}P-MRS. At 50% maximal voluntary contraction, patients with COPD exhibited a much higher Pi/PCr ratio than did healthy control subjects (3.34 ± 0.89 versus 0.49 ± 0.05). Finally, Mannix and colleagues (254) found an increased relative contribution to ATP production from anaerobic sources and a reduced contribution from oxidative phosphorylation in severely hypoxemic patients with COPD. In the aggregate, these studies confirm an abnormality of exercising skeletal muscle oxidative metabolism in the hypoxemic patient with COPD.

Recovery times for PCr are increasingly used to assess mitochondrial density and function (255). The time to resynthesize PCr was more than twice as long in patients with COPD than in control subjects in two studies (200, 253), but normal in another (252). Because intracellular hydrogen slows the creatine kinase reaction, modifications of PCr resynthesis measurement (256, 257) and ADP recovery (258) should be used to assess skeletal muscle mitochondrial function in COPD in the future. Quantification of skeletal muscle oxidative function is also possible by calculating Vmax for mitochondrial ATP synthesis (252). These noninvasive measurements should help determine if an intrinsic limb muscle mitochondrial defect exists in COPD.

Overall, the results of ^{31}P-MRS are consistent with the low level of oxidative enzymes in the quadriceps described by Maltais and colleagues (211, 226). Recently, however, increased cytochrome oxidase activity (COX) and upregulated mitochondrial gene expression of COX have been reported in skeletal muscle of patients with COPD and hypoxemia requiring continuous oxygen therapy (259). Because COX is the last enzyme of the oxidative phosphorylation chain, it can be speculated that upregulation of COX in these patients might reflect a compensatory phenomenon in face of cellular hypoxia, similar to that seen in peripheral vascular diseases (260,261).

c. Acid-base Balance. The Stewart analysis (262) of acid-base control states that hydrogen ion concentration of a physiologic solution is dependent on the strong ion difference (SID), P_{CO_2} and the total concentration and dissociation constant of weak acids and bases [Atot]. During brief, intense exercise in the normal human, two thirds of the rise in exercising skeletal muscle intracellular hydrogen ion concentration ($[H^+_i]$) is mediated by narrowing of the SID, in turn because of accumulation of lactate and efflux of K^+ from the cell (263). Another 25% of the increased [Hi] is related to increased total concentration of weak acids such as the histidine groups of protein and P_i as well as their collective apparent equilibrium constant. Only 10% of the increase in $[H^+_i]$ is thought to be dependent on P_{CO_2}. PCr^{2-} hydrolysis consumes a proton, results in loss of a strong anion, and increases buffering capacity through accumulation of P_i. pHi recovers through pHi-dependent (264) recruitment of an active sarcolemmal carrier mechanism for lactate (265–267), sodium-proton-antiport and bicarbonate-chloride exchange.

The majority of ^{31}P-MRS studies cited above have shown abnormal acidification of the myocyte during exercise in the patient with COPD. It has been speculated that the major cause is narrowing of SID, which is in turn related to intracellular lactate anion accumulation. No study to date, however, has directly examined the relative contributions of P_{CO_2}, weak acids, SID, and transmembrane ion transport to hydrogen ion change in the skeletal muscle of the patient with COPD.

B. ETIOLOGY OF SKELETAL MUSCLE DYSFUNCTION IN COPD

1. Related to COPD

It is apparent that skeletal muscle metabolism is altered in COPD. The ^{31}P-MRS technique has been used to assess muscle energy status (200, 216, 251, 252). The PCr/Pi ratio is lower and recovery after exercise is slower in patients with COPD than in healthy control subjects. Other studies show a lower content of oxidative fiber types and a higher content of glycolytic fiber types (203, 204, 268), lower activities of oxidative and higher activities of glycolytic enzymes (210, 211), and lower levels of ATP and PCr (210, 269). These data indicate that a shift from oxidative metabolism to glycolytic metabolism occurs in peripheral skeletal muscle of patients with COPD at low levels of exercise.

We are at the beginning of a search to understand the mechanisms underlying these muscle abnormalities. Few studies in patients with COPD help to define which pathophysiologic factors present in COPD might impact appreciably on skeletal muscles. Data from other human disease, animal models, and tissue culture suggest that hypoxia and hypercapnia, inflammation, and chronic malnutrition are leading candidates.

a. ***Hypoxia*** Chronic hypoxia has an adverse effect on skeletal muscles. In humans exposed to high altitude hypoxia over a pe-

riod of 6 wk, glycolytic enzyme activities were elevated and activities of enzymes involved in the citric acid cycle, the fatty acid oxidation, and the respiratory chain were decreased (270). It has been shown that hypoxia induces acute inhibition of mitochondrial protein synthesis in brine shrimp embryos (271). Hypoxia induces decreased levels of creatine phosphate and citric acid cycle intermediates in rats exposed to intermittent hypoxia for 5 d (272). In rats exposed to different degrees of intermittent hypoxia the incorporation of glucose-carbon into glycogen was increased (273). In another study, chronic intermittent hypoxia caused decreased glycogen, glucose, and glucose-6-phosphate concentrations accompanied by elevated hexokinase activity and decreased mitochondrial enzyme activities (272). These effects of hypoxia have been shown to be greater in the elderly (274).

Hypoxia itself can contribute to oxidative stress. For example, increased antioxidant activity has been found in muscle from rats exposed to intermittent hypoxia (275) and in patients exposed to acute hypoxia (276). Because the shift to glycolytic metabolism, the oxidative capacity of skeletal muscle decreases. Information on oxidative stress comes from studies of ischemia and reperfusion injury in heart muscle. Upon reperfusion after ischemia, free oxygen radicals are formed that directly and also indirectly cause damage to proteins and membranes, resulting in loss of ability to produce ATP because of a calcium overload in mitochondria (277-280). The fact that vitamin E attenuates muscle damage in rats (281, 282) and the fact that vitamin E protects human skeletal muscle from damage during surgical ischemia-reperfusion (283) support this theory.

In conclusion, adaptation to hypoxia makes muscle tissue more vulnerable to oxidative stress, which in turn leads to a malfunction in ATP generation and increases the accumulation of inosine monophosphate (IMP) in skeletal muscles (284). Inosine monophosphate has been detected in the resting skeletal muscles of patients with COPD (285).

b. ***Hypercapnia.*** Acute or chronic hypercapnia is frequently present in patients with COPD suffering from acute or chronic respiratory insufficiency. Acute hypercapnia contributes to intracellular acidosis in patients with acute respiratory failure. The level of intracellular acidosis is significantly related to arterial carbon dioxide tension. In skeletal muscles of patients with acute respiratory failure, intracellular acidosis seems to be linked to reduced potassium and magnesium content (286). Studies in isolated diaphragm preparations have demonstrated that acute changes in CO_2 are associated with reversal of the net acid efflux as well as with a reduced efflux of lactate and pyruvate. These conditions result in a decreased intracellular pH (287). Intracellular acidosis has marked effects on the enzymatic machinery of muscle cells. By far the most important pathway by which energy is released from the-glucose molecule is by the process of glycolysis followed by oxidation of the end-products of this glycolytic process. Phosphofructokinase forms a critical enzyme in this process of glycolysis. In frog muscle intracellular acidosis completely blocks the activity of this enzyme (288).

Studies in humans suggest an overall derangement of cellular energy metabolism in acute respiratory failure, manifested by marked decreases in muscle ATP and phosphocreatine contents as well as significant decreases in the total adenosine nucleotide pool (269, 285). Remarkably, no significant relationships have been detected in these studies between the main parameters of energy metabolism and intracellular pH. These changes in energy metabolism are temporary and reversible after therapeutic intervention (269).

Different results are reported in animal models, possibly depending on the species studied or on the nature of the ***in vivo*** and ***in vitro*** models. Incubation of rat muscle tissue with high CO_2 results in decreased levels of phosphocreatine content, increase in ADP, and a decrease of the ATP to ADP ratio (284). In contrast, it was demonstrated that oxidative phosphorylation is not inhibited by acidosis in hypercapnic rabbit muscles (289) and that the behaviour of the phosphate metabolites was not different between hypercapnic and normocapnic conditions in rat diaphragms (290).

Further studies are needed to unravel more systematically the metabolic effects of gas exchange abnormalities in clinical conditions as well as ***in vivo*** animal models.

c. Inflammation. Inflammation, local or systemic, is a characteristic of COPD, and this process intensifies oxidative stress. Reactive oxidants, specifically reactive oxygen intermediates (ROI) and nitric oxide (NO), are produced in large quantities by immune cells during inflammation.The redox homeostasis of the cell can be considered as important as the acid-base status of the cell since ROI and NO directly influence an array of redox-sensitive regulatory proteins and thereby modulate cellular processes from carbohydrate metabolism to calcium homeostasis, from mitochondrial oxygen consumption to membrane transport (291).

Skeletal muscle myocytes contain numerous pathways by which ROI may be produced. These include electron carriers on the inner mitochondrial membrane, membrane-bound oxidoreductases, the cyclooxygenase pathway and cytosolic xanthine oxidase. Furthermore, free radicals seem to be obligatory for optimal contractile function since ROI concentration increases markedly in muscle tissue during contraction, and depletion of ROI depresses the twitch response of incubated rat diaphragm (292,293). One mechanism whereby ROI might promote excitation-contraction coupling is by enhancing calcium release from the sarcoplasmatic reticulum. Overproduction of ROI by skeletal muscle may lead to a nonpathologic form of oxidative stress, as occurs in muscle fatigue during heavy exercise (294). The dynamic balance in the redox buffer system is perturbated by depletion of the intracellular antioxidant pool, which consists mainly of reduced glutathione (GSH). As a result of the ROI overstimulated calcium release, calcium homeostasis is disturbed and a calcium-dependent proteolytic pathway is activated, leading to muscle protein degradation (295). Another form of oxidative stress that is not the result of inflammation has been described in skeletal muscle atrophied by immobilization. Here, decreased total cell glutathione, increased intracellular concentrations of oxidized glutathione (GSSG), and lipid peroxidation were found. Treatment with vitamin E, an antioxidant, significantly attenuates these effects as well as the rate of atrophy, suggesting a contributing role of oxidative stress (296).

Nitric oxide (NO), the other major oxidative reactant, is constituitively coexpressed by two NO synthase (NOS) isoforms in skeletal muscle; the neuronal-type of NOS, ncNOS (which is predominantly expressed by type II muscle fibers) and endothelial NOS, ecNOS (which occurs independent of the fiber type). NO is also involved in excitation-contraction coupling, in which it seems to oppose the action of ROI (292). Besides this physical effect of NO, recent research suggests a direct role for NO in skeletal muscle cell metabolism, namely, the regulation of exercise-stimulated glucose transport (297, 298). An inducible form of NOS (iNOS) has been found in skeletal muscle, and its induction can lead to increase of oxidative stress response in skeletal muscle tissue (299).

Muscle proteins can be oxidatively damaged and the activation of an energy-independent proteolytic pathway accelerates muscle protein degradation (300). The administration of tumor necrosis factor alpha (TNF-u), a proinflammatory cy-

tokine involved in the endobronchial inflammatory process, can contribute to the skeletal muscle catabolism (301,302). It is hypothesized that the release of amino acids as a result of these catabolic effects on the muscle tissue contributes to the synthesis of acute phase proteins by the liver in inflammatory conditions.

d. *Nutrition.* In contrast to the effects of hypoxia, hypercapnia, and inflammation, the effects of nutritional depletion and muscle wasting on peripheral skeletal muscle function in COPD is reasonably well documented. Prolonged nutritional depletion is associated with proportionate reductions in muscle mass, whereas the mechanical effectiveness of the residual myofibrillar material remains unaffected (303). The effects of nutritional depletion on type II fibers are of greater magnitude than on type I fibers; greater atrophy of type II fibers ensures that a greater percentage of the remaining total muscle area will be composed of slow oxidative fibers whose resistance to fatigue is greater than that of fast fibers. Therefore the tension of the muscles generated during basal activities is well preserved, but the maximum power output may be impaired as progressively greater number of fast fibers are recruited. The high oxidative capacity of type I fibers can be considered as a metabolic adaptation to a process of glucose sparing by a greater reliance on fat as an energy substrate. It has been demonstrated in healthy men that the predominence of fat combustion during exercise is related to the percentage of slow-twich fibers in the quadriceps femoris muscle (304).

Clinical studies have investigated the effects of nutritional depletion in various disorders on peripheral skeletal muscle function using neurophysiologic tests. They have focused primarily on the adductor pollicis muscle. Nutritional depletion is associated with a loss of force at higher stimulation frequencies, slowing of the relaxation rate after supramaximal stimulation and a reduction in muscle endurance (305).

As a simpler alternative to neurophysiologic testing, voluntary tests of maximal muscle strength such as handgrip strength and quadriceps force have been used. Upper extremity as well as lower extremity muscle function are clearly decreased after nutritional depletion (199). Maximal voluntary contraction using a handgrip dynamometer is also a useful functional indicator of nutritional status, particularly in differentiating subjects with chronic undernutrition from those who are underweight and not undernourished but have a similar body mass index (306).

Alterations in muscle function may occur prior to evidence of decreased muscle mass. On a body compositional level, recent studies have shown that nutritional depletion and refeeding alter total body potassium earlier than and differently from the way in which body nitrogen is altered. These findings suggest that an early effect of nutritional depletion and repletion is associated with alterations in membrane ion transport (307,308)

Limited clinical data are available regarding the relative contribution of nutritional depletion on muscle enzyme capacity and energy-rich substrates in COPD. Depletion of high energy phosphate compounds (ATP and PCr) and cations (Mg and K) occurs in the respiratory muscles of patients with respiratory failure caused by acute or chronic lung disease, and undernourished patients have the more severe derangements of muscle composition (309). Depletion of energy-rich compounds and alterations in muscle enzyme capacity have also been demonstrated in resting muscle of patients with clinically stable COPD, but no stratification by type and severity of nutritional depletion has been performed. In malnourished surgical patients, fructose biphosphatase activity was decreased by 44%, phosphofructokinase activity by 40%, and hexokinase activity by 37% compared with normally nourished control subjects comparable in age, sex, and habitual activity (310). The changes were associated with smaller muscle fibers and a smaller proportion of type II fibers. These data were confirmed in patients with anorexia nervosa where activities of glycolytic enzymes were 50% lower than those in sedentary control subjects, whereas the activities of enzymes of the mitochondrial oxidative pathways were involved to a lesser extent (311).

It is yet unclear to what extent altered metabolic processes, muscle mass, and muscle function are interrelated during acute and chronic hypoenergetic feeding. It is hypothesized that muscle wasting per se is an important determinant of muscle strength, whereas the associated alterations in muscle metabolism are important determinants of work capacity. Experimental data in rats, furthermore, indicate differences in the metabolic and functional response to hypoenergetic feeding between type I and type II fibers (312), which could be important in evaluating the contribution of acute and chronic nutritional depletion on peripheral skeletal muscles.

2. Related to Comorbid Conditions

Patients with COPD often have comorbid conditions such as electrolyte disturbances, cardiac failure, deconditioning, diabetes, and hypertension that may affect skeletal muscle function. Some of these comorbid conditions are addressed in the present section. In general, it is unclear whether the effect on the muscles of these comorbid conditions is different in patients with COPD from that in other patients.

a. *Electrolyte Imbalance.* Electrolyte disturbances may profoundly affect skeletal muscle function. However, few studies on the effects of electrolyte disturbances have been performed in patients with COPD. Most studies have been performed in critically ill patients.

Hypophosphatemia (313,314) hypomagnesemia (315), hypermagnesemia (316), hypocalcemia (316, 317), hypokalemia (316, 318), hyperkalemia (316, 318), hyponatremia (316), hypernatremia (316), and hypochloremia (319) all lead to muscle weakness. If these electrolyte disturbances are severe, cell destruction, myopathy, and rhabdomyolysis may follow. The most commonly recognized causes of myopathy are hypophosphatemia and hypokalemia (316).

Hypokalemia is frequently caused by diuretic therapy. It is associated with muscle weakness and, if severe, it may also lead to rhabdomyolysis (316). This is probably caused by muscle glycogen depletion. This depletion enhances the probability of rhabdomyolysis during exercise by a similar mechanism operant in patients with McArdle's disease, in whom phophorylase is lacking, which prevents glycogen from being utilized (316).

Hypophosphatemia is frequently present in patients with respiratory illness particularly with respiratory infections (320). Indeed, in one study, 17% of the patients admitted for respiratory illness and 28% of the patients admitted for respiratory infections demonstrated hypophosphatemia (320). It is further associated with alcohol abuse (321), gram-negative sepsis (322), and COPD with hypercapnic respiratory failure (323,324). Hypophosphatemia is associated with low intracellular ATP levels, which may form the basis of the observed muscle weakness (325,326). Low intracellular ATP levels have also been shown to be present in patients with COPD during acute exacerbations (269). In these patients quadriceps phosphorus content was reduced as well. There was a poor correlation between serum and intramuscular phosphorus levels. The low intramuscular phosphorus levels may be associated with chronic malnutrition (323,324). There appears to be failure of the normal renal response to hypophosphatemia in patients with COPD.

Acute phosphate depletion may be associated with membrane dysfunction, leading to high intracellular water, high intracellular potassium, and low intracellular sodium, which also leads to contractile dysfunction (327). Intravenous administration of phosphate has been shown to improve diaphragmatic function in mechanically ventilated patients with hypophosphatemia and acute respiratory failure (328).

Hypomagnesemia is frequently associated with alcohol abuse (329-331) and use of diuretics (331). Intramuscular magnesium may be low in alcoholics despite normal serum levels (330). Both alcoholic and nonalcoholic subjects with hypomagnesemia have lower isometric quadriceps strength than do alcoholic and nonalcoholic subjects with normal serum magnesium levels (329). Intravenous administration of magnesium was shown to improve respiratory muscle power in patients with hypomagnesemia (332).

b. ***Cardiac Failure.*** The effects of cardiac failure on skeletal muscle function has received considerable attention, but there are no data on the effect of cor pulmonale on muscle function in COPD. It can be speculated that the effects of left ventricular failure on muscle function is unlikely to be an appropriate model for the effects of cor pulmonale and right ventricular failure on muscle function, as occurs in COPD. Thus, the data in the literature concerning primary congestive heart failure (CHF) are summarized only briefly here. Measurements of skeletal muscle function in patients with cardiac failure have shown a tendency for muscle strength to decrease (333), while other studies did not find a decrease in strength (334, 335). Marked reductions in static and dynamic endurance of large skeletal muscles such as the quadriceps, as well as of smaller muscles such as foot dorsiflexors, have consistently been detected (333-335). Deconditioning may play a role in the muscle weakness induced by cardiac failure, as the upper limbs seem to be less affected than the lower limbs (333).

Muscle biopsies in patients with CHF reveal structural changes such as increased lipid deposition and interstitial cellularity, as well as muscle fiber atrophy (336). Reduction in oxidative enzyme capacity and maintained glycolytic and glycogenolytic enzyme function have also been demonstrated (336-339). These results could be related to the finding of an increase in the percentage of type II (fast-twitch) fibers and a reduced proportion of type I (slow-twitch) oxidative fibers (336, 337, 339). Analysis of the type II fibers shows that the IIb fibers are responsible for the increase in the percentage of the type II fibers (337,339). Variable degrees of fiber atrophy have been found. Sullivan and colleagues demonstrated a type IIb atrophy in peripheral muscles of patients with CHF (337), whereas Mancini and colleagues (339) found an atrophy of both IIa and IIb fibers. It should be noted that the changes described clearly contrast with the changes observed with aging where a reduction in the number of type II fibers has been consistently observed (see below).

Several hypotheses have been tested in order to explain these alterations. Reduced skeletal muscle blood flow, deconditioning, and circulating cytokines have been suggested. Tumor necrosis factor is a cytokine known to induce skeletal muscle catabolism (301). As studies have shown elevated serum levels of TNFα in chronic heart failure (340), its effects on limb muscle could possibly explain part of the skeletal muscle abnormalities in CHF.

c. Detraining. Deconditioning of peripheral muscles is an adaptation to disuse. Reduced activity under normal conditions causes mild deconditioning. More pronounced adaptations are observed with unloading, microgravity, or prolonged bed rest. Immobilization in a cast causes the most dramatic muscular alterations (341). In chronic illnesses such as COPD, patients are subjected to varying degrees of deconditioning by reduced activity or prolonged bed rest.

Deconditioning of peripheral muscles is characterized by muscle fiber atrophy. In general, the atrophy is reversible and affects both type I and type II fibers, with a distinct preference for type I fibers. However, this is largely dependent upon the preexisting fiber distribution in the examined muscle and the experimental method used to produce deconditioning. Thirty days of bed rest caused more pronounced decreases in type II fiber area in the vastus lateralis muscle in human subjects (342). Antigravity muscles crossing a single joint and containing a relatively large proportion of type I fibers appear to be most affected by deconditioning atrophy (343). The atrophy is rapid initially, with the largest degree occurring during the first week (344). With increasing duration of deconditioning, progressively greater decrements in muscle mass are observed (341). Atrophy results in muscle weakness, but the observed decrease in muscle force-generating capacity may be greater than expected on the basis of the atrophy because of impairment of the motoneuron excitability and to reduced ability to activate motor units maximally during voluntary contractions (345).

Changes resembling the skeletal muscle alterations occurring with deconditioning have been described in patients with COPD. They include reduction in oxidative enzyme capacity and atrophy of type I fibers (346-348). In addition, prolonged inactivity has been reported to reduce the proportion of type I fibers (349) as has been observed in patients with COPD (203,204).

The mechanism of the muscle fiber atrophy caused by deconditioning remains unclear. Cell protein content rapidly decreases because of reduced synthesis (350) and increased degradation. Myofibrillar proteins are more affected than are membrane and sarcoplasmatic proteins (351). The factors regulating protein turnover in deconditioning are not well understood. A potential regulatory role has been attributed to Id proteins, or "Inhibitor of Differentiation" proteins, a class of transcription factors regulating transcription of the myogenic program (352).

d. ***Age-related Changes.*** Muscle force is known to decrease by 30 to 40% between 30 and 80 yr of age (353-355). The decrease in muscle strength correlates well with the decrease in muscle mass. By 60 to 70 yr of age, muscle mass in humans decreases by 25 to 30% (356). This is mainly due to a reduction in fiber cross-sectional area and the atrophy predominantly affects type II fibers (357). However, there also appears to be a continuous loss of muscle fibers throughout the life span (356). The decrease in fiber number is about 24% in the elderly. Before 60 to 70 yr of age there is little change in fiber cross-sectional area. In subjects older than 70 yr of age the mean area of type II fibers decreases by approximately 15% and the percentage of type II fibers decreases by 40% (358). In elderly bedridden patients there may be virtually complete loss of type IIa fibers.

Much of the age-related atrophy may be due to motor-unit remodeling. This occurs at the neuromuscular junction by the processes of denervation, axonal sprouting, and reinnervation. As a whole, type I motor units increase considerably in size because of selective denervation in type II fibers and faster reinnervation by collateral sprouting from type I motor units (357). As a consequence, the number of motor units decreases 75% with increasing age in some human muscles (359). The process of age-related denervation atrophy may be aggravated by an increased susceptibility of muscles in the elderly to contraction-induced injury (360) and by the impaired capacity for regeneration (361).

Although it has been suggested that the decrease in force with aging is entirely due to the decrease in muscle mass (356),

it is likely that specific muscle force (i.e., muscle force per unit cross-sectional area) also decreases with increasing age (355, 362, 363), although this has been disputed (146). In rodents, about 20% of the decrease in specific force is not accounted for by muscle atrophy (361, 364, 365). Because the increase in connective tissue also cannot completely explain the decrease in specific force (366), the specific force decrease must be related to a decrease in the number of cross-bridges per unit muscle area or to a decrease in the average force developed per cross-bridge (361,365). These qualitative age-related changes in rodent muscle function with increasing age have recently been confirmed in single cells from human quadriceps muscle. Specific tension was reduced in the type I and type IIa fibers (367).

To the best of our knowledge there are no data on the effects of aging on skeletal muscle function. in patients with COPD. More specifically, it is unclear whether the decline in skeletal muscle function normally observed with age would be more pronounced in these patients.

3. Corticosteroids

Steroid myopathy is defined as muscle weakness that occurs in individuals who are being treated with cortiocosteroids but who do not have any other neuromuscular disease. In COPD, the most commonly encountered drug-related side effect in skeletal muscles is associated with the use of oral corticosteroids. Both animal and clinical studies have shown that both the peripheral and respiratory muscles are affected by prolonged administration of corticosteroids.

a, ***Acute and Chronic Steroid-induced Myopathy.*** Steroid-induced myopathy may present in two distinct patterns: acute and chronic steroid myopathy. Acute steroid myopathy is a rare complication of intravenous treatment with corticosteroids (368, 369). Generalized muscle weakness occurs 5 to 7 d after the onset of treatment with high intravenous doses of corticosteroids. Rhabdomyolysis occurs in the affected muscles with high levels of serum creatine kinase and myoglobinuria. Muscle biopsies show focal and diffuse necrosis and atrophy of all fiber types. Recovery may be prolonged to more than 6 mo. Specific cases of this complication in patients with COPD have not been described.

Chronic steroid myopathy, in contrast, is the classic type of steroid-induced myopathy, occurring after prolonged oral administration of lower doses of steroids, e.g., prednisolone in a dose of 10 mg/d or more. Fluorinated steroids cause weakness and myopathy more often than nonfluorinated steroids (370-374). Proximal muscle weakness is a prominent clinical feature. Serum levels of muscle enzymes are usually normal, but LDH is elevated. Urinary creatine excretion is increased preceding the clinical appearance of myopathy. Rhabdomyolysis is absent. Atrophy of type IIb fibers is observed in muscle biopsies. Recovery of chronic steroid myopathy takes many weeks to months.

b. ***Steroid-induced Changes in Skeletal Muscles of Patients with COPD.*** The relationship between peripheral and respiratory muscle strength and average daily dose of steroids was analyzed in 21 patients with COPD or asthma (215). The average daily dose of steroids taken in the previous 6 mo varied from 1.4 to 21.3 mg (average, 4.3 mg). Eight of these 21 patients suffered from generalized muscle weakness. The average daily dose of methylprednisolone during the previous 6 mo exceeded 4 mg in seven of these eight patients, in contrast to only three of the 13 patients with normal muscle strength. Multiple regression analysis of the relationship between quadriceps force and steroid dose showed that the average daily dose explained 51% of the variance in quadriceps force. These relationships were independent of the degree of airflow obstruction, estimated by percent predicted FEV_1 (215).

Functional and histologic characteristics of the peripheral muscles have been described in patients with COPD and steroid-induced myopathy, as compared with control patients with COPD matched for age, sex, and degree of airflow obstruction (375). Steroid-induced myopathy was associated with severe peripheral muscle weakness, quadriceps force in the mypopathy versus control patients being 23 ± SD 14 versus 71 ± 23% predicted, respectively. In the patients with COPD and steroid-induced myopathy LDH levels were increased (697 ± 301 versus 421 ± 128 IU/L, $p < 0.001$) and 24 h urine creatine excretion was increased (990 ± 609 versus 159 ± 219 mg, $p < 0.001$).

A quadriceps biopsy of a patient with COPD and steroid-induced myopathy as compared with a control patient with COPD is shown in Figure 2. Myopathy biopsies were characterized by increased variation in diameter of fibers, with several angular atrophic fibers and diffuse necrotic and basophilic

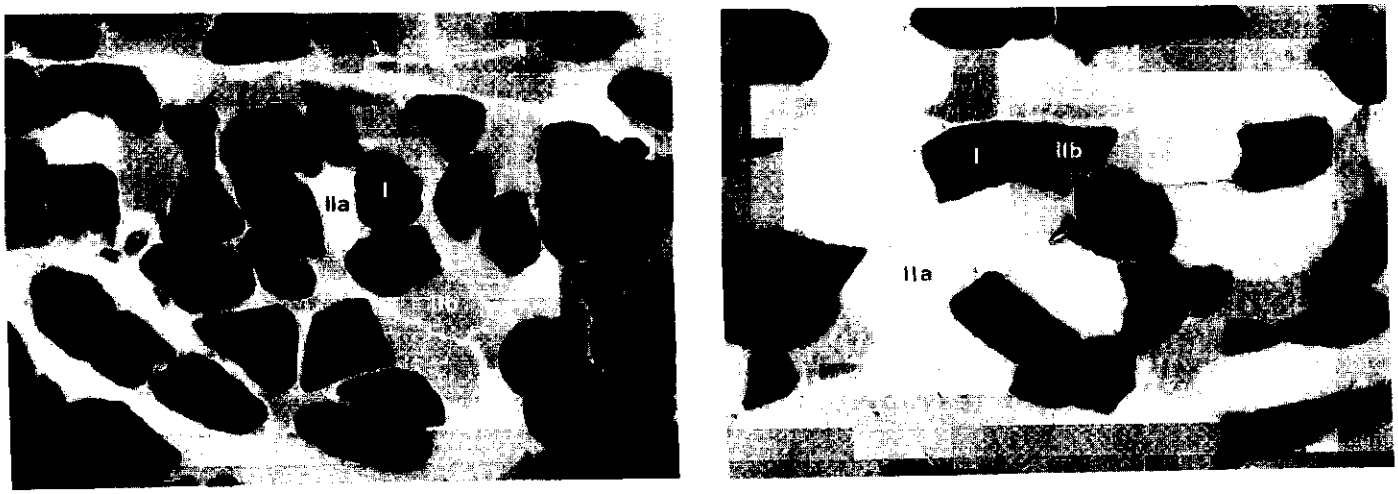

figure 2. Quadriceps biopsy from a patient with steroid-induced myopathy (*left* panel) compared with a control patient with COPD (right panel). Note increased variation in muscle fiber diameters, increases in the amount of connective tissue, increased number of central and subsarcolemmal nuclei, and diffuse necrotic fibers in the patient with steroid-induced myopathy. Representative fiber types (I, Ha, IIb) are labeled. (Reprinted from Reference 375, with permission.)

fibers (Figure 2). In addition, increased amount of connective tissue between fibers and increased number of subsarcolemmal and central nuclei were present. On ATPase stain, diffuse fiber atrophy predominantly affecting type IIb fibers was present, but type IIa and, to a lesser extent, type I fiber atrophy was also present (Figure 3) (375). It may be speculated that the loss of body weight in this study may play a role in the observed pattern of generalized fiber atrophy. Patients with COPD and steroid-induced myopathy had a lower body mass index than did control patients with COPD (19 ± 3 versus 23 ± 4 kg/m^2, $p < 0.05$). This contention is supported by observations in animal studies. Indeed, in the rat, malnutrition has been shown to cause a more generalized pattern of fiber atrophy than treatment with triamcinolone (376). Moreover, prednisolone reduced power output of the diaphragm more than in weight-paired control animals (377).

Clinically, follow-up of patients with COPD and steroid-induced myopathy showed that survival was reduced in comparison with control patients with COPD with a similar degree of airflow obstruction ($p < 0.025$) (375). Four of the eight patients with steroid-induced myopathy died within 6 mo after diagnosis in ventilatory failure. In a control group of 24 patients with COPD with a similar degree of airflow obstruction, only two patients died in the same period because of causes unrelated to COPD.

c. Mechanism of Steroid-induced Myopathy. Corticosteroids may affect the production of contractile proteins and the turnover of biochemical substrates in skeletal muscle. This is likely to be a generalized process, affecting both peripheral and respiratory muscles. Most data relevant to the specific mechanism of steroid-induced damage to skeletal muscle has been obtained in studies of the diaphragm muscle of lower animals.

Corticosteroids may downregulate insulinlike growth factor 1 (IGF-1), and thus may downregulate protein synthesis and increase intracellular proteolysis. Administration of corticosteroids has been shown to reduce myofibrillar and sarcoplasmatic protein concentration in rat diaphragm (378). Protein synthesis is primarily inhibited in type II fibers, mainly by downregulating peptide initiation on the ribosomes (379). Also, increased cytoplasmatic protease activity may lead to myofibrillar destruction (380). In this way glucocorticoids inhibit protein synthesis and may accelerate myofibrillar and soluble protein degradation in skeletal muscle.

In addition, carbohydrate metabolism is altered in steroid myopathy. Reduced muscle glycogen phophorylase activity (381) and increased glycogen synthetase activity (382) lead to an increased intramuscular concentration of glycogen. An increased concentration of glycogen has been reported in rabbit diaphragm (383). In addition, there is a reduction in creatine kinase activity (384). This impairment in glycolytic activity may in part be compensated by increasing oxidative metabolism (385). Possibly, the differences in response to steroids are in part explained by different contents of oxidative enzymes in type I and IIa fibers compared with type IIb fibers. Corticosteroids may also affect energy production in skeletal muscle. Citrate synthase activity is reduced in rat diaphragm (385, 386), but an effect on succinate dehydrogenase activity was not observed (387). Finally, it has been postulated that corticosteroids may impair diaphragm function by reducing myofibrillar density and/or by slowing cross-bridge kinetics (387). It is not known if different types of corticosteroids affect skeletal muscle via a similar pathway. The fluorinated steroid triamcinolone affects the diaphragm in a different way from that of the nonfluorinated steroid prednisolone (388).

d. *Clinical Implications.* Steroid-induced myopathy may affect skeletal muscles in many patients with COPD. Histologically, both myopathic changes and type IIb fiber atrophy are observed in the muscles involved. This pattern of specific fiber atrophy may be compounded by concomitant malnutrition, which causes generalized fiber atrophy. Fluorinated steroids seem to cause this type of alterations more often than nonfluorinated steroids. The clinical data described above suggest that there is a relationship between dose, duration, and the extent of functional and structural alterations, but other factors such as the level of physical activity and nutritional status also influence the severity of the clinical presentation of steroid-induced myopathy. It also is unclear how long the myopathy persists after systemic steroids are discontinued. Are patients with COPD destined to have long-term muscle dysfunction after a course of oral steroids?

Future studies are required to establish more firmly the relationship between steroid-induced myopathy and mortality. The development of molecular probes might enable a rapid diagnosis from analysis of muscle specimens.

C. FUNCTIONAL IMPACT ON EXERCISE TOLERANCE

Dyspnea, impaired exercise tolerance, and reduced quality of life are common complaints in patients with COPD. Several pieces of evidence point to the fact that these are not simply consequences of the loss of pulmonary function. Reduced exercise capacity shows only a weak relation to lung function impairment (389). Moreover, medication may improve pulmonary function in COPD, but it has no clear effect on exercise capacity (390). In addition, lung transplantation, in spite of yielding substantial improvement in lung function measurements, improves exercise capacity only partially (348,391). No significant differences in post-transplant exercise capacity were detected between single or double lung transplantation (391).

The importance of peripheral skeletal muscle dysfunction in the impairment of exercise capacity in patients with COPD was suggested by Killian and colleagues (392). They observed that both patients with COPD and normal subjects frequently reported that the sensation of leg fatigue limited exercise. Impaired peripheral skeletal muscle function and (upper and

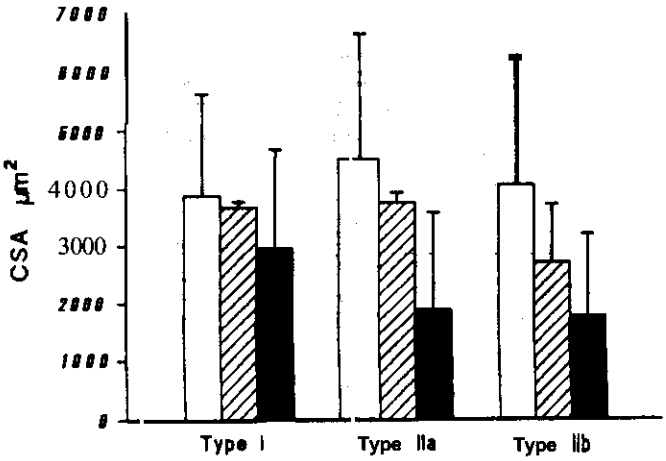

Figure 3. Mean cross-sectional area (CSA) of type I, IIa, and IIb fibers in quadriceps biopsies of healthy subjects (open bars), control patients with COPD (*hatched* bars), and patients with steroid-induced myopathy (*closed* bars). Generalized fiber atrophy, predominantly affecting type IIa and IIb fibers, is observed in the steroid-induced myopathy patients. (Reprinted from Reference 375, with permission.)

lower extremity) exercise limitation will be discussed from the point of view of reduced strength and reduced endurance capacity of these muscles.

1. Peripheral Muscle Strength

Reduced strength is observed in peripheral muscles of patients with COPD (212, 213, 215). Quadriceps force correlates significantly with 6-min walking distance and maximal oxygen uptake (212, 213). Muscle strength was also significantly correlated with symptom intensity during incremental exercise testing (213). These findings are based on stepwise multiple regression analysis and therefore do not allow conclusions on a causal relationship. Two additional observations make a causal relationship more likely. Firstly, changes in muscle strength have been demonstrated to correlate significantly with change in exercise capacity (393). Secondly, peripheral muscle strength training has been shown to improve maximal muscle strength, exercise endurance capacity, and quality of life (394).

Reduced walking distance was shown to correlate significantly with the creatinine-height index in underweight patients with COPD, implying correlation with reduced fat-free body mass available for exercise (395). Recently, depletion of fat-free body mass was also found to correlate with reduced $\dot{V}O_2max$ in COPD (396).

2. Peripheral Muscle Endurance

Deterioration of endurance capacity of peripheral muscles is also likely to contribute to reduced exercise capacity. Low intensity endurance muscle training has been shown to significantly improve limb muscle endurance, but not muscle strength (397). Whole-body endurance performance (walking) improved significantly more in the low-intensity muscle training group than in the control group (397).

Information on muscle endurance capacity can also be derived from muscle metabolism measurements. Although previously questioned (398), it is now well established that an early onset of anaerobic muscle metabolism during incremental exercise contributes to exercise limitation in COPD (211, 243, 399). Maltais and colleagues (211) found a significant relationship between muscle aerobic enzyme levels and maximal oxygen uptake. In lung transplant patients, maximal oxygen uptake was significantly reduced and significantly correlated with abnormalities of skeletal muscle oxidative capacity (227). In contrast, Satta and colleagues (207) studied a group of patients with COPD and found a low exercise capacity and significant alterations in fiber type proportions in the quadriceps muscle, but no significant correlation between them. Further, in one study exercise training in patients with COPD has been shown to improve both exercise capacity and oxidative enzyme activity of the peripheral muscles, but no significant correlation between these improvements was obtained (226).

During constant work rate exercise, the contribution of aerobic and anaerobic metabolism to total muscle metabolism can be studied in the steady state. In patients with both mild and severe COPD, improved aerobic capacity is reflected by showing that, for a given level of exercise, the levels of lactate and ventilation are lower (226, 243, 400). This also reflects the link between skeletal muscle function and exercise capacity in COPD.

3. Upper versus Lower Extremity Exercise

Most attention has been given to lower extremity exercise. However, in activities of daily living upper extremity muscles are importantly involved. Although arm exercise is often intermittent and relieved by rest periods, patients with COPD frequently report limitations in these activities (401). These can be attributed to various factors. Firstly, muscles involved in upper extremity exercise are also necessary for breathing and arm exercise is associated with dyssynchronous breathing in patients with COPD (402). Secondly, body positions that involve bracing of the arms enable the patient to obtain higher levels of ventilation (403), presumably because arm bracing limits upper extremity activities. Thirdly, for equal work rates, ventilation and oxygen consumption are generally higher for arm than for leg exercise (404,405). This is probably due to an earlier onset of anaerobic metabolism for the arms than for the legs. Moreover, static muscle work to stabilize the trunk and shoulder during upper extremity exercise contributes to a lower mechanical efficiency of arm exercise. Lastly, there are differences in the extent of muscle weakness in upper and lower extremities in COPD. Quadriceps strength has been shown to be more reduced than handgrip strength (212), suggesting that this would impair activities of lower extremities more than upper extremity activities. However, recent studies of upper extremity strength have shown that weakness of the proximal arm muscles is more prominent than in muscles of the forearm (214,406).

Reduced exercise capacity and muscle weakness render patients with COPD disabled and are associated with high utilization of health care resources (407, 408). Poor exercise capacity and peripheral muscle weakness have also been shown to contribute to mortality (409,410). Moreover, patients with COPD and respiratory muscle myopathy and weakness have a higher mortality rate than do control patients with COPD (375).

III. Effects of Interventions on Skeletal Muscle Dysfunction in COPD

A. EXERCISE TRAINING

1. Effects of Training on Peripheral Muscle Function in Normal Subjects

The peripheral skeletal muscle exhibits great plasticity by adapting its morphologic and metabolic properties differently depending on the training strategy used. When submitted to endurance training, it undergoes several changes that improve its capacity for aerobic metabolism. The notion that the proportion of type I and II fibers is not influenced by training has been challenged by studies showing an increase in type I fibers with a reciprocal decrease in type IIb after 6 to 15 wk of intense training (411,412). Evaluation of the contractile protein composition of the skeletal muscle provides further evidence supporting that a fast to slow type fiber conversion may occur with endurance training (413). Subpopulations of type II fibers are also modified with endurance training, as evidenced by the transformation of type IIb muscle fiber into type IIa (171, 414–416). The volume of type I fibers and the mitochondrial number are expanded and the activities of mitochondrial enzymes such as citrate synthase (CS) and 3-hydroxyacyl-CoA-dehydrogenase (HADH) are enhanced (171, 414, 415, 417). Improved muscle capillarization and increased myoglobin levels also occur, which facilitate oxygen delivery and extraction (418,419).

These changes are accompanied by smaller increases in muscle and blood lactic acid concentrations for a given level of heavy exercise (171, 414, 420–422), which may, in part, reflect an improved oxidative capacity of the trained muscles (171, 211, 423, 424). This contention is consistent with the correlation described between the work rate at which arterial lactic acid increases during exercise and the level of aerobic enzyme activities in normal subjects (171,423) in patients with COPD (211), and in those with chronic heart failure (424).

The skeletal muscle adaptation induced by resistive training is characterized by increases in muscle mass and strength (171, 415). A decrease in type IIb fibers and an increase in type IIa fibers occur with this type of training, but hypertrophy of both fiber types has been reported (415, 425, 426). The aerobic capacity of the skeletal muscle is not substantially modified by resistive training (171).

The structural and biochemical changes in the muscle will occur, provided that the training stimulus in terms of fre-

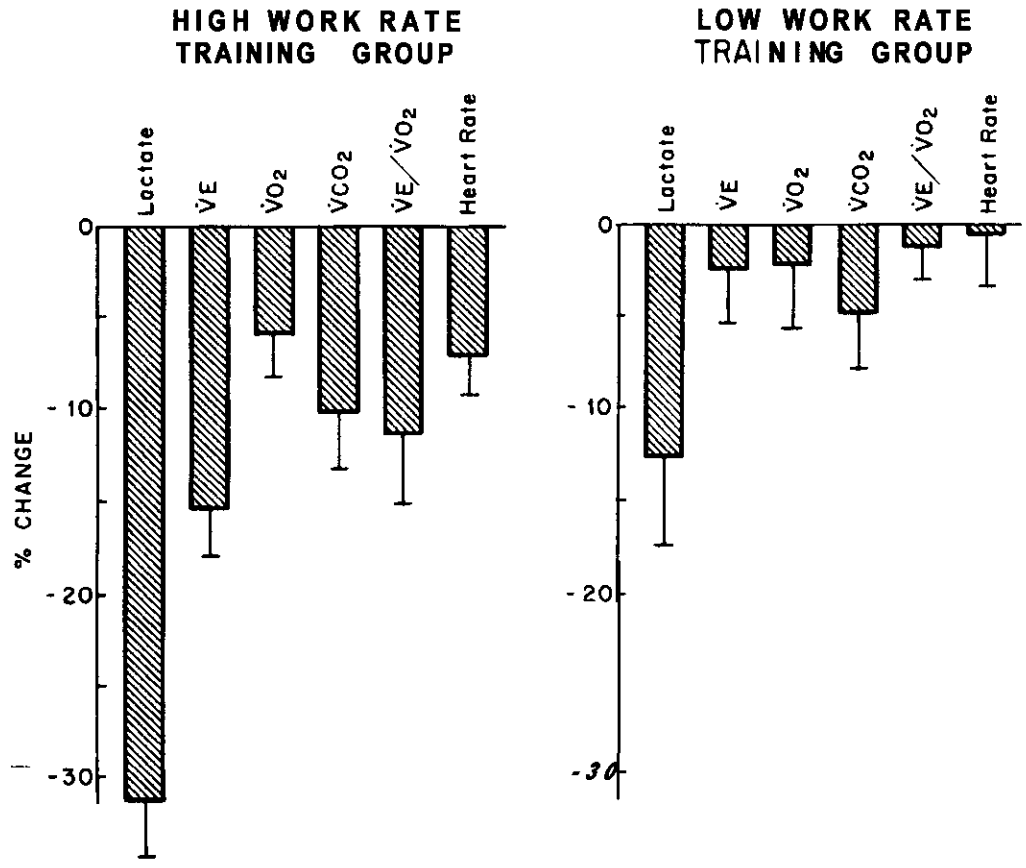

figure 4. Changes in physiologic responses to an identical exercise task (in a constant work rate test) produced by two exercise training strategies in patients with COPD. (Left *panel*) High work rate training group (n = 11). (Right panel) Low work rate training group (n = 8). Note that patients performed the same total work in their training program irrespective of group assignment because the lower work rate training group was assigned longer daily sessions. Percent change is calculated from the average change in response at the time the pretraining study ended. *Vertical lines* represent 1 SEM. Decreases in blood lactate, ventilation, O_2 uptake, CO_2 output, ventilatory equivalent for O_2, and heart rate are observed for both training regimens, but decreases are appreciably greater for the high work rate training group. (Reprinted from Reference 243, with permission.)

quency, intensity, and duration is adequate. A program lasting 5 to 10 wk, with exercise sessions held three to five times per week, each lasting 30 to 45 min is considered to be satisfactory (427). For endurance training of healthy subjects, an intensity lying between 50 and 60% of the maximal exercise capacity is generally recommended, although significant improvement in physical fitness may be obtained with lower exercise intensity if the duration of training is prolonged (428,429). This demonstrates that the intensity and duration of training are interrelated with the combination of these two factors, the total amount of work performed above the "minimum intensity" being important in determining the effectiveness of an exercise program (428).

2. Exercise Training In COPD

Exercise training is now recognized as an essential component of pulmonary rehabilitation in patients with COPD (6, 8, 239, 243, 430–433). Proposed mechanisms of improvement include better motivation, desensitization to dyspnea, and improved technique and performance (434). Until recently, it was thought that these patients could not achieve a sufficiently high level of training to induce skeletal muscle changes similar to those found in normal subjects after a training program (398, 435). Recent studies have shown that this concept is incorrect and strongly support the view that peripheral muscle function can be improved with a variety of training strategies in patients with COPD (205, 226, 243, 394, 397, 436, 437).

a. ***Lower Limb Endurance Training.*** The training strategies most commonly used in patients with COPD are walking, treadmill, or cycling exercise; a typical program includes three to five weekly exercise sessions for 6 to 12 wk (8, 239, 243, 394, 397, 430–433). It has been recently demonstrated that patients with COPD can sustain the necessary training intensity and duration for a physiologic adaptation to training to occur (226, 243,437). Indirect evidence supporting the development of a skeletal muscle adaptation to lower limb endurance training in COPD include a reduction in exercise lactic acidosis and CO_2 production (243, 438, 439) (Figure 4), faster O_2 kinetics (437), and an improved quadriceps endurance (436). A recent study indicates that a 12-wk leg-cycling exercise program increases the activity of two mitochondrial enzymes in patients with severe COPD, a sure sign of skeletal muscle adaptation (226) (Figure 5). These results contradict those obtained by Belman and Kendregan (435) who failed to show any increase in mitochondrial enzyme activities after 6 wk of exercise training in patients with COPD. The lack of improvement in their study can probably be explained by a lower intensity of training (440).

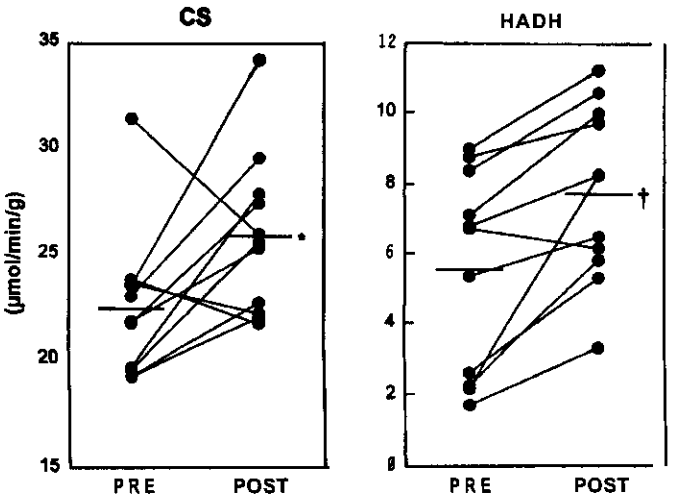

Figure 5. Pretraining and post-training values for the activity of citrate synthase (CS) and 3-hydroxyacyl CoA dehydrogenase (HADH) obtained in 11 patients with COPD. Horizontal bars represent group mean values. The activities of both enzymes increased significantly after training. *$p < 0.05$; †$p < 0.01$. (Reprinted from Reference 226, with permission.)

There is as yet no consensus on the optimal training intensity prescription for patients with COPD (441). As in normal subjects, the effectiveness of the exercise program is probably related to the total amount of training performed (the product of training intensity and duration). However, higher intensity training seems to be of advantage. This contention is supported by a study of Casaburi and colleagues (243) which showed that the magnitude of the physiologic improvement after exercise training was significantly greater in patients training at high intensity training (~ 80% maximum exercise capacity) as opposed to low intensity (~ 40% maximum exercise capacity) despite the fact that both groups performed the same total work (Figure 4) (243). The individual tolerance should be taken into account when prescribing the intensity of training, but most patients with moderate to severe COPD can safely tolerate training intensity ranging from 60 to 80% of their pretraining exercise capacity. At this training intensity, physiologic improvement is likely to occur (226, 239, 243, 437).

b. ***Lower Limb Strength Training.*** The effects of strength training in patients with COPD have been systematically evaluated in only one study (394). Simpson and colleagues (394) studied 34 patients with severe COPD randomized to a control group or to 8 wk of strength training consisting of three different muscle exercises (one for the arms, two for the legs). With this training strategy, muscle strength increased by 16 to 40% depending on the muscle group evaluated, and thig'was associated with an improvement in the endurance time to whole-body submaximal exercise. Changes in muscle mass were not evaluated. Clark and colleagues (397) found that a program consisting of a variety of low intensity peripheral muscle exercises improved the endurance to isolated muscle endurance exercises. It should be recognized, however, that the improvement in effort-dependent measures of muscle strength and endurance may not be definitive evidence of a muscle physiologic adaptation and may simply reflect a better motivation and/or a more efficient neuromuscular activation (415).

*c. **Upper Extremity Training.*** Because the utilization of upper limb muscle often induces severe dyspnea, specific arm endurance training has been used in patients with COPD (402, 442, 443). In these patients, shoulder girdle muscles such as pectoralis major and latissimus dorsi may serve as accessory respiratory muscles (218, 219). When involved in upper arm activities, their participation in ventilation decreases and, consequently, more work has to be performed by the diaphragm (444). Studies of arm training, using arm cranking or unsupported arm exercises, have shown beneficial effects on arm-specific endurance exercises and decreased metabolic and ventilatory requirements for arm activities (435, 445). Although one study has failed to show improvement in triceps oxidative capacity in patients with COPD undergoing 6 wk of upper arm training (435), the absence of a muscle adaptation may have been due to a low training intensity. Although it has yet to be conclusively demonstrated that this strategy improves arm muscle function or the functional status of the patients, it is generally recommended that arm training be incorporated in rehabilitative programs for patients with COPD (8,446).

3. Implications of Improved Skeletal Muscle Function in COPD

In normal subjects, improvement in peripheral muscle function is believed to play an important role in explaining the increases in exercise tolerance and in the ability to tolerate submaximal exercise that occur in response to exercise training (414). Several observations suggest that this may also be true in patients with COPD. The reduction in lactic acidosis for a given exercise work rate that accompanies exercise training decreases the carbon dioxide output (243). The resulting fall in ventilatory requirement may be of great benefit for these ventilatory-limited patients by allowing them to tolerate a given exercise level for a longer period (243, 447). The decrease in muscle acidosis may also be beneficial by delaying the onset of muscle fatigue (167, 448, 449). Also, improved muscle strength may decrease the intensity of perceived muscle effort (213). Patients are likely to tolerate exercise longer if they feel less discomfort coming from the exercising muscles.

In summary, substantial evidence indicates that peripheral muscle function can be improved following a rigorous exercise program in patients with COPD. Further work is needed to define the optimal training strategy in these patients and to determine to what extent the training-induced skeletal muscle changes contribute to enhanced exercise tolerance.

B. OXYGEN THERAPY

Several studies have shown that exercise performance is enhanced when hypoxemic patients with COPD breathe an increased fraction of inspired O_2 (450–455). The mechanisms whereby O_2 supplementation improves exercise performance are incompletely understood, but they may include reduced ventilatory requirement (455, 456), relief of pulmonary vasoconstriction (457), and improved systemic O_2 delivery (457-459). Because limb muscle oxidative capacity is depressed in some patients with COPD (203, 210) and may be due to impaired tissue oxygenation (203), supplemental O_2 might also improve exercise performance by increasing limb muscle O_2 utilization. Long-term O_2 therapy (LTOT) may permit muscle adaptations to occur that further improve limb muscle O_2 utilization.

1. Acute O_2 Supplementation

The acute administration of supplemental O_2 to hypoxemic patients with COPD during exercise has been shown to enhance limb muscle oxidative capacity (253, 254). Payen and colleagues (253) used phosphorus magnetic resonance spectroscopy (^{31}P-MRS) during exercise in seven hypoxemic patients with COPD and found reduced indices of muscular oxidative metabolism during exercise, including an early fall in muscle intracellular pH (pHi), increase in Pi/PCr ratio, and reduction in the resynthesis of PCr after exercise compared with age-matched control subjects. These indices improved, although incompletely, when supplemental O_2 was administered during exercise. Using similar methods, Mannix and colleagues (254) calculated the relative contributions of anaerobic sources and oxidative phosphorylation to exercising skeletal muscle ATP production in COPD. They concluded that ATP production from oxidative phosphorylation is decreased in COPD, but that it can be reversed by supplemental O_2. Although neither systemic nor regional O_2 delivery was measured, these two studies suggest that reduced oxidative phosphorylation in exercising patients with severe COPD is due, at least in part, to a deficiency in O_2 availability.

In hypoxemic patients with COPD, supplemental O_2 acutely can increase muscle O_2 availability by augmenting systemic O_2 delivery via increases in both arterial oxygen content (Ca_{O_2}) and cardiac output (457–459). Reduced ventilatory muscle energy requirements may also increase regional O_2 delivery to limb muscles (240). In recent years, the idea that cellular respiration is O_2-dependent has come into question, however. For example, Connett and colleagues (460) found the P_O, in contracting lactate-producing dog gracilis muscle to be higher than the value when respiration in isolated mitochondria becomes impaired (461). It has been argued, however, that the P_O, where maximal respiration is affected could be higher in exercising muscle tissue than in isolated mitochondria (462). Indeed, O_2 dependence of cellular metabolism has been observed in cultured cells (463) as well as in animals (464). Additionally, a linear relationship has been found between skeletal muscle bioenergetic state, as reflected by the ratio of phosphocreatine to inorganic phosphate (PCr/Pi), and O_2 delivery in an isolated rat hindlimb preparation (465).

2. Long-term O_2 Therapy

As with the acute administration of supplemental O_2, LTOT has been associated with indices of improved muscle oxidative capacity (269, 466). For instance, Gertz and colleagues (269) showed that peripheral muscles in hypoxemic patients with COPD were deficient in PCr and ATP, and that these changes were reversed with LTOT. Jakobsson and Jorfeldt (466) noted similar improvements in bioenergetic state of quadriceps muscles after 8 mo of LTOT, whereas control patients with COPD suffered a further decline during this period. However, this same group (210) found no significant changes in muscle oxidative enzyme activity after 7 mo of LTOT in hypoxemic patients with severe COPD. These findings suggest that the intrinsic abnormalities of muscle bioenergetic state in hypoxemic patients with COPD can be, in part, improved by increasing muscle O_2 availability through the use of LTOT.

LTOT may improve muscle O_2 availability more than does acute O_2 supplementation through the physiologic adaptations associated with increased physical activity that are facilitated by oxygen supplementation. These include increases in both systemic O_2 delivery, mediated by an elevated stroke volume relative to work rate (467) and regional O_2 delivery, through development of a more extensive skeletal muscle microcirculatory network (171) during exercise. Furthermore, the adverse consequences of physical detraining on muscle oxidative enzyme activity (468–470) and fiber-type distribution (471) may be reversed with LTOT. However, a randomized controlled study involving 24 patients with severe COPD who developed hypoxemia during exercise failed to demonstrate significantly improved exercise performance after training with supplemental O_2 compared with training on room air (472). Finally, supplemental O_2 may improve appetite, meal-related symptoms, meal O_2 desaturation, and neuropsychiatric function. All of these factors have been implicated in the progressive muscle wasting seen in COPD (473), which might be reversed with LTOT. Studies have failed to demonstrate significant changes in body weight in patients receiving LTOT, however (3,474). Whether or not LTOT enhances overall exercise capacity more than acute O_2 administration in hypoxemic patients with COPD, via these or other mechanisms, remains to be determined.

Contrary to the notion that limb muscle aerobic function is diminished by reduced O_2 delivery are the results of studies involving patients with peripheral artery disease in which increases in oxidative enzyme activity have been reported by some investigators (260, 261). Similar results have been described in healthy subjects training under ischemic conditions (475). Therefore, reduced O_2 availability to exercising limb mus-

cles through hypoxemia or through underperfusion may have different influences on limb muscle aerobic function.

3. Unanswered Questions

Therefore, both acute and long-term O_2 supplementation have been demonstrated to favorably affect limb muscle function in hypoxemic patients with COPD; these effects may account for some of the improvement in exercise performance accompanying O_2 supplementation. Several important issues remain unresolved, including: (I) the importance of increased muscle O_2 availability, permitted with supplemental O_2, in improving overall exercise performance in hypoxemic patients with COPD; (2) whether or not the immediate beneficial effects of O_2 supplementation are complemented with additional benefits afforded by LTOT; (3) the contribution, if any, of improvements in nutrition and training that may be permitted with LTOT; and (4) whether or not physical training under carefully controlled hypoxic or ischemic conditions may ultimately improve limb muscle oxidative capacity.

C. NUTRITIONAL SUPPLEMENTATION

1. Rationale

Therapeutic management of weight loss and muscle wasting in patients with COPD has attracted interest only recently. Previously it was generally considered as a terminal progression of the disease process and therefore inevitable and irreversible. Several studies, however,. have shown that weight loss and a low body mass index are associated with increased mortality independent of disease severity (476,477). The rationale for nutritional therapy is based on studies reporting that muscle wasting is a significant independent correlate of muscle weakness (199), peak exercise capacity (396), and quality of life (478) in patients with COPD. In order to evaluate the effectiveness of nutritional support in COPD, it is important to review prospective randomized controlled intervention studies, taking into consideration the setting of the study, markers of nutritional status, and the duration of nutritional therapy and follow-up.

2. Nutritional Support of In-patients

The first clinical trials in patients with COPD consisted of short-term in-patient nutritional intervention. Two studies reported an increase in body weight and muscle function after 2 to 3 wk of enteral and parenteral nutritional support (479, 480). In one study (480) it was shown that the increase in body weight, nitrogen balance, and peripheral skeletal muscle function after 2 wk of parenteral nutrition was similar in depleted patients with and without lung disease. Subsequently, an in-patient study of patients with COPD (481) investigated the effects of oral liquid supplements over a 3 mo period and found significant weight gain associated with an increase in measures of muscle strength as well as in 6-min walking distance.

3. Nutritional Support of Out-patients

Since 1986, several nutritional intervention studies in stable out-patients with COPD have been published (482,483). Comparison between these studies is limited because of the variety of study designs, characteristics of the study populations, nutritional markers, duration of follow-up, and small patient numbers. In only one of them was a substantial weight gain (4.2 kg after 3 mo of oral support) achieved, whereas average weight gain in other studies was less than 1.5 kg in 8 wk. In general, improvements in muscle strength were demonstrated only when clear weight gain was obtained. The reported poor treatment response in the out-patient setting may be attributed partly to inadequate assessment of energy requirements (484) and to the observation that patients were taking supplements instead of their meals. An important parameter of any nutritional intervention is the caloric supplementation that is achieved. Rochester (485) has posited that the repletion regimen must supply 50% more calories than actual resting energy expenditure to provide meaningful improvements. In order to be able to provide a sufficient caloric supply, the effect of an aggressive nutritional support regimen in patients with severe COPD and weight loss not responding to oral supplementation was studied (486). During an interval of 4 mo, nocturnal enteral nutrition support via percutaneous endoscopic gastrostomy tube was provided to maintain a total daily caloric intake greater than two times resting energy expenditure. In a preliminary report (486), it was shown that, despite the magnitude of the intervention, a mean weight gain of only 3.3 kg (6% of body weight at baseline) was seen in the treated group. The majority of the increase in body weight was fat mass, and no significant improvement in physiologic function was observed. The limited therapeutic impact of isolated aggressive nutrition may be related to the absence of a comprehensive rehabilitative strategy or to the fact that the studied patients were not only in a hypermetabolic state but were also suffering from increased protein breakdown (487).

4. Nutrition and Rehabilitation

In a large clinical trial the effects of a daily nutritional supplement as an integrated part of an 8-wk pulmonary rehabilitation program were studied (488). Significant weight gain was shown (0.4 kg/wk), despite a daily supplementation which was less than in some of the previous out-patients studies. The combined treatment of nutrition and exercise not only increased body weight but also resulted in a significant improvement of fat-free mass and respiratory muscle strength, although the increase in fat-free mass was observed predominantly in the first 4 wk of treatment. Exercise in this study consisted of moderate intensity general physical training with particular attention to exercise in relation to daily activities. Also in the above-cited study (488) a substantial proportion of patients did not respond to the therapy, i.e., did not reach weight gain or showed no improvement in respiratory muscle function. In a post-hoc survival analysis of this trial, the clinical relevance of treatment response in terms of weight gain and functional improvement was clearly indicated because weight gain (> 2 kg in 8 wk) in depleted and nondepleted patients and increase in maximal inspiratory pressure (Prmax) adjusted for baseline Prmax during rehabilitation were related to improved overall survival (489) (Figure 6). Furthermore, on Cox regression analysis, after adjustment for the influence of sex, age, smoking, and baseline spirometry, arterial blood gases, and body mass index, both weight gain and body mass index remained significant predictors of survival.

Theoretically, noncompliance to the treatment could have contributed to nonresponse. However, patients were enrolled in a pulmonary rehabilitation program allowing good control. Another possible explanation for the lack of response to nutritional supplementation could be the presence of alterations in intermediary metabolism superposed on the elevated energy metabolism. In a recent study, Schols and colleagues (490) showed that some of the hypermetabolic patientsdisplayed elevated levels of acute-phase proteins and soluble TNF receptors in peripheral blood. These patients were also characterized by depletion of fat-free mass, independent of the body mass index. Di Francia and coworkers (244) recently reported a significant relation between weight loss and TNF-α. From the combined results of these studies, it is hypothesized that tissue

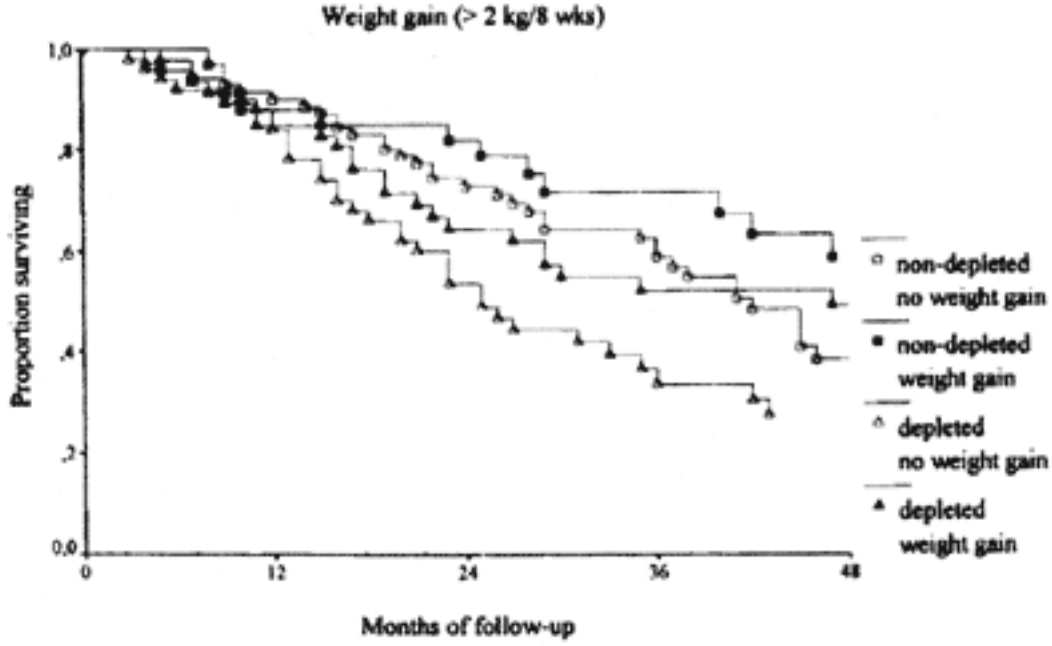

Figure 6. Weight gain after an intervention predicts an improved survival in patients with COPD. Patients with COPD ($n = 203$, average $FEV_1 = 34\%$ predicted) undergoing an 8-wk pulmonary rehabilitation program were randomized to receive nutritional supplementation, anabolic steroid administration, or neither intervention. In a post-hoc survival analysis, patients were divided into four groups: (*1*) low initial body weight and little weight gain (< 2 kg) (*open triangles*), (*2*) low initial body weight and greater weight gain (> 2 kg) (*closed triangles*), (*3*) higher initial body weight and little weight gain (*open squares*), and (*4*) higher initial body weight and greater weight gain (*closed squares*). Both higher initial body weight and weight gain during the 8-wk intervention predict better survival. (Reprinted from Reference 489, with permission.)

depletion in patients may be related in part to a systemic catabolic response induced by inflammation, which cannot be reversed by caloric support only. Further studies are indicated to confirm this hypothesis and to identify further baseline characteristics of nonresponders.

5. Mechanisms of Improved Peripheral Muscle Function after Nutritional Therapy

As indicated above, most nutritional supplementation studies in COPD investigated clinically stable patients and primary outcome measures of intervention were body weight, body composition, muscle function, and exercise tolerance. No studies have yet investigated the mutual relationship between changes in body composition and function in depleted patients with COPD after nutritional supplementation. Studies in other chronic wasting conditions indicate that peripheral skeletal muscle function is modulated partly by nutritionally induced changes in muscle mass but also, even prior to evidence of increased muscle mass (491), by cellular alterations such as an increase in total body potassium despite insignificant changes in total body nitrogen (310) and alterations in cellular energy metabolism (491). However, further work is needed to investigate the modulating effects of caloric support alone as well as of bioactive nutrients on muscle energy and intermediary metabolism.

6. Recommendations

- Nutritional supplementation should be considered for patients with COPD suffering from involuntary weight loss and for all depleted patients.
- When the primary problem is a negative energy balance, which can be due to either a decreased dietary intake or elevated energy requirements, it is appropriate to institute oral or enteral caloric and protein support to achieve a positive energy balance and stimulate protein synthesis in combination with exercise as anabolic stimulus to enhance gain in fat-free mass.
- The effectiveness of other anabolic stimuli such as growth hormone and anabolic steroids is yet under debate, as discussed in the next section. However in depleted patients these treatments are likely to require superimposed nutritional support to be effective.

D. ANABOLIC HORMONE SUPPLEMENTATION

Normal muscle growth and development is dependent on an appropriate hormonal milieu. Inadequate anabolic hormonal stimulation results in muscle wasting. It is an attractive, though unproven, hypothesis that an appreciable portion of skeletal muscle dysfunction in COPD results from hormonal abnormalities. The possibility that supplementation of the anabolic hormones can reverse muscle abnormalities is just starting to be evaluated.

Two major hormone systems that act on the muscles have been described well, and other hormonal influences are starting to be recognized.

1. The Growth Hormone System

Growth hormone (GH) is secreted by the pituitary. Although it has some effects of its own on the muscles, the major effect

is on the liver and other tissues, which then produce insulin-like growth factors (IGF), polypeptides with a molecular structure similar to insulin (492). The major IGF in terms of its action on the muscles is IGF-1 (493). IGF-1 is also produced within the muscle cell; intracellular production may well exceed the importance of circulating IGF-1 (494).

Growth hormone administration has been found to be effective in allowing GH-deficient children to achieve normal stature (495). In GH deficient adults,, subcutaneous GH administration three to five times per week increases muscle mass (496–501) decreases limb fat (499, 501), and improves muscle strength (496, 500) and exercise endurance (498, 500, 502). In healthy young subjects, GH administration increases IGF-1 levels, stimulates muscle protein synthesis (87), and increases lean body weight (503). However, GH supplementation has not been found to increase strength in healthy young subjects (504).

Recent studies have focused on the response of elderly subjects to GH administration. Increases in IGF-l(505 to 509) and muscle mass (506,508 to 510) have been found, but improvements in muscle strength (508, 509) or endurance (509) have not been reported.

Other reports concern effects of growth hormone administration to patients with muscle wasting related to chronic disease. In patients with HIV-associated wasting, GH supplementation resulted in increases in body weight and lean body mass (511,512); a modest increase in exercise tolerance was demonstrated in one study (511). In severely ill patients with COPD, short-term GH administration yielded a positive nitrogen balance, but no apparent changes in muscle strength (513, 514), though in an uncontrolled study Pape and colleagues (515) found that respiratory muscle strength was increased. In a randomized trial, Burdet and colleagues (516) administered growth hormone or placebo for 3 wk to underweight patients with severe COPD who were undergoing a rehabilitation program. Lean body mass increased only in the growth hormone group (by 6%), but exercise tolerance increased in neither group. In another recent randomized trial, Casaburi and colleagues (201) administered growth hormone or placebo for 6 wk to patients with severe COPD who were undergoing a rigorous training program. Lean body mass increased by 6% in the growth hormone group but not in the placebo group. Endurance exercise tolerance increased equally in the two groups; growth hormone did not enhance the exercise tolerance gains associated with endurance training.

There has been a debate regarding the cost-effectiveness of growth hormone supplementation (517-519). On the basis of the studies published so far, it may be tentatively concluded that, except in specific deficiency states, administration of growth hormone is hard to justify in view of the high cost of therapy.

2. The Anabolic Steroids

In men, testosterone has a profound anabolic effect on muscle. Testosterone production by the gonads is stimulated by the pituitary hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). There is a negative feedback loop such that low circulating testosterone levels induce the pituitary to secrete more LH and FSH. In women, a similar system exists, though the principal gonadal hormone is estradiol. In women, estradiol has anabolic effects on muscles, as does testosterone (520), though circulating testosterone levels are an order of magnitude lower in women than in men. However, there have been few scientific studies of sex steroid supplementation in women.

In hypogonadal men, replacement doses of testosterone substantially increase muscle mass and strength (521, 522). However, until recently it was not clear whether testosterone supplementation had anabolic effects in healthy eugonadal men (523, 524). It was argued that the dozen or so studies reporting anabolic effects of testosterone and other anabolic steroids (mainly performed in the 1970s) were flawed because of poor experimental controls and effort-dependent outcome measures (523). However, it has recently been shown in a randomized, double-blinded placebo-controlled trial that supraphysiologic doses of testosterone increase muscle size and strength substantially (525). Moreover, the benefits of a strength training program were additive to those of testosterone supplementation.

Evidence is accumulating that older men whose testosterone levels are mildly low respond to testosterone replacement with increased body mass and strength (95, 526). There is an active controversy regarding the place of anabolic steroids in the treatment of the frail elderly (517,527). One aspect relates to a risk-benefit assessment. The predominant worry is that testosterone replacement therapy will unmask subclinical prostate cancer in older men. Other concerns relate to increased HDL levels, increased hematocrit, liver toxicity, and aggressive behavior (528). However, several recent trials of relatively short-term testosterone administration to older men have failed to reveal adverse side effects (95,526). A reevaluation of the health risks of anabolic steroids is in progress (528).

Limited information is available concerning the effects of anabolic steroid supplementation in COPD. Schols and colleagues (488) administered a relatively low dose of nandrolone or placebo to 217 men and women with COPD who were also randomized to receive nutritional supplementation. Small improvements in lean body mass and respiratory muscle strength were demonstrated in the nandrolone, but not the placebo, group and no adverse side effects were reported. In another study, 6 mo of oral stanozolol produced a mean 1.8-kg increase in body weight in 10 underweight patients with COPD, but significant improvements in endurance exercise capacity were not demonstrated (529).

Several questions remain to be answered before anabolic steroids can be prescribed to combat the muscle dysfunction seen in patients with COPD. We must (*1*) define the dosage that appropriately balances risks and benefits, (2) determine whether endurance as well as strength is improved, and (3) understand the interaction between exercise training and anabolic steroid administration.

3. Other Anabolic Drugs

In addition to their bronchodilator effects, β_2-adrenergic drugs have been investigated for their potential to induce muscle cell growth. In animal models, when chronically given, these drugs have been shown to promote muscle protein gain, increase fiber size, and improve muscle strength (530, 531). These anabolic effects are mediated through β_2-adrenoreceptor activation on the muscle cells (530). Among the β_2-agonists, those with longer duration of action seem to be more effective (530), and intravenous administration seems to induce a greater effect (532). Studies in humans have yielded mixed results. Salbutamol improved muscle performance in one (533), but not in another (534) study. Orally administered clenbuterol produced mild increases in leg extensor strength in orthopedic patients (535). In patients with COPD, high dose inhaled salbutamol did not alter anthropomorphic measurements or handgrip strength (536).

It seems quite likely that the next few years will see a flurry of reports from molecular biology laboratories of novel molecules that mediate anabolic effects on muscle. One such molecule is vascular endothelial growth factor, which apparently is

capable of inducing capillary growth in skeletal muscle (537). Another molecule has been dubbed myostatin; in rats its inhibition yields profound muscle hypertrophy (538). Two breeds of cattle said to be "double-muscled" (substantial increases in muscle mass) have been found to have defects in the chromosomes coding for the myostatin gene (539,540).

E. LUNG TRANSPLANTATION AND LUNG VOLUME REDUCTION SURGERY

1. Lung Transplantation

Lung transplantation has evolved into an accepted treatment of end-stage pulmonary parenchymal and pulmonary vascular disease. Four distinct lung transplant procedures are now performed routinely: heart-lung (HLTx) (541), single-lung SLTx (542), and bilateral sequential lung (BSLTx) (543) transplantation, and, far less commonly, living donor lobar transplants (544). In post-transplant patients, incremental cardiopulmonary exercise testing has shown a low peak work rate, low $\dot{V}o_2$peak (41 to 57% predicted) (4, 545–556) and an early lactate threshold (548, 549, 556) with leg tiredness being the predominant symptom at exercise termination (549). Exercise limitation appears to be independent of transplant type (4, 545-555) or pretransplant diagnosis (555), and it shows no substantial improvement with time after transplant (549, 555, 557). Although stable lung transplant recipients many months post-transplantation demonstrate a modest 14% improvement in $\dot{V}o_2$max with 6-wk supervised exercise training (558), there are no published studies demonstrating that as a group they ever approach predicted $\dot{V}o_2$max (348).

A number of potential mechanisms of exercise limitation are known. SLTx recipients may approach or reach ventilatory limitation at peak exercise, those with native lung emphysema frequently reaching expiratory flow limitation (559). Furthermore, SLTx recipients for pulmonary hypertension may have cardiac limitation because of poor right ventricular performance in the setting of elevated pulmonary vascular resistance (556). In HLTx, an impaired chronotropic response of the denervated heart or cardiac Plograft dysfunction may be factors, but stable cardiac transplant recipients appear to have a normal cardiac output in relationship to work rate (560). Importantly, BSLTx recipients generally have near normal lung function with mildly reduced diffusing capacity, but they terminate exercise well short of ventilatory or cardiac limitation (229). Mild anemia caused in part by the marrow suppression of azathioprine and renal toxicity secondary to cyclosporin is seen commonly (561) and may be a significant contributing factor to exercise limitation. The consistency of reduced exercise capacity across different lung transplant patients led early to the suggestion that a unifying factor, e.g., a skeletal muscle injury or deconditioning (549), may exist.

Abnormal skeletal muscle oxidative capacity, as evidenced by a greater resting intracellular acidosis with earlier fall in intracellular pH on exercise, has been demonstrated by ^{31}P magnetic resonance spectroscopy in the quadriceps muscle of stable lung transplant recipients (227). Although as yet only reported in preliminary form, an array of abnormalities have been demonstrated in the quadriceps femoris muscle of the lung transplant recipient. Oxidative enzyme activity and mitochondrial ATP production are reduced (562). It is not yet clear if this is predominantly due to a persistence post-transplant of the reduction in type I muscle fibers with increase in type II fiber proportion reported in patients with severe emphysema (203), or whether an acquired qualitative mitochondrial abnormality also coexists. Sarcoplasmic reticulum function of quadriceps femoris muscle may be reduced when account is taken of the marked switch in muscle fiber type proportions (563). An abnormally large rise in plasma potassium in relation to work rate is seen in heart and lung transplant recipients (564), but no clear abnormality of Na/K^+ ATPase pump density or activity has yet been demonstrated (565).

Considerable speculation exists as to whether the skeletal muscle abnormalities seen in the lung transplant recipient represent persistence of a pretransplant abnormality (e.g., deconditioning) or are due to transplantation itself (e.g., the effects of transplant surgery, sepsis, prolonged ICU stay, and the effects of corticosteroids, muscle relaxants, and cyclosporin A) or, as seems most likely, a combination of etiologies. Abnormalities of skeletal muscle oxidative metabolism previously demonstrated in patients with COPD (228) and in those with cystic fibrosis (566) may simply be due to deconditioning that persists post-transplant.

The lack of substantial improvement in exercise capacity even several years after lung transplantation (557) suggests that deconditioning alone is not the explanation, although the possibility exists that deconditioning is so severe that many years of intense rehabilitation may be required to reverse it. Improved cardiac function and reduced respiratory muscle work may improve perfusion to the exercising muscle (240). Beneficial effects on tissue oxygen delivery may be in part countered by anemia post-lung transplantation. Drugs effecting skeletal muscle (e.g., corticosteroids and/or cyclosporin A) are probably very important post-transplant factors. Both *in vivo* and *in vitro* studies in rats show that high doses of cyclosporin A impair exercise endurance and substantially reduce mitochondrial oxidative capacity (567,568). Severe pretransplant muscle deconditioning and the marked effect of cyclosporin A on skeletal muscle mitochondria post-transplantation would appear to be the most important factors.

2. Volume Reduction Surgery

Although surgery for bullous emphysema has been reported as early as the 1940s (569), recently an explosion of interest has occurred in techniques of lung volume reduction surgery (LVRS) for more diffuse forms of emphysema. Improvement in FEV_1, vital capacity, 6-min walk distance, $Pa_{,}$, Pa_{CO_2}, breathlessness (Borg scale) at equivalent work rate, quality of life (570,571) peak work rate, and peak $\dot{V}o_2$ have been reported after LVRS, but substantial exercise limitation persists (572).

The physiologic mechanisms by which these benefits are achieved have been investigated. One key benefit of LVRS is improved elastic recoil of the lungs (573) leading to reduced dynamic airway collapse and reduced resistive work of breathing. A reduction in dead space ventilation is also noted (572). Increased peak inspiratory pressures measured at the mouth, the nose, and across the diaphragm suggest improved mechanical performance of the diaphragm and intercostals (574), although a contribution of abdominal muscle function has been recently postulated (575). The resulting reduced work of breathing and increased maximal voluntary ventilation appear to be correlated with the improved exercise capacity (572). In addition, respiratory drive is reduced (576) and cardiac function (stroke volume) may improve at a given level of exercise after LVRS (572).

Improvements in peripheral skeletal muscle function may be very significant as LVRS allows: (I) a greater physiologic training effect, predominantly by delaying the point of ventilatory limitation; (2) improving systemic oxygen delivery; and (3) improved limb blood flow by reducing blood flow demands of the unloaded respiratory muscles (240). As yet, an improvement in lactate threshold has not been reported after LVRS. This may be due to exercise termination occurring at a

very low $\dot{V}o_2$peak despite LVRS, a $\dot{V}o_2$peak level that is still under the lactate threshold. Curiously, some patients show improvements in 6-min walk distance despite little change in FEV_1 (577). Although the cross-sectional area of thigh muscle is increased at 3 mo post LVRS (577), suggesting improvements in peripheral skeletal muscle, no evidence is presently published demonstrating improvement in fiber type or oxidative capacity of skeletal muscle after LVRS.

3. Implications

It was hoped that lung transplantation would demonstrate if and to what degree the peripheral skeletal muscle abnormalities could be reversed in patients with COPD. However, confounding factors, particularly medications, are likely to make these data difficult to interpret. Considerable debate exists as to how much the improvement in exercise capacity and quality of life relates to the mechanical improvements consequent to LVRS directly and how much is due to improvements in peripheral skeletal muscle function because of the extensive rehabilitation that typically occurs before LVRS and then in the postoperative rehabilitation period. Studies of peripheral skeletal muscle function should help clarify the contribution of pre- and post-LVRS rehabilitation and the degree to which the muscle injury can be reversed.

Suggestions for Future Research

Skeletal muscle dysfunction has only recently been recognized as a clinical feature in patients with COPD. An appreciable body of research has helped to define the mechanisms of the dysfunction, to investigate the consequences, to quantify the dysfunction, and to try to reverse this skeletal muscle dysfunction. However, more research is needed to further unravel the ***mechanisms*** of skeletal dysfunction and the ***consequences*** for exercise performance. We also need more insight in clinical tools to ***diagnose*** skeletal dysfunction and finally, of course, more research has to be devoted to ***treatment*** modalities to reverse or to prevent skeletal muscle dysfunction in COPD. Both clinical and basic research must be involved in answering these questions.

A. MECHANISMS OF SKELETAL MUSCLE DYSFUNCTION AND EXERCISE LIMITATION

Skeletal muscle dysfunction can be explained in two ways: reduction of force generating capacity or alterations in muscle energy metabolism. The reduction of the force generation in the muscle is due to loss of protein. Several potential causes have been identified such as disuse, corticosteroids, hypoxemia, hypercapnia, and malnutrition. Future research should focus on determining which pathways interfere with growth regulation in the muscle such as IGF-1 and IGF binding proteins, growth and differentiation factor 8 (GDF-8), and related TGF-β. Potential factors that interfere with growth regulation are cytokines, inactivity, oxidative stress, and drugs. These factors need to be studied in patients with COPD in more detail.

Altered energy metabolism is another important factor interfering with muscle function. Recent studies suggest that decreased blood flow to leg muscles of patients with COPD at submaximal work rate (as compared with healthy subjects) is not a factor limiting O_2 transport. Future research must be focused on the nature of the intrinsic muscle dysfunction. This can be examined by comparison between control subjects and patients with COPD during exercise with constant O_2 delivery conditions. An effective strategy would be to match patients and healthy subjects for age, anthropometric measures, and level of activity while heart disease, peripheral vascular disease, and anemia should be excluded. Other potential limiting factors such as ventilation and diffusion in the lung should be avoided by exercising small muscle groups and adjusting inspiratory oxygen fraction. Another area requiring investigation is the identification of COPD-related factors leading to muscle dysfunction. Is deconditioning the dominant mechanism in most patients?

B. CLINICAL DIAGNOSTIC TOOLS

Noninvasive measurements of muscle mass (magnetic resonance imaging and CT scan) are available now and might become diagnostic tools for clinical evaluation in the coming years. The same holds true for dual energy X-ray absorptometry (DEXA). Bioelectrical impedance is easily applied in clinical practice, but not yet validated in patients with COPD. The additional information of these measurements of muscle mass should be compared with the clinical assessment of muscle strength or endurance to validate their usefulness.

Measurements of muscle energetics have become more assessable with ^{31}P magnetic resonance spectroscopy and muscle biopsy to determine muscle enzymes and fiber typing, but these tools are not available for routine clinical evaluation. The additional diagnostic value of these measurements should be substantiated. Exercise protocols for smaller muscle groups that measure muscle endurance, $\dot{V}o_2$ kinetics, or lactate profile might also be helpful in identifying abnormalities in peripheral skeletal muscle function in clinical evaluation.

As most patients with more advanced COPD experience difficulty in upper extremity activities, assessment of these muscle groups needs further attention.

C. TREATMENT MODALITIES

Peripheral skeletal muscle dysfunction in COPD has been shown to be reversible to some extent by exercise training. However, further optimization of exercise intensity and exercise modalities (endurance training, interval training, localized skeletal muscle training, upper arm training) is needed. In contrast to general exercise training (walking, running, or cycling), strength training or endurance training of small muscle groups may provide high intensity stress without compromising oxygen availability or ventilatory capacity. This may allow patients with more advanced disease to exercise their muscles at high intensities. As yet no studies are available to substantiate this.

The effectiveness of other treatment modalities such as oxygen therapy, anabolic agents, and nutrition should be studied per se or in combination with exercise training. Oxygen therapy can be considered to improve oxygen availability, allowing an increased exercise intensity. In contrast, it is conceivable that carefully controlled hypoxemic conditions might also enhance training effects. The optimal substrate mix and quantity of nutritional interventions is another area for future studies. The use of anabolic steroids should be assessed for their risks and their effects on endurance and strength, as well for their interaction with exercise training.

In addition to outcome measures already discussed, we need a better understanding of the mechanisms by which these interventions improve skeletal muscle function. The introduction of methodology of basic research such as the assessment of growth factors muscle enzymes, and fiber typing in muscle biopsies of skeletal muscles before and after these interventions may open up new possibilities for therapy of muscle dysfunction.

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References

1. American Thoracic Society. 1995. ATS Statement: standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 152:S77–S121.
2. Medical Research Council Working Party. 1981. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancer* i:681–686.
3. Nocturnal Oxygen Therapy Trial Group. 1980. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. *Ann. Intern. Med.* 93:391–398.
4. Levine, S. M., A. Anzueto, J. I. Peters, T. Cronin, E. Y. Sako, S. G. Jenkinson, and C. L. Bryan. 1994. Medium term functional results of single-lung transplantation for endstage obstructive lung disease. *Am. J. Respir. Crit. Care Med.* 150:398–402.
5. Gaissert, H. A., E. P. Trulock, J. D. Cooper, R. S. Sundaresan, and G. A. Patterson. 1996. Comparison of early functional results after volume reduction or lung transplantation for chronic obstructive pulmonary disease. *J. Thorac. Cardiovasc. Surg.* 111:296–307.
6. Casaburi, R. 1993. Exercise training in chronic obstructive lung disease. *In* R. Casaburi and T. L. Petty, editors. Principles and Practice of Pulmonary Rehabilitation. Saunders, Philadelphia. 204–224.
7. Casaburi, R., and T. L. Petty. 1993. Preface. *In* R. Casaburi and T. L. Petty, editors. Principles and Practice of Pulmonary Rehabilitation. Saunders, Philadelphia. xi-xii.
8. Ries, A. L., B. W. Carlin, V. Carrieri-Kohlman, R. Casaburi, B. R. Celli, C. F. Emery, J. E. Hodgkin, D. A. Mahler, B. Make, and J. Skolnick. 1997. Pulmonary rehabilitation: evidence based guidelines. *Chest* 1121363-1396.
9. Haas, F., J. Salazar-Schicchi, and K. Axen. 1993. Desensitization to dyspnea in chronic obstructive pulmonary disease. *In* R. Casaburi and T. L. Petty, editors. Principles and Practice of Pulmonary Rehabilitation. Saunders, Philadelphia. 241-251.
10. DeTroyer, A., and N. B. Pride. 1995. The chest wall and respiratory muscles in chronic obstructive pulmonary disease. *In* Ch. Roussos, editor. The Thorax, Part C: Disease, 2nd ed. Marcel Dekker, New York. 1975–2006.
11. Fiatarone, M. A., E. C. Marks, N. D. Ryan, C. N. Meredith, L. A. Lipsitz, and W. J. Evans. 1990. High-intensity strength training in nonagenarians. *J.A.M.A.* 263:3029–3034.
12. Sherrington, C. S. 1906. The Integrative Action of the Nervous System. Yale University Press, New Haven, CT.
13. Liddell, E. G. T., and C. S. Sherrington. 1925. Recruitment and some other factors of reflex inhibition. *Proc. R. Soc. Lond. B Biol. Sci.* 97:488–518.
14. Sherrington, C. S. 1929. *Some* functional problems attaching to convergence (Ferrier Lecture). *Proc. R. Soc. Lond. B Biol. Sci.* **105:332–**362.
15. Burke, R. E., D. N. Levine, and F. E. Zajac. 1971. Mammalian motor units: physiological-histochemical correlation in three types in cat gastrocnemius. *Science* 174:709–712.
16. Burke, R. E., D. N. Levine, P. Tsairis, and F. E. Zajac. 1973. Physiological types and histochemical profiles in motor units of the cat gastrocnemius. *J. Physiol. (Lond.)* 234:723–748.
17. Burke, R. E. 1981. Motor units: anatomy, physiology and functional organization. *In* L. D. Peachey, editor. Handbook of Physiology: The Nervous System. Motor Control. American Physiological Society, Bethesda, MD. 345422.
18. Enad, J. G., M. Fournier, and G. C. Sieck. 1989. Oxidative capacity and capillary density of diaphragm motor units. *J. Appl. Physiol. 67:620–*627.
19. Fournier, M., and G. C. Sieck. 1988. Mechanical properties of muscle units in the cat diaphragm. *J. Neurophysiol.* 59:1055–1066.
20. Hamm, T. M., P. M. Nemeth, L. Solanki, D. A. Gordon, R. M. Reinking, and D. G. Stuart. 1988. Association between biochemical and physiological properties in single motor units. *Muscle Nerve* 11:245–254.
21. Nemeth, P. M., D. Pette, and G. Vrbova. 1981. Comparison of enzyme activities among single muscle fibres within defined motor units. *J. Physiol. (Lond.)* 311:489–495.
22. Nemeth, P. M., L. Solanki, D. A. Gordon, T. M. Hamm, R. M. Reinking, and D. G. Stuart. 1986. Uniformity of metabolic enzymes within individual motor units. *J. Neurosci.* 6:892–898.
23. Sieck, G. C., and M. Fournier. 1989. Diaphragm motor unit recruitment during ventilatory and nonventilatory behaviors. *J. Appl. Physiol. 66: 2539-2545.*
24. Sieck, G. C., M. Fournier, Y. S. Prakash, and C. E. Blanco. 1996. Myosin phenotype and SDH enzyme variability among motor unit fibers. *J. Appl. Physiol.* 80:2179–2189.
25. Larsson, L., T. Ansved, I,. Edstrom, L. Gorza, and S. Schiaffino. 1991. Effects of age on physiological, immunohistochemical and biochemical properties of fast-twitch single motor units in the rat. *J. Physiol. (Lond.)* 443:257–275.
26. Larsson, L., L. Edstrom, B. Lindegren, L. Gorza, and S. Schiaffino. 1991. MHC composition and enzyme-histochemical and physiological properties of a novel fast-twitch motor unit type. *Am. J. Physiol.* 261:C93–C101.
27. Peter, J. B., R. J. Barnard, V. R. Edgerton, C. A. Gillespie, and K. E. Stempel. 1972. Metabolic profiles of three fiber types of skeletal muscle in guinea pigs and rabbits. *Biochemistry* 11:2627–2633.
28. Brooke, M. H., and K. K. Kaiser. 1970. Three "myosin adenosine triphosphatase" systems: the nature of their pH lability and sulfhydryl dependence. *J. Histochem. Cytochem.* 18:670–672.
29. Brooke, M. H., E. Williamson, and K. K. Kaiser. 1971. The behavior of four fiber types in developing and reinnervated muscle. *Arch. Neurol.* 25:360–366.
30. Ennion, S., J. Sant'Ana Pereira, A. J. Sargeant, A. Young, and G. Goldspink. 1995. Characterization of human skeletal muscle fibres according to the myosin heavy chains they express. *J. Muscle Res. Cell Motil.* 16:35–43.
31. Gorza, L. 1990. Identification of a novel type 2 fiber population in mammalian skeletal muscle by combined use of histochemical myosin ATPase and anti-myosin monoclonal antibodies. *J. Histochem. Cytochem.* 38:257–265.
32. Schiaffino, S., L. Gorza, S. Sartore, L. Saggin, S. Ausoni, M. Vianello, K. Gundersen, and T. Lomo. 1989. Three myosin heavy chain isoforms in type 2 skeletal muscle fibres. *J. Muscle Res. Cell Motil.* 10: 197-205.
33. Sieck, G. C., W. Z. Zhan, Y. S. Prakash, M. J. Daood, and J. F. Watchko. 1995. SDH and actomyosin ATPase activities of different fiber types in rat diaphragm muscle. *J. Appl. Physiol.* 79:1629–1639.
34. Termin, A., R. S. Staron, and D. Pette. 1989. Myosin heavy chain isoforms in histochemically defined fiber types of rat muscle. *Histochemistry* 92:453–457.
35. Green, H. J., H. Reichmann, and D. Pette. 1982. A comparison of two ATPase based schemes for histochemical muscle fibre typing in various mammals. *Histochemistry* 76:21–31.
36. Reichmann, H., and D. Pette. 1982. A comparative microphotometric study of succinate dehydrogenase activity levels in type I, IIA and IIB fibres of mammalian and human muscles. *Histochemistry* 74:27–41.
37. Nemeth, P. M., and D. Pette. 1980. The interrelationship of two systems of fiber classification in rat EDL muscle. *J. Histochem. Cytochem.* 28:193.
38. Henneman, E. 1957. Relation between size of neurons and their susceptibility to discharge. Science 126:1345–1346.
39. Henneman, E., and L. M. Mendell. 1981. Functional organization of motoneuron pool and its inputs. *In* J. M. Brookhart and V. B Mountcastle, editors. Handbook of Physiology, Section I: The Nervous System, Vol. III, Part 1. American Physiological Society, Bethesda, MD. 423-507.
40. Fleshman, J. W., J. B. Munson, G. W. Sypert, and W. A. Friedman. 1981. Rheobase, input resistance, and motor-unit type in medial gastrocnemius motoneurons in the cat. *J. Neurophysiol.* 46:1326–1338.
41. Zajac, F. E., and J. S. Faden, 1985. Relationship among recruitment order, axonal conduction velocity, and muscle-unit properties of type-identified motor unis in cat plantaris muscles. *J. Neurophysiol. 53:* 1303-1322.
42. Zengel, J. E., S. A. Reid, G. W. Sypert, and J. B. Munson. 1985. Membrane electrical properties and prediction of motor unit type of medial gastrocnemius motoneurons in the cat. *J. Neurophysiol.* 53:1323-1344.
43. Dick, T. E., F.-J. Kong, and A. J. Berger. 1987. Correlation of recruitment order with axonal conduction velocity for supraspinally driven diaphragmatic motor units. *J. Neurophysiol.* 57:245–259.
44. Jodkowski, J. S., F. Viana, T. E. Dick, and A. J. Berger. 1987. Electrical properties of phrenic motoneurons in the cat: correlation with inspiratory drive. *J. Neurophysiol.* 58:105–124.
45. Walmsley, B., J. A. Hodgson, and R. E. Burke. 1978. Forces produced by medial gastrocnemius and soleus muscles during locomotion in freely moving cats. *J. Neurophysiol.* 41:1203–1216.
46. Sieck, G. C., R. B. Trelease, and R. M. Harper. 1984. Sleep influences on diaphragmatic motor unit discharge. *Exp. Neurol.* 85:316–335.
47. Bodine, S. C., R. R. Roy, E. Eldred, and V. R. Edgerton. 1987. Maximal force as a function of anatomical features of motor units in the cat tibialis anterior. *J. Neurophysiol.* 57:1730–1745.

48. Chamberlain, S., and D. M. Lewis. 1989. Contractile characteristics and innervation ratio of rat soleus motor units. *J.* Physiol. *(Lond.)* 412:1–21.
49. Edstrom, L., and E. Kugelberg. 1968. Histochemical composition, distribution of fibres and fatiguability of single motor units: anterior tibial muscle of the rat. *J. Neurol. Neurosurg. Psychiatry* 31:424–433.
50. Fryer, M. W., and D. G. Stephenson. 1996. Total and sarcoplasmic reticulum calcium contents of skinned fibres from rat skeletal muscle. *J. Physiol. (Lond.)* 493:357–370.
51. Fryer, M. W., and I. R. Neering. 1989. Actions of caffeine on fast- and slow-twitch muscles of the rat. *J. Physiol. (Lond.)* 416:435–454.
52. Salviati, G., and P. Volpe. 1988. Ca^{2+} release from sarcoplasmic reticulum of skinned fast- and slow-twitch muscle fibers. *Am. J. Physiol.* 254:C459–C465.
53. Delbono, O., and G. Meissner. 1996. Sarcoplasmic reticulum Ca^{2+} release in rat slow- and fast-twitch muscles. *J. Membr. Biol.* 151:123–130.
54. Ferguson, D. G., and C. Franzini-Armstrong. 1988. The Ca^{2+}-ATPase content of slow and fast twitch fibers of guinea pig. Muscle Nerve 11:561–570.
55. Schiaffino, S., and C. Reggiani. 1996. Molecular diversity of myofibrillar proteins: Gene regulation and functional significance. *Physiol. Rev.* 76:371–423.
56. Laszewski-Williams, B., R. L. Ruff, and A. M. Gordon. 1989. Influence of fiber type and muscle source on Ca^{2+} sensitivity of rat fibers. *Am. J. Physiol.* 256:C420–C427.
57. Mounier, Y., X. Holy, and L. Stevens. 1989. Compared properties of the contractile system of skinned slow and fast rat muscle fibres. *Pflugers Arch.* 415:136–141.
58. Stephenson, D. G., and D. A. Williams. 1981. Calcium-activated force responses in fast- and slow-twitch skinned muscle fibres of the rat at different temperatures. *J. Physiol. (Lond.)* 317:281–302.
59. Stephenson, D. G., and Q. G. Forrest. 1980. Different isometric force • $[Ca^{2+}]$ relationships in slow and fast twitch skinned muscle fibres of the rat. *Biochim. Biophys. Acta* 589:358–362.
60. Sieck, G. C., Y. S. Han, Y. S. Prakash, and K. A. Jones. 1998. Cross-bridge cycling kinetics, actomyosin ATPase activity and myosin heavy chain isoforms in skeletal and smooth respiratory muscles. *Comp. Biochem. Physiol.* 119:435–450.
61. Sieck, G. C., and Y. S. Prakash. 1997. Cross bridge kinetics in respiratory muscles. *Eur. Respir. J.* 10:2147–2158.
62. Bottinelli, R., S. Schiaffino, and C. Reggiani. 1991. Force-velocity relations and myosin heavy chain isoform compositions of skinned fibres from rat skeletal muscle. *J. Physiol. (Lond.)* 437:655–672.
63. Eddinger, T. J., and R. L. Moss. 1987. Mechanical properties of skinned single fibers of identified types from rat diaphragm. *Am. J. Physiol.* 253:C210–C218.
64. Reiser, P. J., R. L. Moss, G. G. Giulian, and M. L. Greaser. 1985. Shortening velocity in single fibers from adult rabbit soleus muscles is correlated with myosin heavy chain composition. *J. Biol. Chem. 260:* 9077-9080.
65. Fitts, R. H., K. S. McDonald, and J. M. Schluter. 1991. The determinants of skeletal muscle force and power: their adaptability with changes in activity pattern. *J. Biomech.* 24:111–122.
66. Watchko, J. F., and G. C. Sieck. 1993. Respiratory muscle fatigue resistance relates to myosin phenotype and SDH activity during development. *J. Appl. Physiol.* 75:1341–1347.
67. Tavill, A. S. 1972. Progress report: the synthesis and degradation of liver produced proteins. *Gut* 13:225–241.
68. Giordano, M., and P. Castellino. 1997. Correlation between amino acid induced changes in energy expenditure and protein metabolism in humans. *Nutrition* 13:309–312.
69. Stein, T. P., and G. P. Buzby. 1981. Protein metabolism in surgical patients. *Surg. Clin. North Am.* 61:519–526.
70. Schlichtig, R., and S. M. Ayres. 1988. Protein metabolism: adaptations for starvation and stress. In R. Schlichtig and S. M. Ayres, editors. Nutritional Support of the Critically Ill. Year Book Medical Publishers, Inc., Chicago. 27-47.
71. Haas, A. L., and T. J. Siepmann. 1997. Pathways of ubiquitin conjugation. *FASEB J.* 11:1257–1268.
72. Mitch, W. E, and A. L. Goldberg. 1996. Mechanisms of muscle wasting. The role of the ubiquitin-proteasome pathway. *N Engl. J. Med. 335:* 1897–1905.
73. Medina, R., S. S. Wing, and A. L. Goldberg. 1995. Increase in levels of polyubiquitin and proteasome mRNA in skeletal muscle during starvation and denervation atrophy. *Biochem. J.* 307:631–637.
74. Mitch, W. E., R. Medina, S. Greber, R. C. May, B. K. England, S. R. Price, J. L. Bailey, and A. L. Goldberg. 1994. Metabolic acidosis stimulates muscle protein degradation by activating the adenosine triphosphate-dependent pathway involving ubiquitin and proteasomes. *J. Clin. Invest.* 93:2127–2133.
75. Wing, S. S., A. L Haas, and A. L. Goldberg. 1995. Increase in ubiquitin-protein conjugates concomitant with the increase in proteolysis in rat skeletal muscle during starvation and atrophy denervation. *Biochem. J. 3071639-U.*
76. Tiao, G., J. M. Fagan, N. Samuels, J. H. James, K. Hudson, M. Lieberman, J. E. Fisher, and P. 0. Hasselgren. 1994. Sepsis stimulates nonlyososomal, energy-dependent proteolysis and increases ubiquitin mRNA levels in rat skeletal muscle. *J. Clin. Invest.* 94:2255–2264.
77. Tiao, G., S. Hobler, J.-J. Wang, T. A. Meyer, F. A. Luchette, J. E. Fisher, and P.-O. Hasselgren. 1997. Sepsis is associated with increased mRNAs of the ubiquitin-proteasome proteolytic pathway in human skeletal muscle. *J. Clin. Invest.* 99:163–168.
78. Llovera, M., C. Garcia-Martinez, N. Agell, F. J. Lopez-Soriano, and J. M. Argiles. 1997. TNF can directly induce the expression of ubiqu&in-dependent proteolytic system in rat soleus muscles. *Biochem. Biophys. Res. Commun.* 230:238–241.
79. Price, S. R., J. L. Bailey, X. Wang, C. Jurkovitz, B. K. England, X. Ding, L. S. Phillips, and W. E. Mitch. 1996. Muscle wasting in insulinopenic rats results from activation of the ATP-dependent, ubiquitin-proteasome pathway by a mechanism including gene transcription. *J. Clin. Invest.* 98:1703–1708.
80. Temparis, S. M., M. Asensi, D. Taillandier, E. Aurousseau, D. Labaud, A. Obled, D. Béchet, M. Ferrara, J. M. Estrela, and D. Attaix. 1994. Increased ATP-ubiquitin-dependent proteolysis in skeletal muscles of tumor-bearing rats. Cancer *Res.* 54:5568–5573.
81. Auclair, D., D. R. Garrel, A. C. Zerouala, and L. H. Ferland. 1997. Activation of the ubiquitin pathway in rat skeletal muscle by catabolic doses of glucocorticoids. *Am. J. Physiol. Paris* 272:C1007–C1016.
82. Wing, S. S., and N. Bedard. 1996. Insulin-like growth factor I stimulates degradation of an mRNA transcript encoding the 14 kDa ubiquitin-conjugating enzyme. *Biochem. J.* 319:455–461.
83. Wing, S. S., and D. Banville. 1994. 14-kDa ubiquitin-conjugating enzyme: structure of the rat gene and regulation upon fasting and by insulin. *Am. J. Physiol.* 267:E39–E48.
84. Florini, J. R., D. Z. Ewton, and S. A. Coolican. 1996. Growth hormone and the insulin-like growth factor system in myogenesis. *Endocr. Rev.* 17:481–517.
85. Holly, J. M. P., and J. A. H. Wass. 1989. Insulin-like growth factors: autocrine, paracrine or endocrine? New perspectives of the somatomedin hypothesis in the light of recent developments. *J. Endocrinol.* 122611618.
86. Jones, J. I., and D. R. Clemmons. 1995. Insulin-like growth factors and their binding proteins: biologic actions. *Endocr. Rev.* 16:33–34.
87. Fryburg, D. A., R. A. Gelfand, and E. J. Barrett. 1991. Growth hormone acutely stimulates forearm muscle protein synthesis in normal humans. *Am. J. Physiol.* 260:E499–504.
88. Fryburg, D. A. 1994. Insulin-like growth factor I exerts growth hormone and insulin-like actions on human muscle protein metabolism. *Am. J. Physiol.* 267:E331–336.
89. Allen, R. E., and L. K. Boxhorn. 1989. Regulation of skeletal muscle satellite cell proliferation and differentiation by transforming growth factor-beta, insulin-like growth factor-I, and fibroblast growth factor. *J. Cell Physiol* 138:311–315.
90. Campion, D. R. 1984. The muscle satellite cell: a review. *Int. Rev. Cytol.* 87:225–251.
91. Mooradian, A. D., J. E. Morley, and S. G. Korenman. 1987. Biological actions of androgens. *Endocrinol. Rev.* 8:1–28.
92. Florini, J. R. 1970. Effects of testosterone on qualitative pattern of protein synthesis in skeletal muscle. *Biochem.* 9:909–912.
93. Griggs, R. C., W. Kingston, R. F. Jozefowicz, B. E. Herr, G. Forbes, and D. Halliday. 1989. Effect of testosterone on muscle mass and muscle protein synthesis. *J. Appl. Physiol.* 66:498–503.
94. Brodsky, I. G., P. Balagopal, and K. S. Nair. 1996. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men. *J. Clin. Endocrinal. Metab.* 81:3469–3475.
95. Urban, R. J., Y. H. Bodenburg, C. Gilkison, J. Foxworth, A. R. Coggan, R. R. Wolfe, and A. Ferrando. 1995. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. *Am. J. Physiol. 269:* E820–826.
96. Florini, J. R. 1987. Hormonal control of muscle growth. *Muscle Nerve* 10:577–598.
97. Fryburg, D. A., E. J. Barrett, R. J. Louard, R. J. Gelfand. 1990. Effect of starvation on human muscle protein metabolism and its response to insulin. *Am. J. Physiol.* 259:E477–482.

98. Gelfand, R. A., and E. J. Barrett. 1987. Effect of physiologic hyperinsulinemia on skeletal muscle protein synthesis and breakdown in man. *J. Clin. Invest* 80:1–6.
99. Louard, R. J., D. A. Fryburg, R. A. Gelfand, and E. J. Barrett. 1992. Insulin sensitivity of protein and glucose metabolism in human forearm skeletal muscle. *J. Clin.* Invest. 90:2348–2354.
100. Fryburg, D. A., and E. J. Barrett. 1995. Insulin, growth hormone, and IGF-1 regulation of protein metabolism. *Diabetes Rev.* 3:93–112.
101. Rooyackers, 0. E., and K. S. Nair. 1997. Hormonal regulation of human muscle protein metabolism. *Annu. Rev. Nutr.* 17:457–485.
102. Gibson, J. N., N. L. Poyser, W. L. Morrison, C. M. Scrimgeour, and M. J. Rennie. 1991. Muscle protein synthesis in patients with rheumatoid arthritis: effect of chronic corticosteroid therapy on prostaglandin F_2 availability. *Eur. J. Clin. Invest.* 21:406–412.
103. Fitzpatrick, G. F., M. M. Meguid, P. H. Gitlitz, and M. F. Brennan. 1977. Glucagon infusion in normal man: effects on 3-methylhistidine excretion and plasma ammo acids. *Metabolism 26477485.*
104. Fryburg, D. A., R. A. Gelfand, L. A. Jahn, D. Oliveras, R. S. Sherwin, L. Sacca, and E. J. Barrett. 1995. Effects of epinephrine on human muscle glucose and protein metabolism. *Am. J. Physiol.* 268:E55–59.
105. Garlick, P. J., H. J. Bums, and R. M. Palmer. 1988. Regulation of muscle protein turnover: possible implications for modifying the responses to trauma and nutrient intake. *Baillieres Clin. Gastroenterol.* 2:915–940.
106. Stiegler, H., K. Rett, M. Wicklmayr, and H. Mehnert. 1989. Metabolic effects of prostaglandin El on human skeletal muscle with special regard to the amino acid metabolism. *Vasa* 28:14–18.
107. Muller, M. J., and H. J. Seitz. 1984. Thyroid hormone action on intermediary metabolism. Part III: protein metabolism in hyper and hypothyroidism. *Klin. Wochenschr.* 62:97–102.
108. Biolo, G., G. Toigo, B. Ciocchi, R. Situlin, F. Iscra, A. Gullo, and G. Guamieri. 1997. Metabolic response to injury and sepsis: changes in protein metabolism. *Nutrition* 13:52S–57S.
109. Rennie, M. J., and D. J. Millward. 1983. 3-methylhistidine excretion and the urinary 3-methylhistidine/creatinine ratio are poor indicators of skeletal muscle protein breakdown. *Clin. Sci.* 65:217–225.
110. Forbes, G. B., and J. C. Reina. 1970. Adult lean body mass declines with age. *Metabolism* 19653663.
111. Welle, S., J. Thornton, R. Jozefowicz, and M. Statt. 1993. Myofibrillar protein synthesis in young and old men. *Am. J. Physiol.* 264:E693–E698.
112. Kelijman, M. 1991. Age-related alterations of growth hormone/insulin-like-growth-factor I axis. *J. Am. Geriatr. Soc.* 39:295–307.
113. Tenover, J. S., A. M. Matsumoto, S. R. Plymate, and W. J. Bremner. 1987. Effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: response to clomiphene citrate. *J. Clin. Endocrinol. Metab.* 65:1118–1126.
114. Vermeulen, A. 1991. Androgens in the aging male. *J. Clin. Endocrinol. Metab.* 73:221–224.
115. Fagiolo, U., A. Cossarizza, E. Scala, E. Fanales-Belasio, C. Ortolani, E. Cozzi, D. Monti, C. Fanceschi, and R. Paganelli. 1993. Increased cytokine production in mononuclear cells of healthy elderly people. *Eur. J. Immunol.* 23:2375–2378.
116. Heymsfield, S. B., C. Arteag, C McManus, J. Smith, and S. Moffitt. 1983. Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method. *Am. J. Clin. Nutr.* 37:478–494.
117. Rathmacher, J. A., P. J. Flakoll, and S. L. Nissen. 1995. A compartmental model of 3-methylhistidine metabolism in humans. *Am. J. Physiol.* 269:E193–198.
118. Rennie, M. J., K. Smith, and P. W. Watt. 1994. Measurement of human tissue protein synthesis: an optimal approach. *Am. J. Physiol. 266:* E298–307.
119. Nair, K. S., D. Halliday, and R. C. Griggs. 1988. Leucine incorporation into mixed skeletal muscle protein in humans. *Am. J. Physiol. 254:* E208–213.
120. Czerwinski, S. M., R. Zak, T. T. Kurowski, M. T. Falduto, and R. C. Hickson. 1989. Myosin heavy chain turnover and glucocorticoid deterrence by exercise in muscle. *J. Appl. Physiol.* 67:2311–2315.
121. Gregory, P., R. B. Low, and W. S. Stirewalt. 1987. Fractional synthesis rates *in vivo* of skeletal muscle myosin isoenzymes. *Biochem. J. 245:* 133-137.
122. Balagopal, P., 0. Ljungqvist, and K. S. Nair. 1997. Skeletal muscle myosin heavy chain synthesis rate in healthy humans. *Am. J. Physiol. 272:* E45–E50.
123. Wang, Z. M., R. N. Pierson, Jr., and S. B. Heymsfield. 1992. The five-level model: a new approach to organizing body composition research. *Am. J. Clin. Nutr.* 56:19–28.
124. Forbes, G. B. 1987. Human Body Composition. Springer-Verlag. New York.
125. Burkinshaw, L., G. L. Hill, and D. B. Morgan. 1978. Assessment of the distribution of protein in the human body by in *vitro* neutron activation analysis. International Symposium on Nuclear Activation Techniques in the Life Sciences. International Atomic Energy Association, Vienna.
126. Cohn, S. H., D. Vartsky, S. S. Yasumura, A. Sawitsky, I. Zanzi, A. Vaswani, and K. J. Ellis. 1980. Compartmental body composition based on total body nitrogen, potassium and calcium. *Am. J. Physiol.* 39:E524–530.
127. Heymsfield, S. B., A. P. Tighe, and Z. Wang. 1994. Nutritional assessment by anthropometric and biochemical methods *In* M. E. Shils, J. A. Olson. and M. Shike. editors. Modem Nutrition in Health and Disease, 8th ed. Lea and Febiger, Philadelphia. 812-841.
128. Durnin, J. V. G. A., and J. Womersley. 1974. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged 16 to 72 years. *Br. J. Nutr. 132:* 77-97.
129. Schols, A. M. W. J., E. F. M. Wouters, P. B. Soeters, and K. R. Westerterp. 1991. Body composition by bioelectrical impedance analysis compared to deuterium dilution and skinfold anthropometry in patients with chronic obstructive pulmonary disease. *Am. J. Clin. Nutr.* 53:421–424.
130. Chumlea, W. C., and R. N. Baumgartner. 1990. Bioelectric impedance methods for the estimation of body composition. *Can. J. Sport Sci.* 15:172–179.
131. Heymsfield, S. B., R. Smith, M. Aulet, B. Benson, S. W. Lichtman, J. Wang, and R. N. Pierson, Jr. 1990. Appendicular skeletal muscle mass: measurement by dual photon absorptiometry. *Am. J. Clin. Nutr. 52:* 214-218.
132. de Bruin, P. F., J. Ueki, A. Watson, and N. B. Pride. 1997. Size and strength of the respiratory and quadriceps muscles in patients with chronic asthma. *Eur. Respir. J.* 10:59–64.
133. Baumgartner, R., R. Rhyne, C. Troup, S. Wayne, and P. Garry. 1992. Appendicular skeletal muscle areas assessed by magnetic resonance imaging in older persons. *J. Gerontol. Med. Sci.* 47:M67–M72.
134. Sjostrom, L. A. 1991. A computer-tomography based multicompartment body composition technique and anthropmetric predictions of lean body mass. total and subcutaneous adipose tissue. *Int. J. Obes.* 15:19–20.
135. Chumlea, W. C., A. F. Roche, and I. Rogers. 1984. Replicability for anthroqometrv jn the elderlv. *Hum. Biol.* 56:329–337.
136. Heymsfield, S. B., C. McManus, J. Smith, V. Stevens, and D. W. Nixon. 1982. Anthropometric measurement of muscle mass: revised equations for calculating bone free arm muscle area. *Am. J. Clin. Nutr. 36:* 680690.
137. Wang, Z. M., M. Visser, R. Ma, R. N. Baumgartner, D. Kotler, D. Gallagher, and S. B. Heymsfield. 1996. Skeletal muscle mass: evaluation of neutron activation and dual energy x-ray absorptiometry methods. *J. Appl. Physiol.* 80:824–831.
138. Chumlea, W. C., S. S. Guo, B. Vellas, and Y. Guigoz. 1995. Techniques of assessing muscle mass and function (sarcopenia) for epidemiological studies of the elderly. *J. Gerontol. A Biol. Sci. Med. Sci.* 50:45–51.
139. Coggan, A. R. 1995. Muscle biopsy as a tool in the study of the aging. *J. Gerontol. A Biol. Sci. Med. Sci.* 50:30–34.
140. Halkiaer-Kristensen. J.. and T. Ineemann-Hansen. 1981. Variations in single fibre areas and fibre composition in needle biopsies from the human quadriceps muscle. *Scand. J. Clin. Lab. Invest.* 41:391–395.
141. Simoneau, J.-A., G. Lortie, M. R. Boulay, M.-C. Thibault, and C. Bouchard. 1986. Repeatability of fibre type and enzyme activity measurements in human skeletal muscle. *Clin. Physiol.* 6:347–356.
142. Gür, H., and L. Larsson. 1991. Regional differences in the influence of the interval between removal and freezing of muscle samples on muscle fibre size. *Acta Physiol. Scand.* 143:445–446.
143. Smerdu, V., I. Karsch-Mizrachi, M. Campione, L. Leinwand, and S. Schiaffino. 1994. Type IIx myosin heavy chain transcripts are expressed in type IIb fibers of human skeletal muscle. *Am. J. Physiol.* 267:C1723–1728.
144. McArdle, W. D., F. I. Katch, and V. L. Katch. 1994. Training muscles to become stronger. In Essentials of Exercise Physiology. Lea and Febiger, Philadelphia. 370-397.
145. Hurley, B. F. 1995. Age, gender and muscular strength. *J. Gerontol. A Biol. Sci. Med. Sci.* 50:41–44.
146. Frontera, W. G., V. A. Hughes, K. J. Lutz, and W. J. Evans. 1991. A cross sectional study of muscle strength and mass in 45-78 year old men and women. *J. Appl. Physiol.* 71:644–650.

147. Sapega, A. A., J. A. Nichols, D. Sokolow, and A. Saraniti. 1982. The nature of torque overshoot in cybex isokinetic dynamometry. *Med. Sci. Sports Exerc.* 14:368–375.
148. Winter, D. A., R. P. Wells, and G. W. Orr. 1981. Errors in the use of isokinetic dynamometers. *Eur. J. Appl. Physiol.* 46:397–408.
149. Stone, M., and H. O'Bryant. 1987. Weight Training: A Scientific Approach. Bellwether Press, Minneapolis, MN. 166-173.
150. Weibel, E. R. 1984. The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System. Harvard University Press, Cambridge, MA.
151. Piiper, J., and P. Scheid. 1981. Model for capillary-alveolar equilibration with special reference to O_2 uptake in hypoxia. *Respir. Physiol.* 46:193–208.
152. Wagner, P. D., and J. B. West. 1980. Ventilation-perfusion relationships. *In* J. B. West, editor. Pulmonary Gas Exchange, Vol. 1. Academic Press, New York. 219-262.
153. Agusti, A. G. N., J. Cotes, and P. D. Wagner. 1997. Responses to exercise in lung diseases. *In* B. J. Whipp and J. Roca, editors. Clinical Exercise Testing. *Eur. Respir. Monograph.* 6:32–50.
154. Rowell, L. B. 1993. Human Cardiovascular Control. Oxford University Press, New York.
155. Wittenberg, B., J. Wittenberg, and P. Caldwell. 1975. Role of myoglobin in the oxygen supply to red skeletal muscle. *J. Biol. Chem. 250:* 9038-9043.
156. Richardson, R. S., E. A. Noyszewski, K. F. Kendrick, J. S. Leigh, and P. D. Wagner. 1995. Myoglobin O_2 desaturation during exercise: evidence of limited O_2 transport. *J. Clin.* Invest. 96:1919–1926.
157. Groebe, K., and G. Thews. 1990. Calculated intra- and extracellular gradients in heavily working red muscle. *Am. J. Physiol.* 259:H84–92.
158. Honig, C. R., T. E. J. Gayeski, W. J. Federspiel, A. Clark, Jr., and P. Clark. 1984. Muscle O_2 gradients from hemoglobin to cytochrome: new concepts, new complexities. *Adv. Exp. Med. Biol.* 169:23–38.
159. Bebout, D. E., M. C. Hogan, S. C. Hempleman, and P. D. Wagner. 1993. Effects of training and immobilization on $\dot{V}o_2$ and Do_2 in dog gastrocnemius muscle *in situ*. *J. Appl. Physiol.* 74:1697–1703.
160. Wagner, P. D. 1993. Algebraic analysis of the determinants of $\dot{V}o_2max$. *Respir. Physiol.* 93:221–237.
161. Wagner, P. D. 1996. A theoretical analysis of factors determining $\dot{V}o_2max$ at sea level and altitude. *Respir. Physiol.* 106:329–343.
162. Woledge, R. C., N. A. Curtin, and E. Homsher. 1985. Energetic Aspects of Muscle Contraction. Academic Press, San Diego, CA.
163. Gibbs, C. L. 1987. Comparative muscle energetics and the cost of activation. *Proc. Aust. Physiol. Pharmacol. Soc.* 18:115–123.
164. Spriet, L. L., M. Soderlund, M. Bergstrom, and E. Hultman. 1987. Anaerobic energy release in skeletal muscle during electrical stimulation in man. *J. Appl. Physiol.* 62:611–615.
165. Fitts, R. H. 1994. Cellular mechanisms of muscle fatigue. *Physiol. Rev.* 74:49–94.
166. di Prampero, P. E., U. Boutellier, and P. Pretsch. 1983. Oxygen deficit and stores at onset of muscular exercise in humans. *J. Appl. Physiol.* 55:146–153.
167. Westerblad, H., J. A. Lee, J. Lannergren, and D. G. Allen. 1991. Cellular mechanisms of fatigue in skeletal muscle. *Am. J. Physiol.* 261: C195–C209.
168. Phillipi, M., and A. H. Sillau. 1994. Oxidative capacity distribution in skeletal muscle fibers of the rat. *J. Exp. Biol.* 189:1–11.
169. Hoppeler, H., 0. Mathieu, R. Krauer, H. Claassen, R. B. Armstrong, and E. R. Weibel. 1981. Design of the mammalian respiratory system: VI. Distribution of mitochondria and capillaries in various muscles. *Respir. Physiol.* 44:87–1 11.
170. Wilson, D. F. 1995. Energy metabolism in muscle approaching maximal rates of oxygen utilization. *Med. Sci. Sports Exerc.* 27:54–59.
171. Saltin, B., and P. D. Gollnick. 1983. Skeletal muscle adaptability: significance for metabolism and performance. In L. D. Peachey, editor. Handbook of Physiology: Skeletal Muscle. American Physiological Society, Bethesda, MD. 555–631.
172. Bergstrom, J., and E. Hultman. 1988. Energy cost and fatigue during intermittent electrical stimulation of human skeletal muscle. *J. Appl. Physiol.* 65:1500–1505.
173. Karlsson, J. 1971. Lacate and phosphagen concentrations in working muscle of man. *Acta Physiol. Scand.* 81:1–72.
174. Chase, P. B., and M. J. Kushmerick. 1988. Effects of pH on contraction of rabbit fast and slow skeletal muscle *fibers. Biophys. J.* 53:935–946.
175. Metzger, J. M., and R. L. Moss. 1987. Greater hydrogen ion-induced depression of tension and velocity in skinned single fibers of rat fast than slow muscles. *J. Physiol. (Lond.)* 393:727–742.
176. Westerblad, H., J. D. Bruton, and J. Lannergren. 1997. The effect of intracellular pH on contractile function of intact, single fibres of mouse muscle declines with increasing temperature. *J. Physiol. (Lond.) 500:* 193-204.
177. Cooke, R., G. Franks, G. B. Luciani, and E. Pate. 1988. The inhibition of rabbit skeletal muscle contraction by hydrogen ions and phosphate. *J. Physiol. (Lond.)* 395:77–97.
178. Westerblad, H., and D. G. Allen. 1992. Myoplasmic free Mg^{2+} concentration during repetitive stimulation of single fibres from mouse skeletal muscle. *J. Physiol. (Lond.) 453:* 413434.
179. Lamb, G. D., and D. G. Stephenson. 1991. Effects of Mg^{2+} on the control of Ca^{2+} release in skeletal muscle fibers of the toad. *J. Physiol. (Lond.)* 434:507–528.
180. Andrade, F. H., M. B. Reid, D. G. Allen, and H. Westerblad. 1998. Effect of hydrogen peroxide and dithiothreitol on contractile function of single skeletal muscle fibres from mouse. *J. Physiol. (Lond.) 509:* 565-575.
181. Brotto, M. A. P., and T. M. Nosek. 19%. Hydrogen peroxide disrupts calcium release from the sarcoplasmic reticulum of rat skeletal muscle fibers. *J. Appl. Physiol.* 81:731–737.
182. Reid, M. B. 1998. Muscle fatigue: mechanisms and regulation. *In C.* K. Sen, L. Packer, and 0. Hanninen, editors. Exercise and Oxygen Toxicity, 2nd ed. Elsevier Science B. V., Amsterdam. (In press)
183. Sjogaard, G., R. P. Adams, and B. Saltin. 1985. Water and ion shifts in skeletal muscle of humans with intense dynamic knee extension. *Am. J. Physiol.* 248:R190–R196.
184. Westerblad, H., J. A. Lee, A. G. Lamb, S. R. Bolsover, and D. G. Allen. 1990. Spatial gradients of intracellular calcium in skeletal muscle during fatigue. *Pfluegers Arch.* 415:734–740.
185. Kosmas, E. N., S. A. Hussain, J. M. Montserrat, and R. D. Levy. 19%. Relationship of peak exercise capacity with indexes of peripheral muscle vasodilation. *Med. Sci. Sports Exerc.* 28:1254–1259.
186. Bangsbo, J., K. Madsen, B. Kiens, and E. A. Richter. 19%. Effect of muscle acidity on muscle metabolism and fatigue during intense exercise in man. *J. Physiol. (Lond.)* 495:587–596.
187. Green, D. J., G. O'Driscoll, B. A. Blanksby, and R. R. Taylor. 1996. Control of skeletal muscle blood flow during dynamic exercise: contribution of endothelium-derived nitric oxide. *Sports Med.* 21:119-146.
188. Rowell, L. B. 1997. Neural control of muscle blood flow: importance during dynamic exercise. *Clin. Exp. Pharmacol. Physiol.* 24:117–125.
189. Dempsey, J. A., C. A. Harms, and D. M. Ainsworth. 1996. Respiratory muscle perfusion and energetics during exercise. *Med. Sci. Sports Exerc.* 28:1123–1128.
190. Gandevia, S. G. 1996. Insights into motor performance and muscle fatigue based on transcranial stimulation of the human motor cortex. *Clin. Exp. Pharmacol. Physiol.* 23:957–960.
191. Raven, P. B., J. T. Potts, and X. Shi. 1997. Baroreflex regulation of blood pressure during dynamic exercise. *Exerc. Sport Sci. Rev. 25:* 365-389.
192. Eldridge, F. L. 1994. Central integration of mechanisms in exercise hyperpnea. *Med. Sci. Sports Exerc.* 26:319–327.
193. Sieck, G. C., and Y. S. Prakash. 1996. Fatigue at the neuromuscular junction. Branch point vs. presynaptic vs. postsynaptic mechanisms. *Adv. Exp. Med. Biol.* 384:83–100.
194. Garland, S. J., and M. P. Kaufman. 1995. Role of muscle afferents in the inhibition of motomeurons during fatigue. *Adv. Exp. Med. Biol.* 384:271–278.
195. Vollestad, N. K. 1997. Measurement of human muscle fatigue. *J. Neurosci. Methods* 74:219–227.
1%. Gandevia, S. C., G. M. Allen, and D. K. McKenzie. 1996. Central fatigue: critical issues, quantification, and practical applications. *Adv. Exp. Med. Biol.* 384:281–294.
197. Merton, P. A. 1954. Voluntary strength and fatigue. *J. Physiol (Lond.)* 128:553–564.
198. Schols, A. M. W. J., P. B. *Soeters,* A. M. C. Dingemans, R. Mostert, P. J. Frantzen, and E. F. M. Wouters. 1993. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am. Rev. Respir. Dis.* 147:1151-1156.
199. Engelen, M. A. M., A. M. W. J. Schols, W. C. Baken, G. J. Wesseling, and E. F. M. Wouters. 1994. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in an outpatient population with chronic obstructive pulmonary disease. *Eur. Respir. J.* 7:1793–1797.
200. Wuyam, B., J. F. Payen, P. Levy, H. Bensai'dane, H. Reutenauer, J. F. Le Bas, and A. L. Benabid. 1992. Metabolism and aerobic capacity of skeletal muscle in chronic respiratory failure related to chronic ob-

structive pulmonary disease. *Eur. Respir. J.* 5:157–162.

201. Casaburi, R., E. Carithers, J. Tosolini, J. Phillips, and S. Bhasin. 1997. Randomized placebo controlled trial of growth hormone in severe COPD patients undergoing endurance training (abstract). *Am. J. Respir. Crit. Care Med.* 155:A498.
202. Hughes, R. L., H. Katz, V. Sahgal, J. A. Campbell, R. Hartz, and T. W. Shields. 1983. Fiber size and energy metabolites in five separate muscles from patients with chronic obstructive lung disease. *Respiration* 44:321–328.
203. Jakobsson, P., L. Jorfeldt, and A. Brundin. 1990. Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD), with and without chronic respiratory failure. *Eur. Respir. J.* 3:192–196.
204. Hildebrand, I. L., C. Sylven, M. Esbjornrsson, K. Hellstrom, and E. Jansson. 1991. Does chronic hypoxaemia induce transformation of fibre types? *Acta Physiol. Scand.* 141:435–439.
205. Whittom, F., J. Jobin, P.-M. Simard, P. Leblanc, C. Simard, S. Bernard, R. Belleau, and F. Maltais. 1998. Histochemical and morphological characteristics of the vastus lateralis muscle in COPD patients. *Med. Sci. Sports Exerc.* 30:1467–1474.
206. Sato, Y., T. Asoh, Y. Honda, Y. Fujimatso, I. Higuchi, and K. Oizumi. 1997. Morphologic and histochemical evaluation of muscle in patients with chronic pulmonary emphysema manifesting generalized emaciation. *Eur. Neurol.* 37:116–121.
207. Satta, A., G. B. Migliori, A. Spanevello, M. Neri, R. Bottinelli, M. Canepari, M. A. Pellegrino, and C. Reggiani. 1997. Fibre types in skeletal muscles of chronic obstructive pulmonary disease patients related to respiratory function and exercise tolerance. *Eur. Respir. J.* 10:2853–2860.
208. Möller, P., K. Hellstrom, and I. L. Hermansson. 1984. Myoglobin content in leg muscle in patients with chronic obstructive lung disease. *Respiration* 45:35–38.
209. Simard, C., F. Maltais, P. Leblanc, P. M. Simard, and J. Jobin. 1996. Mitochondrial and capillarity changes in vastus lateralis muscle of COPD patients: electron microscopy study. *Med. Sci. Sports Exerc.* 28:S95.
210. Jakobsson, P., L. Jordfelt, and J. Hemiksson. 1995. Metabolic enzyme activity in the quadriceps femoris muscle in patients with severe chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 151:374–377.
211. Maltais, F., A.-A. Simard, C. Simard, J. Jobin, P. Desgagnés, and P. LeBlanc. 1996. Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am. J. Respir. Crit. Care Med.* 153:288–293.
212. Gosselink, R., T. Troosters, and M. Decramer. 1996. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am. J. Respir. Crit. Care Med.* 153:976–980.
213. Hamilton, A. L., K. J. Killian, E. Summers, and N. L. Jones. 1995. Muscle strength, symptom intensity and exercise capacity in patients with cardiorespiratory disorders. *Am. J. Respir. Crit. Care Med.* 152:2021–2031.
214. Bernard, S., P. Leblanc, F. Whittom, G. Carrier, J. Jobin, R. Belleau, and F. Maltais. 1998. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 158:629–634.
215. Decramer, M., L. M. Lacquet, R. Fagard, and P. Rogiers. 1994. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am. Rev. Respir. Dis.* 150:11–16.
216. Kutsuzawa, T., S. Shioya, D. Kurita, M. Haida, Y. Ohta, and H. Yamabayashi. 1992. ^{31}P-NMR study of skeletal muscle metabolism in patients with chronic respiratory impairment. *Am. Rev. Respir. Dis.* 146:1019–1024.
217. Newell, S. Z., D. K. McKenzie, and S. C. Gandevia. 1989. Inspiratory and skeletal muscle strength and endurance and diaphragmatic activation in patients with chronic airflow limitation. Thorax 44:903–912.
218. Orozco-Levi, M., J. Gea, J. Sauleda, J. M. Corominas, J. Minguella, X. Aran, and J. Broquetas. 1995. Structure of the latissimus dorsi muscle and respiratory function. *J. Appl. Physiol.* 78:1132–1139.
219. Muza, S. R., G. Criner, and S. G. Kelsen. 1991. Pectoralis muscle recruitment during weaning in patients with chronic respiratory failure (abstract). *Am. Rev. Respir. Dis.* 143:A163.
220. Zattara-Hartmann, M. C., M. Badier, C. Guillot, C. Tomei, and Y. Jammes. 1995. Maximal force and endurance to fatigue of respiratory and skeletal muscles in chronic hypoxemic patients: the effects of oxygen breathing. *Muscle Nerve* 18:495–502.
221. Serres, I., V. Gautier, A. L. Varray, and C. G. Préfaut. 1998. Impaired skeletal muscle endurance related to physical inactivity and altered lung function in COPD patients. *Chest* 113:900–905.
222. Gallagher, C. G. 1994. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. *Clin. Chest Med.* 15:305–328.
223. Levison, H., and R. M. Chemiack. 1968. Ventilatory cost of exercise in chronic obstructive pulmonary disease. *J. Appl. Physiol.* 25:21–27.
224. Nery, L. E., K. Wasserman, J. D. Andrews, D. J. Huntsman, J. E. Hansen, and B. J. Whipp. 1982. Ventilatory and gas exchange kinetics during exercise in chronic ariways obstruction. *J. Appl. Physiol.* 53:1594–1602.
225. Agusti, A. G., and J. A. Barberà. 1994. Chronic pulmonary diseases: chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. *Thorax* 49:924–932.
226. Maltais, F., P. Leblanc, C. Simard, J. Jobin, C. Bérubé, J. Bruneau, L. Carrier, and R. Belleau. 1996. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 154442447.
227. Evans, A. B., A. J. Al-Himyary, M. I. Hrovat, P. Pappagianopoulos, J. C. Wain, L. C. Ginns, and D. M. Systrom. 1997. Abnormal skeletal muscle oxidative capacity after lung transplantation by ^{31}P-MRS. *Am. J. Respir. Crit. Care Med.* 155:615–621.
228. Kutsuzawa, T., S. Shioya, D. Kurita, M. Haida, Y. Ohta, and H. Yamabayashi. 1995. Muscle energy metabolism and nutritional status in patients with chronic obstructive pulmonary disease: a ^{31}P magnetic resonance study. *Am. J. Respir. Crit. Care Med.* 152:647–652.
229. Williams, T. J., and G. I. Snell. 1997. Early and long-term functional outcomes in unilateral, bilateral, and living-related transplant recipients. *Clin. Chest Med.* 18:245–257.
230. Light, R. W., H. M. Mintz, G. S. Linden, and S. E. Brown. 1984. Hemodynamics of patients with severe chronic obstructive pulmonary disease during progressive upright exercise. *Am. Rev. Respir. Dis. 130:* 391-395.
231. Marcus, J. H., R. L. McLean, G. M. Duffell, and R. H. Ingram. 1970. Exercise performance in relation to the pathophysiologic type of chronic obstructive pulmonary disease. *Am. J. Med.* 49:14–22.
232. Spiro, S. G., H. L. Hahn, R. H. T. Edwards, and N. B. Pride. 1975. An analysis of the physiological strain of submaximal exercise in patients with chronic obstructive bronchitis. *Thorax* 30:415–425.
233. Wehr, K. L., and R. L. Johnson. 1976. Maximal oxygen consumption in patients with lung disease. *J. Clin. Invest.* 56:880–890.
234. Montes de Oca, M., J. Rassulo, and B. R. Celli. 1996. Respiratory muscle and cardiopulmonary function during exercise in very severe COPD. *Am. J. Respir. Crit.* Care *Med.* 154:1284–1289.
235. Raffestin, B., P. Escourrou, A. Legrand, P. Duroux, and A. Lockhart. 1982. Circulatory transport of oxygen in patients with chronic airflow obstruction exercising maximally. *Am. Rev. Respir. Dis.* 125:426–431.
236. Sala, E., J. Roca, R. M. Marrades, J. Alonso, J. M. Gonzalez de Suso, A. Moreno, J. A. Barberà, J. Nadal, L. de Jover, R. Rodriguez-Roisin, and P. D. Wagner. 1998. Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* (In press)
237. Maltais, F., J. Jobin, M. J. Sullivan, S. Bernard, F. Whittom, K. J. Killian, M. Desmeules, M. Bélanger, and P. Leblanc. 1998. Lower limb metabolic and hemodynamic responses during exercise in normal subjects and in COPD. *J. Appl. Physiol.* 84:1573–1580.
238. Albert, R. 1997. Is pulmonary rehabilitation an effective treatment for chronic obstructive pulmonary disease? *No. Am. J. Respir. Crit. Care Med.* 155:784–785.
239. Ries, A., R. Kaplan, T. Limberg, and L. Prewit. 1995. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann. Intern. Med.* 122:823–832.
240. Harms, C. A., M. A. Babcock, S. R. McClaran, D. F. Pegelow, G. A. Nickele, W. B. Nelson, and J. A. Dempsey. 1997. Respiratory muscle work compromises leg blood flow during maximal exercise. *J. Appl. Physiol.* 82:1573–1583.
241. Mithoefer, J. C., F. D. Holford, and J. F. H. Keighley. 1974. The effect of oxygen administration on mixed venous oxygenation in chronic obstructive pulmonary disease. *Chest* 66:122–132.
242. Sieck, G. C., and B. D. Johnson. 1996. Metabolic and structural alterations in skeletal muscle with hypoxia. *In* G. G. Haddad and G. Lister, editors. Tissue Oxygen Deprivation: From Molecular to Integrated Function. Marcel Dekker, New York. 779-827.
243. Casaburi, R., A. Patessio, F. Ioli, S. Zanaboni, C. F. Donner, and K. Wasserman. 1991. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am. Rev. Respir. Dis.* 143:9–18.

244. Di Francia, M., D. Barbier, J. L. Mege, and J. Orehek. 1994. Tumor necrosis factor-alpha levels and weight loss in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 150:1453–1455.

245. Sridhar, M. K. 199.5. Why do patients with emphysema lose weight? *Lancet* 345:1190–1191.

246. de Godoy, I., M. Donahoe, W. J. Calhoun, J. Mancino, and R. M. Rogers. 1996. Elevated TNF-α production by peripheral blood monocytes of weight-losing COPD patients. *Am. J. Respir. Crit. Care Med.* 153:633–637.

247. Sapega, A. A., D. P. Sokolow, T. J. Graham, and B. Chance. 1987. Phosphorus nuclear magnetic resonance: a non-invasive technique for the study of muscle bioenergetics during exercise. Review. *Med. Sci. Sports Exerc.* 19:410–420.

248. Meyer, R. A., M. J. Kushmerick, and T. R. Brown. 1982. Application of ^{31}P NMR spectroscopy to the study of striated muscle metabolism. *Am. J. Physiol.* 242:C1–C11.

249. Meyer, R. A., H. L. Sweeney, and M. J. Kushmerick. 1984. A simple analysis of the "phosphocreatine shuttle." *Am. J. Physiol.* 246:C365–c377.

2.50. Boska, M. 1991. Estimating the ATP cost of of force production in the human gastrocnemius/soleus muscle group using ^{31}P-MRS and ^{1}H-MRI. *NMR Biomed.* 4:173–181.

251. Tada, H., H. Kato, T. Misawa, F. Sasaki, S. Hayashi, H. Takahashi, Y. Kutsumi, T. Ishizaki, T. Nakai, and S. Miyabo. 1992. ^{31}P-Nuclear magnetic resonance evidence of abnormal skeletal muscle metabolism in patients with chronic lung disease and congestive heart failure. *Eur. Respir. J.* 5:163–169.

252. Thompson, C., R. Davies, G. Kemp, D. Taylor, G. Radda, and B. Rajagopalan. 1993. Skeletal muscle metabolism during exercise and recovery in patients with respiratory failure. *Thorax* 48:486–490.

253. Payen, J.-F., B. Wuyam, P. Levy, H. Reutenauer, P. Stieglitz, B. Paramelle, and J.-F. Le Bas. 1993. Muscular metabolism during oxygen supplementation in patients with chronic hypoemia. *Am. Rev. Respir. Dis.* 147:592–598.

254. Mannix, E., M. Boska, P. Galassetti, G. Burton, F. Manfredi, and M. Farber. 1995. Modulation of ATP production by oxygen in obstructive lung disease as assessed by ^{31}P-MRS. *J. Appl. Physiol.* 78:2218–2227.

255. Arnold, D., P. Mathews, and G. Radda. 1995. Investigation of human mitochondrial myopathies by phosphorus magnetic resonance spectroscopy. *Ann. Neurol.* 18:189–196.

256. Kemp, G. J., D. J. Taylor, C. H. Thompson, L. J. Hands, B. Rajagopalan, P. Styles, and G. K. Radda. 1993. Quantitative analysis by ^{31}P magnetic resonance spectroscopy of abnormal mitochondrial oxidation in skeletal muscle during recovery from exercise. *NMR Biomed.* 6:302–310.

257. Takahashi, H., M. Inaki, K. Fujimoto, S. Katsuta, I. Anna, M. Niitsu, and Y. Itai. 1995. Control of the rate of phosphocreatine resynthesis after exercise in trained and untrained human quadriceps muscles. *Eur. J. Appl. Physiol.* 71:396–404.

258. Argov, Z., N. DeStefano, and D. Arnold. 1996. ADP recovery after a brief ischemic exercise in normal and diseased human muscle: a ^{31}P MRS study. *NMR Biomed.* 9:165–172.

259. Sauleda, J., F. Garcia-Palmer, R. J. Wiesner, S. Tarraga, I. Harting, P. Tomás, C. Gómez, C. Saus, A. Palou, and A. G. N. Agustí. 1998. Cytochrome oxidase activity and mitochondrial gene expression in skeletal muscle of patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 157:1413–1417.

260. Jansson, E., J. Johansson, C. Sylven, and L. Kaijser. 1988. Calf muscle adaptation in intermittent claudication: side-differences in muscle metabolic characteristics in patients with unilateral arterial disease. *Clin. Physiol.* 8:17–29.

261. Lundgren, F., A.-G. Dahllof, T. Schersten, and A.-C. Bylund-Fellenius. 1989. Muscle enzyme adaptation in patients with peripheral insufficiency: spontaneous adaptation, effect of different treatment and consquences on walking performance. *Clin. Sci.* 77:485–493.

262. Stewart, P. 1983. Modem quantitative acid-base chemistry. Can. *J. Physiol. Pharmacol.* 61:1444–1461.

263. Lindinger, M. I. 1995. Review: origins of [H+] changes in exercising skeletal muscle. *Can. J. Appl. Physiol.* 20:357–368.

264. Kemp, C. J., C. H. Thompson, A. L. Sanderson, and G. K. Radda. 1994. pH control in rat skeletal muscle during exercise, recovery from exercise, and acute respiratory acidosis. *Mag. Reson. Med.* 31:103–109.

265. Roth, D. A., and G. A. Brooks. 1990. Lactate and pyruvate transport is dominated by a pH gradient-sensitive carrier in rat skeletal muscle sarcolemmal vesicles. *Arch. Biochem. Biophys. 279386394.*

266. Seo, Y. 1984. Effects of extracellular pH on lactate efflux from frog sartorius muscle. *Am. J. Physiol.* 247:C175–C181.

267. Watt, P. W., P. A. MacLennan, H. S. Hundal, C. M. Kuret, and M. J. Rennie. 1988. L(+)-Lactate transport in perfused rat skeletal muscle: kinetic characteristics and sensitivity to pH and transport inhibitors. *Biochim. Biophys. Acta* 944:213–222.

268. Karlsson, J., B. Diamant, and K. Folkers. 1992. Exercise-limiting factors in respiratory distress. *Respiration* 2:18–23.

269. Gertz, I., G. Hedenstiema, G. Hellers, and J. Wahren. 1977. Muscle metabolism in patients with chronic obstructive lung disease and acute respiratory failure. *Clin. Sci. Mol. Med.* 52:395–403.

270. Howald, H., D. Pette, J.-A. Simoneau, A. Uber, H. Hoppler, and P. Cerretelli. 1990. Effect of chronic hypoxia on muscle enzyme activities. *Int. J. Sports Med.* 11:S10–S14.

271. Kwast, K. E., and S. C. Hand. 1996. Acute depression of mitochondrial protein synthesis during anoxia: contributions of oxygen sensing, matrix acidification, and redox state. *J. Biol. Chem.* 271:7313–7319.

272. Pastoris, O., M. Dossena, P. Foppa, R. Amaboldi, A. Gorini, R. F. Villa, and G. Benzi. 1995. Modifications by chronic intermittent hypoxia and drug treatment on skeletal muscle metabolism. *Neurochem. Res.* 20:143–150.

273. Holm, J., P. Bjorntorp, and T. Schernsten. 1973. Metabolic activity in rat skeletal muscle: effect of intermittent hypoxia. Eur. *J. Clin. Invest.* 3:279–283.

274. Pastoris, O., M. Dossena, R. Arnaboldi, A. Gorini, and R. F. Villa. 1994. Age-related alterations of skeletal muscle metabolism by intermittent hypoxia and TRH-analogue treatment. *Pharmacol. Res.* 30: 171-185.

275. Belykh, A. G., V. M. Gukasov, and S. A. Chukaev. 1992. State of the free-radical oxidation system in normobaric hypoxia. *Fiziol. Zh. 38:* 73-76.

276. Corbucci, G. G., A. Menichetti, A. Cogliati, and C. Ruvolo. 1995. Metabolic aspects of cardiac and skeletal muscle tissues in the condition of hypoxia, ischaemia and reperfusion induced by extracorporeal circulation. *Int. J. Tissue React.* 17:219–225.

277. Ferrari, R., C. Ceconi, S. Carello, 0. Alfieri, and 0. Visioli. 1993. Myocardial damage during ischaemia and reperfusion. *Eur. Heart J.* 14: 25-30.

278. Gardner, T. J. 1994. Oxygen radicals and myocardial stunning. *J. Cardiovac. Surg. (Torino)* 9:422–424.

279. Wang, S. Y., J. R. Clague, and G. A. Langer. 1995. Increase in calcium leak channel activity by metabolic inhibition or hydrogen peroxide in rat ventricular myocytes and its inhibition by polycation. *J. Mol. Cell. Cardiol.* 27:211–222.

280. Smith, D. R., D. Stone, and V. M. Darley Usmar. 1996. Stimulation of mitochondrial oxygen consumption in isolated cardiomyocytes after hypoxia-reoxygenation. *Free Radic. Res.* 24:159–166.

281. Thomas, P. K., J. M. Cooper, R. H. M. King, J. M. Workmon, A. H. V. Schapira, M. A. Gross-Sampson, and D. P. R. Muller. 1993. Myopathy in vitamin E deficient rats: muscle fibre necrosis associated with disturbances of mitochondrial function. *J. Anat.* 183:451–461.

282. Appell, H. J., J. A. R. Duarte, and J. M. C. Soares. 1997. Supplementation of vitamin E may attenuate skeletal muscle immobilization atrophy. *Int. J. Sports Med.* 18:157–160.

283. Novelli, G. P., C. Adembri, E. Gandini, S. Z. Orlandini, L. Papucci, L. Formigli, L. I. Manneschi, A. Quattrone, C. Pratesi, and S. Capaccioli. 1997. Vitamin E protects human skeletal muscle from damage during surgical ischemia-reperfusion. *Am. J. Surg.* 173:206–209.

284. Sahlin, K., L. Edstrom, and H. Sjoholm. 1983. Fatigue and phosphocreatine depletion during carbon dioxide-induced acidosis in rat muscle. *Am. J. Physiol.* 245:C15–C20.

285. Pouw, E. M., A. M. W. J. Schols, G. J. van der Vusse, and E. F. M. Wouters. 1996. Muscle adenine nucleotide status in COPD (abstract). *Am. J. Respir. Crit. Care Med.* 153:A453.

286. Fiaccadori, E., S. Del Canale, P. Vitali, E. Coffrini, N. Ronda, and A. Guariglia. 1987. Skeletal muscle energetics, acid-base equilibrium and lactate metabolism in patients with severe hypercapnia and hypoxemia. *Chest* 92:883–887.

287. Cechetto, D., and G. W. Mainwood. 1978. Carbon dioxide and acid base balance in the isolated rat diaphragm. *Pflügers Arch.* 376:251–258.

288. Trivedi, B., and W. H. Danforth. 1966. Effects of pH on the kinetics of frog muscle phosphofructokinase. *J. Biol. Chem.* 10:4110–4114.

289. Nioka, A., Z. Argov, G. P. Dobson, R. E. Forster, H. V. Subramanian, R. L. Veech, and B. Chance. 1992. Substrate regulation of mitochondrial oxidative phosphorylation in hypercapnic rabbit muscle. *J. Appl. Physiol.* 72:521–528.

290. Fitzgerald, R. S., S. Howell, and W. E. Jacobus. 1988. 31P-NMR study

of resting *in vitro* rat diaphragm exposed to hypercapnia. *J. Appl. Physiol.* 65:2270–2277.

291. Reid, M. B. 1996. Reactive oxygen and nitric oxide in skeletal muscle. New *Physiol. Sci.* 11:114–119.
292. Kohzik, L., M. B. Reid, D. S. Bredt, and J. S. Stamler. 1994. Nitric oxide in skeletal muscle. *Nature* 372:546–548.
293. Reid, M. B., F. A. Khawli, and M. R. Moody. 1993. Reactive oxygen in skeletal muscle: III. Contractility of unfatigued muscle. *J. Appl. Physiol.* 75:1081–1087.
294. Davies, K. J. A., A. T. Quintanilha, G. A. Brooks, and L. Packer. 1982. Free radicals and tissue damage produced by exercise. *Biochem. Biophys. Res. Commun.* 107:1198–1205.
295. Jackson, M. J., and S. O'Farrel. 1993. Free radicals and muscle damage. *Br. Med. Bull. 49630641.*
296. Kondo, H., M. Miura, I. Nakagaki, S. Sasaki, and Y. Itokawa. 1992. Trace. element movement and oxidative stress in skeletal muscle atrophied by immobilization. *Am. J. Physiol.* 262:E583–E590.
297. Roberts, C. K., R. J. Barnard, S. H. Scheck, and T. W. Balon. 1997. Exercise-stimulated glucose transport in skeletal muscle is nitric oxide dependent. *Am. J. Physiol.* 273:E220–E225.
298. Young, M. E., G. K. Radda, and B. Leighton. 1997. Nitric oxide stimulates glucose transport and metabolism in rat skeletal muscle in vitro. *Biochem. J.* 322:223–228.
299. Buck, M., and M. Chojkier. 1996. Muscle wasting and dedifferentiation induced by oxidative stress in a murine model of cachexia is prevented by inhibitors of nitric oxide synthesis and antioxidants. *EMBO J.* 15:1753–1765.
300. Llesuy, S., P. Evelson, B. Gonzalez-Flech, J. Peralta, M. C. Carreras, J. J. Poderoso, and A. Boveris. 1994. Oxidative stress in muscle and liver of rats with septic syndrome. *Free Radic. Biol. Med.* 16:445–451.
301. Flores, E. A., B. R. Bistrain, J. J. Pomposelli, C. A. Dinarello, G. L. Blackburn, and N. W. Istfan. 1989. Infusion of tumor necrosis factor/cachectin promotes muscle catabolism in the rat. *J. Clin.* Invest. 83: 1614–1622.
302. Hall-Angeras, M., U. Angeras, 0. Zamir, P. 0. Hasselgren, and J. E. Fischer. 1990. Interaction between corticosterone and tumor necrosis factor stimulated protein breakdown in rat skeletal muscle similar to sepsis. Surgery 108:460–466.
303. Kelsen, S. G., M. Ference, and S. Kapoor. 1985. Effects of prolonged undernutrition on structure and function of the diaphragm. *J. Appl. Physiol.* 58:1354–1359.
304. Wade, A. J., M. M. Marbut, and J. M. Round. 1990. Muscle fibre type and aetiology of obesity. *Lancer* 335:805–808.
305. Lopes, J., D. M. Russell, J. Whitwell, and K. N. Jeejeebhoy. 1982. Skeletal muscle function in malnutrition. *Am. J. Clin. Nutr.* 36:602–610.
306. Vaz, M., S. Thangam, A. Prabhu, and P. S. Shetty. 1996. Maximal voluntary contraction as a functional indicator of adult chronic undernutrition. *Br. J. Nutr.* 76:9–15.
307. Jeejeebhoy, K. N. 1994. How should we monitor nutritional support: structure or function? New *Horiz.* 2:131–138.
308. Pichard, C., E. Hoshino, J. P. Allard, M. P. Charlton, H. L. Atwood, and K. N. Jeejeebhoy. 1991. Intracellular potassium and membrane potential in rat muscles during malnutrition and subsequent refeeding. *Am. J. Clin. Nutr.* 54:489–498.
309. Fiaccedori, E., P. Zambrelli, and G. Tortorella. 1995. Physiopathology of respiratory muscles in mahmtrition. *Minerva Anestesiol.* 61:93–99.
310. Church, J. M., S. Y. Choong, and G. L. Hill. 1984. Abnormalities of muscle metabolism and histology in malnourished patients awaiting surgery: effects of a course of intravenous nutrition. *Br. J. Surg. 71:* 563-569.
311. Essén, B., L. Fohlin, C. Thorén, and B. Saltin B. 1981. Skeletal muscle fibre types and sizes in anorexia nervosa patients. *Clin. Physiol.* 1: 395–403.
312. Bissonnette, D. J. 1997. Effect of hypoenergetic feeding and high-carbohydrate refeeding on muscle tetantic tension, relaxation rate and fatigue in slow- and fast-twitch muscles in rats. *Am. J. Clin. Nutr. 66:* 293-303.
313. Knochel, J. P. 1977. The pathophysiology and clinical characteristics of severe hypophosphatemia. *Arch. Intern. Med.* 137:203–220.
314. Lotz, M., E. Zisman, and F. C. Bartter. 1986. Evidence for a phosphorus-depletion syndrome in man. N. *Engl. J. Med.* 278:409–415.
315. Klinkerfuss, G., V. Bleisch, M. M. Dioso, and G. T. Perkoff. 1967. A spectrum of myopathy associated with alcoholism: II. Light and electron microscopic observations. *Ann. Intern. Med.* 67:493–510.
316. Knochel, J. P. 1982. Neuromuscular manifestations of electrolyte disorders. *Am. J. Med.* 72:521–535.
317. Ebashi, S., and M. Endo. 1968. Calcium ion and muscle contraction. *Prog. Biophys. Mol. Biol.* 18:123–183.
318. Brown, R. S. 1984. Potassium homeostasis and clinical implications. *Am. J. Med.* 77:3–9.
319. Esau, S. A., and N. Sperulakis. 1986. The effect of low chloride on relaxation in hamster diaphragm muscle. *J. Appl. Physiol.* 61:180–184.
320. Fisher, J., M. Magid, C. Kallman, M. Fanucchi, L. Klein, D. McCarthy, I. Roberts, and G. Schulman. 1983. Respiratory illness and hypophosphatemia. *Chest* 83:504–508.
321. Territo, M. C., and K. R. Tanaka. 1974. Hypophosphatemia in chronic alcoholism. *Arch. Intern. Med.* 134:445–447.
322. Riedler, G. F., and W. A. Scheitlin. 1965. Hypophosphatemia in septicemia: higher incidence in gram-negative than in gram-positive infections. *Br. Med. J.* 1:753–756.
323. Fiaccadori, E., E. Coffrini, N. Ronda, A. Vezzani, G. C. Cacciani, C. Fracchia, C. Rampulla, and A. Borghetti. 1990. Hypophosphatemia in course of chronic obstructive pulmonary disease: prevalence, mechanisms, and relationships with skeletal muscle phosphorus content. *Chest* 97:857–868.
324. Fiaccadori, E., E. Coffrini, C. Fracchia, C. Rampulla, T. Montagna, and A. Borghetti. 1994. Hypophosphatemia and phosphorus depletion in respiratory and peripheral muscles of patients with respiratory failure due to COPD. *Chest* 105:1392–1398.
325. Lichtman, M. A., D. R. Miller, J. Cohen, and C. Waterhouse. 1971. Reduced red cell glycolysis 2,3-diphosphoglycerate, adenosine triphosphate concentration, and increased hemoglobin-oxygen affinity caused by hypophosphatemia. *Ann. Intern. Med.* 74:562–568.
326. Lichtman, M. A., D. R. Miller, and R. B. Freeman. 1969. Erythrocyte adenosine triphosphate depletion during hypophosphatemia in a uremic subject. *N. Engl. J. Med.* 280:24–244.
327. Montanari, A., L. Borghi, A. Curti, M. Mergoni, E. Sani, G. Elia, M. Canali, A. Novavini, and A. Borghetti. 1984. Skeletal muscle abnormalities in acute hypophosphatemia during total parenteral nutrition. Miner. *Electrolyte Metab.* 10:52–57.
328. Aubier, M., D. Murciano, Y. Lecocguic, N. Viires, Y. Jacquens, P. Squara, R. Pariente. 1985. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. *N. Engl. J. Med.* 313:420–424.
329. Stendig-Lingberg, G., J. Bergstrom, and E. Hultman. 1977. Hypomagnesium and muscle electrolytes and metabolites. *Acta Med. Scand.* 201:273–280.
330. Lim, P., and E. Jacob. 1972. Magnesium status of alcoholic patients. *Metabolism* 21:1045–1051.
331. Sullivan, J. F., P. W. Wolpert, R. Williams, and J. Egan. 1969. Serum magnesium in chronic alcoholism. *Ann. N.Y. Acad. Sci.* 162:947–963.
332. Molloy, D. W., S. Dhingra, F. Solven, A. Wilson, and D. S. McCarthy. 1984. Hypomagnesemia and respiratory muscle power. *Am. Rev. Respir. Dis. 1291497498.*
333. Buller, N. P., D. A. Jones, and P. A. Poole-Wilson. 1991. Direct measurement of skeletal muscle fatigue in patients with chronic heart failure. *Br. Heart J.* 65:20–24.
334. Minotti, J. R., P. Pillay, L. Chang, L. Wells, and B. M. Massie. 1992. Neurophysiological assessment of skeletal muscle fatigue in patients with congestive heart failure. *Circulation* 86:903–908.
335. Minotti, J. R., I. Christoph, R. Oka, M. W. Weiner, L. Wells, and B. M. Massie. 1991. Impaired skeletal muscle function in patients with congestive heart failure-relationship to systemic exercise performance. *J. Clin. Invest.* 88:2077–2082.
336. Drexler, H., U. Riede, T. Münzel, H. König, E. Funke, and H. Just. 1992. Alterations of skeletal muscle in chronic heart failure. *Circulation* 85:1751–1759.
337. Sullivan, M. J., H. J. Green, and F. R. Cobb. 1990. Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. *Circulation* 81:518–527.
338. Lipkin, D. P., D. A. Jones, J. M. Round, and P. A. Poole-Wilson. 1988. Abnormalities of skeletal muscle in patients with chronic heart failure. *Int. J. Cardiol.* 18:187–195.
339. Mancini, D. M., E. F. Coyle, A. Coggan, J. Beltz, N. Ferraro, S. Montain, and J. R. Wilson. 1989. Contribution of intrinsic skeletal muscle changes to ^{31}P NMR skeletal muscle metabolic abnormalities in patients with chronic heart failure. *Circulation* 80:1338–1346.
340. Levine, B., J. Kalman, L. Mayer, H. M. Fillit, and M. Packer. 1990. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N. *Engl. J.* Med. 323:236–241.
341. Bloomfield, S. A. 1997. Changes in musculoskeletal structure and function with prolonged bed rest. *Med. Sci. Sports Exerc.* 29:197–206.
342. Hikida, R. S., P. D. Gollnick, G. A. Dudley, V. A. Convertino, and P. Buchanan. 1989. Structural and metabolic characteristics of human

skeletal muscle following 30 days of simulated microgravity. *Aviat. Space Environ. Med.* 60:664–670.
343. Appell, H. J. 1990. Muscular atrophy following immobilisation. *Sports Med.* 10:42–58.
344. Lindboc, C. F., and C. S. Platou. 1984. Effects of immobilization of short duration on the muscle fiber size. *Clin. Physiol.* 4:183–188.
345. Sale, D. G., A. J. McComas, J. D. MacDougall, and A. R. M. Upton. 1982. Neuromuscular adaptation in human thenar muscles following strength training and immobilization. *J. Appl. Physiol.* 53:419–424.
346. Booth, F. W., and P. D. Gollnick. 1983. Effects of disuse on the structure and function of skeletal muscle. *Med. Sci. Sports Exerc.* 15:415–420.
347. Coyle, E. F., W. H. Martin, S. A. Bloomfield, 0. H. Lowry, and J. 0. Holloszy. 1985. Effects of detraining on responses to submaximal exercise. *J. Appl. Physiol. 59: 853-869.*
348. Casaburi, R. 1996. Deconditioning. *In* A. P. Fishman, editor. Pulmonary Rehabilitation. Marcel Dekker, New York. 213-230.
349. Larsson, L., and T. Ansved. 1985. Effects of long-term physical training and detraining on enzyme histochemical and functional skeletal muscle characteristics in man. *Muscle Nerve* 8:714–722.
350. Lieber, R. L. 1992. Skeletal muscle adaptation to decreased use. *In* R. L. Lieber, editor. Skeletal Muscle Structure and Function. Williams & Wilkins, Baltimore. 210–259.
351. Munoz, K. A., S. Sataruf, and M. E. Tischler. 1993. Tie course of the response of myofibrillar and sarcoplasmatic protein metabolism to unweighting of the soleus muscle. *Metabolism* 42:1006–1012.
352. Gundersen, K., and J. P. Merlie. 1994. Id-1 as a posssible transcriptional mediator of muscle disuse atrophy. *Proc. Natl. Acad. Sci. U.S.A.* 91: 3641-3651.
353. Larsson, L., G. Grimby, and J. Karlsson. 1990. Muscle strength and speed of movement in relation to age and muscle morphometry. *J. Appl. Physiol.* 46:451–456.
354. Young, A., M. Stokes, and M. Crowe. 1984. Size and strength of the quadriceps muscle of old and young women. Eur. *J. Clin. Invest.* 14: 282-287.
355. Young, A., M. Stokes, and M. Crowe. 1985. The size and strength of the quadriceps muscle of old and young men. *Clin. Physiol.* 5:145–154.
356. Grimby, G., and B. Saltin. 1983. The aging muscle. *Clin. Physiol. 3:209-218.*
357. Brooks, S. V., and J. A. Faulkner. 1995. Effects of aging on the structure and function of skeletal muscle. In C. S. Roussos, editor. The Thorax, 2nd ed. Marcel Dekker, New York. 295-312.
358. Grimby, G., B. Danneskiold-Samsoe, K. Hvid, and B. Saltin. 1982. Morphology and enzymatic capacity in arm and leg muscles in 78-82 year old men and women. *Acta Physiol. Scand.* 115:124–134.
359. Campbell, M. J., A. J. McComas, and F. Petito. 1973. Physiological changes in aging muscles. *J. Neurol. Neurosurg. Psychiatry* 36:74–182.
360. Zerba, E., T. E. Komorowski, and J. A. Faulkner. 1990. The role of free radicals in skeletal muscle of young, adult and old mice. *Am. J. Physiol.* 258:C249–C435.
361. Brooks, S. V., and J. A. Faulkner. 1990. Contraction-induced injury: recovery of skeletal muscles in young and old mice. *Am. J. Physiol. 258:* C436–C442.
362. Davies, C. T. M., D. 0. Thomas, and M. J. White. 1986. Mechanical properties of young and elderly human muscle. *Acta Med. Scand. Suppl.* 711:219–226.
363. Vandervoort, A. A., J. F. Kramer, and E. R. Wharram. 1990. Eccentric knee strength of elderly females. *J. Gerontol.* 45:B125–B128.
364. Carlson, B. M., and J. A. Faulkner. 1988. Reinnervation of long-term denervated rat muscle freely grafted into an innervated limb. *Exp. Neurol.* 102:50–56.
365. Philips, S. K., S. A. Bruce, and R. C. Woledge. 1991. In mice, the muscle weakness due to age is absent during stretching. *J. Physiol. (Lond.)* 437:63–70.
366. Alnaqeeb, M. A., N. S. Al Zaid, and G. Goldspink. 1984. Connective tissue changes and physical properties of developing and aging skeletal muscle. *J. Anat.* 139:677–689.
367. Larsson, L., L. Xiaopeng, and W. A. Frontera. 1997. Effects of aging on shortening velocity and myosin isoform composition in single human skeletal muscle cells. *Am. J. Physiol.* 272:C638–C649.
368. Williams, T. J., R. E. O'Hehir, D. Czamy, M. Home, and G. Bowes. 1988. Acute myopathy in severe acute asthma treated with intravenously administered corticosteroids. *Am. Rev. Respir. Dis.* 137:460–463.
369. Shee, C. D. 1990. Risk factors for hydrocortisone myopathy in acute severe asthma. *Respir. Med.* 84:229–233.
370. Williams, R. S. 1959. Triamcinolone myopathy. *Lancet* i:698–701.
371. Golding, D. N., S. M. Murray, G. W. Pearch, and M. Thompson. 1961. Corticosteroid myopathy. *Ann. Physiol. Med.* 5:171–176.
372. Afifi, A. K., R. A. Bergman, and J. C. Harvey. 1968. Steroid myopathy. Clinical, histologic and cytologic observations. *Johns Hopkins Med. J.* 123:158–174.
373. Askari, A., P. J. Vignos, and R. W. Moskowitz. 1976. Steroid myopathy in connective tissue disease. *Am. J. Med.* 61:485–492.
374. Ruff, R. L. 1986. Endocrine myopathies. *In* A. G. Engel and B. Q. Banker, editors. Myology. McGraw-Hill, New York. 1871-1906.
375. Decramer, M., V. de Bock, and R. Dom. 1996. Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease. *Am. J. Respir. Crit.* Care *Med.* 153:1958–1964.
376. Dekhuijzen, P. N. R., G. Gayan-Ramirez, A. Bisschop, V. de Bock, R. Dom, and M. Decramer. 1995. Corticosteroid treatment and nutritional deprivation cause a different pattern of atrophy in rat diaphragm. *J. Appl. Physiol.* 78:629–637.
377. van Balkom, R. H. H., W. Z. Zhan, Y. S. Prakash, P. N. R. Dekhuijzen, and G. C. Sieck. 1997. Corticosteroid effects on isotonic contractile properties of rat diaphragm muscle. *J. Appl. Physiol.* 83:1062–1067.
378. Lieu, F., S. K. Powers, R. A. Herb, D. Criswell, D. Martin, C. Wood, W. Stainsby, and C.-L. Chen. 1993. Exercise and glucocorticoid-induced diaphragmatic myopathy. *J. Appl. Physiol.* 75:763–771.
379. Rannels, S. R., D. E. Rannels, A. E. Pegg, and L. S. Jefferson. 1978. Glucocorticoid effects on peptide-chain initiation in skeletal muscle and heart. *Am. J. Physiol.* 235:E134–E139.
380. Mayer, M., and F. Rosen. 1977. Interaction of glucocorticoids and androgens with skeletal muscle. *Metabolism* 26:937–962.
381. Smith, B. 1964. Histological and histochemical changes in the muscles of rabbits given the corticosteroid triamcinolone. *Neurology* 14:857–863.
382. Shoji, S., A. Takagi, H. Sugita, and Y. Toyokura. 1974. Muscle glycogen metabolism in steroid-induced myopathy of rabbits. *Exp. Neurol. 45:* 1-7.
383. Ferguson, G. T., C. G. Irvin, and R. M. Cherniack. 1990. Effects of corticosteroids on diaphragm function and biochemistry in the rabbit. *Am. Rev. Respir. Dis.* 141:156–163.
384. Fernandez-Sola, J., R. Cusso, C. Picado, M. Vernet, J. M. Grau, and A. Urbanomarquez. 1993. Patients with chronic glucocorticoid treatment develop changes in muscle glycogen metabolism. *J. Neurol. Sci.* 117:103–106.
385. Vignos, P. J., and R. Greene. 1973. Oxidative respiration of skeletal muscle in experimental eorticosteroid myopathy. *J. Lab. Clin. Med.* 81:365–378.
386. van Balkom, R. H. H., H. F. M. van der Heijden, H. T. B. van Moerkerk, J. H. Veerkamp, J. A. M. Fransen, L. A. Gmsel, H. Th. M. Folgering, C. L. A. van Herwaarden, and R. N. R. Dekhuijzen. 1996. Effects of different treatment regimens of methylprednisolone on rat diaphragm contractility, immunohistochemistty and biochemistry. *Eur. Respir. J.* 9:1217–1223.
387. Lewis, M. I., S. A. Monn, and G. C. Sieck. 1992. Effect of corticosteroids on diaphragm fatigue, SDH activity, and muscle fiber size. *J. Appl. Physiol.* 72:293–301.
388. Dekhuijzen, P. N. R., G. Gayan-Ramirez, V. de Bock, R. Dom, and M. Decramer. 1993. Triamcinolone and prednisolone affect contractile properties and histopathology of rat diaphragm differently. *J. Clin. Invest.* 92:1534–1542.
389. Wasserman, K., D. Y. Sue, R. Casaburi, and R. B. Moricca. 1989. Selection criteria for exercise training in pulmonary rehabilitation. *Eur. Respir. J. Suppl.* 7:604s–610s.
390. Grove, A., B. J. Lipworth, P. Reid, R. P. Smith, C. G. Ingram, R. J. Jenkins, J. H. Winter, and D. P. Dhillon. 1996. Effects of regular salmeterol on lung function and exercise capacity in patients with chronic obstructive pulmonary disease. *Thorax* 51:689–693.
391. Low, D. E., E. P. Trulock, L. R. Kaiser, M. K. Pasque, C. Dresler, N. Ettinger, and J. D. Cooper. 1992. Morbidity, mortality, and early results of single versus bilateral lung transplantation for emphysema. *J. Thorac Cardiovasc. Surg.* 103:1119–1126.
392. Killian, K. J., P. Leblanc, D. H. Martin, E. Summers, N. L. Jones, and E. J. M. Campbell. 1992. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. *Am. Rev. Respir. Dis.* 146:935–940.
393. Troosters, T., R. Gosselink, H. Rollier, and M. Decramer. 19%. Change in lower limb muscle strength contributes to altered six minute walking distance in COPD. *Eur. Respir. J.* 9:144s.
394. Simpson, K., K. J. Killian, N. McCartney, D. G. Stubbing, and N. L. Jones. 1992. Randomised controlled trial of weightlifting exercise in

patients with chronic airflow limitation. *Thorax* 47:70–75.
395. Schols, A. M. W. J., R. Mostert, P. B. Soeters, and E. F. M. Wouters. 1991. Body composition and exercise performance in patients with chronic obstructive pulmonary disease. *Thorax* 46:695–699.
396. Baarends, E. M., A. M. W. J. Schols, R. Mostert, and E. F. M. Wouters. 1997. Peak exercise in relation to tissue depletion in patients with chronic obstructive pulmonary disease. *Eur. Respir. J.* 10:2807–2813.
397. Clark, C. J., J. E. Cochrane, and E. Mackay. 1996. Low intensity peripheral muscle conditioning improves exercise tolerance and breathlessness in COPD. *Eur. Respir. J.* 9:2590–2596.
398. Belman, M. J. 1986. Exercise in chronic obstructive pulmonary disease. *Clin. Chest Med.* 7:585–587.
399. Patessio, A., R. Casaburi, M. Carone, L. Appendini, C. F. Dormer, and K. Wasserman. 1993. Comparison of gas exchange, lactate, and lactic acidosis thresholds in patients with chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* 148622626.
400. Maltais, F., P. Leblanc, J. Jobin, C. Berube, J. Bruneau, L. Carrier, M. Breton, G. Falardeau, and R. Belleau. 1997. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 155:555–561.
401. Tangri, S., and C. R. Woolf. 1973. The breathing pattern in chronic obstructive lung disease during performance of some common daily activities. *Chest* 63:126–127.
402. Celli, B. R., J. Rassulo, and B. J. Make. 1986. Dyssynchronous breathing during arm but not leg exercise in patients with chronic airflow obstruction. N. *Engl. J. Med.* 314:1485–1490.
403. Banzett, R., G. Topulos, D. E. Leith, and C. Natios. 1983. Bracing arms increases the capacity for sustained hyperpnea. *Am. Rev. Respir. Db.* 133:106–109.
404. Toner, M. M., M. N. Sawka, L. Levine, and K. B. Pandolf. 1983. Cardiorespiratory responses to exercise distributed between upper and lower body. *J. Appl. Physiol.* 541403-1407.
405. Casaburi, R., T. J. Barstow, T. Robinson, and K. Wasserman. 1992. Dynamic and steady state ventilatory and gas exchange responses to arm exercise. *Med. Sci. Sports Exerc. 241365-1374.*
406. Gosselink, R., T. Troosters, and M. Decramer. 1998. Peripheral muscle weakness in upper and lower extremities in COPD patients. *Eur. Respir. J.* 12:345s.
407. Strauss, M. J., D. Conrad, J. P. Logerfo, L. D. Hudson, and M. Bergner. 1986. Cost and outcome of care for patients with chronic obstructive lung disease. Analysis by physician specialty. *Med. Care* 24:915–924.
408. Decramer, M., R. Gosselink, T. Troosters, M. Verschueren, and G. Evers. 1997. Muscle weakness is related to utilization of health care resources in COPD patients. *Eur. Respir. J.* 10:417–423.
409. Intermittent Positive Pressure Breathing Trial Group. 1983. Intermittent positive pressure breathing therapy of chronic obstructive pulmonary disease. *Ann. Intern. Med.* 99:612–620.
410. Decramer, M., R. Gosselink, T. Troosters, and R. Schepers. 1998. Peripheral muscle weakness is associated with reduced survival in COPD (abstract). *Am. J. Respir. Crit.* Care *Med.* 157:A19.
411. Howald, H., H. Hoppeler, H. Claassen, 0. Mathieu, and R. Straub. 1985. Influences of endurance training on the ultrastructural composition of the different muscle fiber types in human. *Pflügers Arch.* 403:369–376.
412. Simoneau, J. A., G. Lortie, M. R. Bonlay, C. M. Marcotte, M. C. Thibault, and C. Bouchard. 1985. Human skeletal muscle fibre type alteration with high-intensity intermittent training. *Eur. J. Appl. Physiol.* 54:250–253.
413. Baumann, H., M. Jäggi, F. Soland, H. Howald, and M. C. Schaub. 1987. Exercise training induces transitions of myosin isoform subunits within histochemically typed human muscle fibers. *Pflügers Arch.* 409:349–360.
414. Holloszy, J. O., and E. F. Coyle. 1984. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *J. Appl. Physiol.* 56:831–838.
415. Rogers, M. A., and W. J. Evans. 1993. Changes in skeletal muscle with aging: effects of exercise training. In J. 0. Holloszy, editor. Exercise and Sports Sciences Reviews. Williams and Wilkins, Philadelphia. 65–102.
416. Andersen, P., and J. Henriksson. 1977. Training induced changes in the subgroups of human type II skeletal muscle fibers. *Acta Physiol. Scand.* 99123-125.
417. Holloszy, J. 0. 1975. Adaptation of skeletal muscle to endurance exercise. *Med. Sci. Sports* 7:155–164.
418. Saltin, B., J. Henriksson, E. Nygaard, P. Anderson, and E. Jansson. 1977. Fiber types and metabolic potentials of skeletal muscles in sedentary man and endurance runners. *Ann. N.Y. Acad. Sci.* 301:3–29.
419. Pattengale, P. K., and J. 0. Holloszy. 1967. Augmentation of skeletal muscle myoglobin by a program of treadmill running. *Am. J. Physiol.* 213:783–785.
420. Holloszy, J. 0. 1967. Effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. *J. Biol. Chem.* 242:2278–2282.
421. Favier, R. J., S. H. Constable, M. Chen, and J. 0. Holloszy. 1986. Endurance exercise training reduces lactate production. *J. Appl. Physiol.* 61:885–889.
422. Casaburi, R., T. W. Storer, I. Ben-Dov, and K. Wasserman. 1986. Effect of endurance training on possible determinants of $\dot{V}O_2$ during heavy exercise. *J. Appl. Physiol.* 62:199–207.
423. Ivy, J. L., R. T. Withers, P. J. Van Handel, D. H. Elger, and D. L. Costill. 1980. Muscle respiratory capacity and fiber type as determinants of the lactate threshold. *J. Appl. Physiol.* 48:523–527.
424. Sullivan, M. J., H. J. Green, and F. R. Cobb. 1991. Altered skeletal muscle metabolic response to exercise in chronic heart failure: relation to skeletal muscle aerobic enzyme activity. *Circulation* 84:1597–1607.
425. Adams, G. R., B. M. Hather, K. M. Baldwin, and G. A. Dudley. 1993. Skeletal muscle myosin heavy chain composition and resistance training. *J. Appl. Physiol.* 74:911–915.
426. Frontera, W. R., C. N. Meredith, K. P. O'Reilly, H. G. Knuttgen, and W. J. Evans. 1988. Strength conditioning in older men: skeletal muscle hypertrophy and improved function. *J. Appl. Physiol.* 64:1038–1044.
427. Casaburi, R. 1994. Physiologic responses to training. *Clin. Chest Med.* 15:215–227.
428. American College of Sports Medicine. 1990. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness in healthy adults. *Med. Sci. Sports Exerc.* 22:265–274.
429. Casaburi, R., T. W. Storer, C. S. Sullivan, and K. Wasserman. 1995. Evaluation of blood lactate elevation as an intensity criterion for exercise training. *Med. Sci. Sports Exerc.* 27:852–862.
430. O'Donnell, D. E., M. McGuire, L. Samis, and K. A. Webb. 1995. The impact of exercise reconditioning on breathlessness in severe chronic airflow limitation. *Am. J. Respir. Crit. Care Med.* 152:2005–2013.
431. Goldstein, R. S., E. H. Gort, D. Stubbing, M. A. Avendano, and G. H. Guyatt. 1994. Randomised controlled trial of respiratory rehabilitation. *Lancer* 344:1394–1397.
432. Cockcroft, A. E., M. J. Saunders, and G. Berry. 1981. Randomised controlled trial of rehabilitation in chronic respiratory disability. *Thorax* 36:200–203.
433. Sinclair, J. M., and C. G. Ingram. 1980. Controlled trial of supervised exercise training in chronic bronchitis. *Br. Med. J.* 1:519–521.
434. Belman, M. J. 1993. Exercise in patients with chronic obstructive pulmonary disease. *Thorax* 48:936–946.
435. Belman, M. J., and B. A. Kendregan. 1981. Exercise training fails to increase skeletal muscle enzymes in patients with chronic obstructive lung disease. *Am. Rev. Respir. Dis.* 123:256–261.
436. Serres, I., A. Varray, G. Vallet, J. P. Micallef, and C. Préfaut. 1997. Improved skeletal muscle performance after individualized exercise training in patients with chronic obstructive pulmonary disease. *J. Cardpulm. Rehabil.* 17:232–238.
437. Casaburi, R., J. Porszasz, M. R. Burns, E. Carithers, R. S. Y. Chang, and C. B. Cooper. 1997. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am. J. Respir. Crit.* Care *Med.* 155:1541–1551.
438. Mohsenifar, Z., D. Horak, H. V. Brown, and S. K. Koemer. 1983. Sensitive indices of improvement in a pulmonary rehabilitation program. *Chest* 83:189–192.
439. Vallet, G., S. Ahmaïdi, I. Serres, C. Fabre, D. Bourgoin, J. Desplan, A. Varray, and C. Préfaut. 1997. Comparison of two training programmes in chronic airway limitation patients: standardized versus individualized protocols. *Eur. Respir. J.* 10:114–122.
440. Haber, P. 1981. Exercise training fails to increase skeletal muscle enzymes in patients with chronic obstructive pulmonary disease (letter). *Am. Rev. Respir. Dis.* 124:347–348.
441. Casaburi, R. 1998. Special considerations for exercise training in chronic lung disease. *In* ACSM's Resource Manual for Guidelines for Exercise Training and Prescription, 3rd ed. Williams and Wilkins, Baltimore, MD. 334-338.
442. Celli, B., F. Martinez, J. Couser, and J. Rassulo. 1990. Factors determining the pattern of ventilatory muscle recruitment (VMR) in patients with chronic obstructive pulmonary disease (COPD). *Chest* 97:68S.

443. Celli, B., G. Criner, and J. Rassulo. 1988. Ventilatory muscle recruitment during unsupported arm exercise in normal subjects. *J. Appl. Physiol.* 64:1936–1941.

444. Martinez, F. J., J. I. Couser, and B. R. Celli. 1991. Respiratory response to arm elevation in patients with chronic airflow obstruction. *Am. Rev. Respir. Dis.* 143:476–480.

445. Martinez, F. J., P. D. Vogel, D. N. Dupont, I. Stanopoulos, A. Gray, and J. F. Beamis. 1993. Supported arm exercise vs unsupported arm exercise in the rehabilation of patients with severe chronic airflow obstruction. *Chest* 103:1397–1402.

446. Lake, F. R., K. Henderson, T. Briffa, J. Openshaw, and A. W. Musk. 1990. Upper-limb and lower-limb exercise training in patients with chronic airflow obstruction. *Chest* 97:1077–1082.

447. Casaburi, R. 1995. Mechanisms of the reduced ventilatory requirement as a result of exercise training. *Eur. Respir. Rev.* 5:42–46.

448. Mainwood, G. W., and J. M. Renaud. 1985. The effect of acid-base balance on fatigue of skeletal muscle. *Can. J. Physiol. Pharmacol. 63:* 403–416.

449. Hultman, E., S. Carale, and H. Sjoholm. 1985. Effect of induced metabolic acidosis on intracellular pH, buffer capacity and contraction force of human skeletal muscle. *Clin. Sci.* 69:505–510.

450. Cotes, J. E., and J. C. Gilson. 1956. Effect of oxygen on exercise ability in chronic respiratory insufficiency. *Lancet* 1:872–876.

451. Vyas, M. N., E. W. Banister, J. W. Morton, and S. Grzybowski. 1971. Response to exercise in patients with chronic airway obstruction: II. Effects of breathing 40 percent oxygen. *Am. Rev. Respir. Dis.* 103: 401–412.

452. Leggett, R. J. E., and D. C. Flenley. 1977. Portable oxygen and exercise tolerance in patients with chronic hypoxic cor pulmonale. *Br. Med. J.* 2:84–86.

453. Bradley, B. L., A. E. Garner, D. Billiu, J. M. Mestas, and J. Forman. 1978. Oxygen-assisted exercise in chronic obstructive lung disease. *Am. Rev. Respir. Dis.* 118:239–243.

454. Scano, G., A. Van Meerhaeghe, R. Willeput, J. P. Vachaudez, and R. Sergysels. 1982. Effect of oxygen on breathing during exercise in patients with chronic obstructive lung disease. *Eur. J. Respir. Dis. 63:* 23–30.

455. Stein, D. A., B. L. Bradley, and W. C. Miller. 1982. Mechanisms of oxygen effects on exercise in patients with chronic obstructive pulmonary disease. *Chest* 81:6–10.

456. Bye, P. T. P., S. A. Esau, R. D. Levy, R. J. Shiner, P. T. Macklem, J. G. Martin, and R. L. Pardy. 1985. Ventilatory muscle function during exercise in air and oxygen in patients with chronic air-flow limitation. *Am. Rev. Respir. Dis.* 132:236–240.

457. Timms, R. M., F. U., Khaja, G. W. Williams, and The Nocturnal Oxygen Therapy Trial Group. 1985. Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. *Ann. Intern. Med.* 102:29–36.

458. Morrison, D. A., and J. R. Stovall. 1992. Increased exercise capacity in hypoxemia patients after long-term oxygen therapy. *Chest 102:542–* 550.

459. Coniveau, M. L., B. J. Rosen, and G. F. Dolan. 1989. Oxygen transport and oxygen consumption during supplemental oxygen administration in patients with chronic obstructive pulmonary disease. *Am. J. Med.* 87:633–637.

460. Connett, R. J., T. E. J. Gayeski, and C. R. Honig. 1984. Lactate accumulation in fully aerobic, working, dog gracilis muscle. *Am. J. Physiol* 246:H120–H128.

461. Chance, B. 196.5. Reaction of oxygen with the respiratory chain in cells and tissues. *J. Gen. Physiol.* 49:163–168.

462. Katz, A., and K. Sahlin. 1988. Regulation of lactic acid production during exercise. *J. Appl. Physiol.* 65:509–518.

463. Wilson, D. F., M. Erencinska, C. Drown, and I. A. Silver. 1977. Effect of oxygen tension on cellular energetics. *Am. J. Physiol.* 233:C135–C140.

464. Gutierrez, G., R. J. Pohil, J. M. Andry, R. Strong, and P. Narayana. 1988. Bioenergetics of rabbit skeletal muscle during hypoxemia and ischemia. *J. Appl. Physiol.* 65:608–616.

465. Idstrom, J.-P., V. H. Subramanian, B. Chance, T. Schersten, and A.-C. Bylund-Fellenius. 1985. Oxygen dependence of energy metabolism in contracting and recovering rat skeletal muscle. *Am. J. Physiol.* 248:H40–H48.

466. Jakobsson, P., and L. Jorfeldt. 1995. Long-term oxygen therapy may improve skeletal muscle metabolism in advanced chronic obstructive pulmonary disease patients with chronic hypoxaemia. *Respir. Med.* 89:471–476.

467. Saltin, B., G. Blomqvist, J. H. Mitchell, R. L. Johnson, Jr., K. Wildenthal, and C. B. Chapman. 1968. Response to exercise after bed rest and after training. A longitudinal study of adaptive changes in oxygen transport and body composition. *Circulation* 38(Suppl. VII): 1–78.

468. Henriksson, J., and J. S. Reitman. 1977. Time course of changes in human skeletal muscle succinate dehydrogenase and cytochrome oxidase activities and maximal oxygen uptake with physical activity and inactivity. *Acta Physiol. Scand.* 99:91–97.

469. Chi, M. M.-Y., C. S. Hintz, E. F. Coyle, W. H. Martin, III, J. L. Ivy, P. M. Nemeth, J. 0. Holloszy, and 0. H. Lowry. 1983. Effects of detraining on enzymes of energy metabolism in individual human muscle fibers. *Am. J. Physiol.* 244:C276–C287.

470. Jansson, E., C. Sylven, I. Arvidsson, and E. Eriksson. 1988. Increase in myoglobin content and decrease in oxidative enzyme activities by leg muscle immobilization in man. *Acta Physiol. Scand.* 132:515–517.

471. Hurme, T., M. Lehto, H. Kalimo, P. Kannus, and M. Jarvinen. 1990. Sequence of changes in fibre size and type in muscle immobilized at various lengths. *J. Sports Traumatol.* 2:77–85.

472. Rooyackers, J. M., P. N. R. Dekhuijzen, C. L. A. Van Herwaarden, and H. T. M. Folgering. 1997. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. *Eur. Respir. J.* 10:1278–1284.

473. Donahoe, M., R. M. Rogers, and J. J. Cottrell. 1992. Is loss of body weight in chronic obstructive pulmonary disease patients with emphysema secondary to low tissue oxygenation? *Respiration* 24(Suppl. 2):33–39.

474. Leggett, R. J., N. J. Cooke, L. Clancy, A. G. Leitch, B. J. Kirby, and D. C. Flenley. 1976. Long-term domiciliary oxygen therapy in cor pulmonale complicating chronic bronchitis and emphysema. *Thorax* 31:414–418.

475. Kaijser, L., C. J. Sundberg, 0. Eiken, A. Nygren, M. Esbjornsson, C. Sylven, and E. Jansson. 1990. Muscle oxidative capacity and work performance after training under local leg ischemia. *J. Appl. Physiol.* 69:785–787.

476. Wilson, D. O., R. M. Rogers, E. Wright, and N. R. Anthonisen. 1967. Body weight in chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* 95:556–566.

477. Gray-Donald, K., L. Gibbons, S. H. Shapiro, P. T. Macklem, and J. G. Martin. 1996. Nutritional status and mortality in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 153:961–966.

478. Shoup, R., G. Dalsky, G. Warner, H. Davies, M. Connors, M. Khan, F. Khan, and R. Zuwallack. 1997. Body composition and health related quality of life in patients with chronic obstructive airways disease. *Eur. Respir. J.* 10:1576–1580.

479. Whittaker, J. S., C. F. Ryan, P. A. Buckley, and J. D. Road. 1990. The effects of refeeding on peripheral and respiratory muscle function in malnourished chronic obstructive pulmonary disease patients. *Am. Rev. Respir. Dis.* 142:283–288.

480. Goldstein, S. A., B. M. Thomashow, V. Kvetan, J. Askanazi, J. M. Kinney, and D. H. Elwyn. 1988. Nitrogen and energy relationships in malnourished patients with emphysema. *Am. Rev. Respir. Db. 138:* 636644.

481. Rogers, R. M., M. Donahoe, and J. P. Costantino. 1992. Physiologic effects of oral supplemental feeding in malnourished patients with chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* 146: 1511-1517.

482. Efthimiou, J., J. Fleming, C. Gomes, and S. G. Spiro. 1988. The effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis. 137:* 1075–1082.

483. Sridhar, M. K., A. Gallaway, M. E. Lean, and S. W. Banham. 1994. An out-patient nutritional supplementation programme in COPD patients. *Eur. Respir. J.* 7:720–724.

484. Baarends, E. M., A. M. W. J. Schols, D. L. E. Pannemans, K. R. Westerterp, and E. F. M. Wouters. 1997. Total free living energy expenditure in severe chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 155:549–554.

485. Rochester, D. F. 1992. Nutritional repletion. *Semin. Respir. Med.* 13: 44-52.

486. Donahoe, M., J. Mancino, J. Constatino, H. Lebow, and R. M. Rogers. 1994. The effect of an aggressive nutritional support regimen on body composition in patients with severe COPD and weight loss (abstract). *Am. J. Respir. Crit. Care Med.* 149:A313.

487. Morrison, W. L., J. N. A. Gibson, C. Scrimgour, and M. J. Rennie. 1988. Muscle wasting in emphysema. *Clin. Sci.* 75:415–420.

488. Schols, A. M. W. J., P. B. Soeters, R. Mostert, R. J. Pluymers, and E. F. M. Wouters. 1995. Physiologic effects of nutritional support

and anabolic steroids in patients with chronic obstructive pulmonary disease: a placebo controlled randomized trial. *Am. J. Respir. Crit. Care Med.* 152:1268–1274.

489. Schols, A. M. W. J., J. Slangen, A. Volovics, and E. F. M. Wouters. 1998. Weight loss is a reversible factor in the prognosis of COPD. *Am. J. Respir. Crit. Care Med.* 157:1791–1797.
490. Schols, A. M. W. J., W. A. Buurman, A. J. Staal-van den Brekel, M. A. Dentener, and E. F. M. Wouters. 1996. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax* 51:819–824.
491. Editors of Nutrition Reviews. 1991. A short course of intravenous nutrition in inflammatory bowel disease improves respiratory and skeletal muscle function. *Nutr. Rev.* 49:317–319.
492. Sara, V. R., and K. Hall. 1990. Insulin-like growth factors and their binding proteins. Physiol. *Rev.* 70:591–614.
493. LeRoith, D., M. Adama, H. Werner, and C. T. Roberts. 1991. Insulin-like growth factors and their receptors as growth regulators in normal physiology and pathologic states. *Trends Endocrinol. Metab.* 2X134-139.
494. Adams, G. R., and F. Haddad. 1996. The relationships among IGF-1, DNA content, and protein accumulation during skeletal muscle hypertrophy. *J. Appl. Physiol.* 81:2509–2516.
495. Tanner, J. M., P. C. R. Hughes, and R. H. Whitehourse. 1977. Comparative rapidity of response of height, limb muscle and limb fat to treatment with human growth hormone in patients with and without growth hormone deficiency. *Acta Endocrinol.* 84:681–696.
496. Cuneo, R. C., F. Salomon, C. M. Wiles, R. Hesp, and P. H. Sonksen. 1991. Growth hormone treatment in growth hormone-deficient adults: I. Effects on muscle mass and strength. *J. Appl. Physiol.* 70: 688-694.
497. Rudman, D., A. G. Feller, L. Cohn, K. R. Shetty, I. W. Rudman, and M. W. Draper. 1991. Effects of human growth hormone on body composition in elderly men. *Horm. Res.* 36:73–81.
498. Nass, R., R. M. Huber, V. Klauss, 0. A. Muller, J. Schopohl, and C. J. Strasburger. 1995. Effect of growth hormone (hGH) replacement therapy on physical work capacity and cardiac and pulmonary function in patients with hGH deficiency acquired in adulthood. *J. Clin. Endocrinol. Metab.* 80:552–557.
499. Baum, H. B. A., B. M. K. Biller, J. S. Finkelstein, K. B. Cannistraro, D. S. Oppenheim, D. A. Schoenfeld, T. H. Michel, H. Wittink, and A. Klibanski. 1996. Effects of physiologic growth hormone therapy on bone density and body composition in patients with adult-onset growth hormone deficiency. *Ann. Intern. Med.* 125:883–890.
500. Jorgensen, J. 0. L., L. Thuesen, T. Ingemann-Hansen, S. A. Pedersen, J. Jorgensen, N. E. Skakkebaek, and J. S. Christiansen. 1989. Beneficial effects of growth hormone treatment in GH-deficient adults. *Lancet* 1:1221–1225.
501. Salomon, F., R. C. Cuneo, R. Hesp, and P. H. Sonksen. 1989. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N. Engl. J. Med.* 321:1797–1803.
502. Cuneo, R. C., F. Salomon, C. M. Wiles, R. Hesp, and P. H. Sonksen. 1991. Growth hormone treatment in growth hormone-deficient adults: II. Effects on exercise performance. *J. Appl. Physiol.* 70:695–700.
503. Crist, D. M., G. T. Peake, P. A. Egan, and D. H. Waters. 1988. Body composition response to exogenous GH during training in highly conditioned adults. *J. Appl. Physiol.* 65:579–584.
504. Yaraskeski, K. E., J. A. Campbell, K. Smith, M. J. Rennie, J. 0. Holloszy, and D. M. Bier. 1992. Effect of growth hormone and resistance exercise on muscle growth in young men. *Am. J. Physiol.* 262:E261–E267.
505. Binnerts, A., J. H. P. Wilson, and S. W. J. Lamberts. 1988. The effects of human growth hormone administration in elderly adults with recent weight loss. *J. Clin. Endocrinol. Metab.* 67:1312–1316.
506. Kaiser, F. E., A. J. Silver, and J. E. Morley. 1991. The effect of recombinant human growth hormone on malnourished older individuals. *J. Am. Geriatr. Soc.* 39:235–240.
507. Marcus, R., G. Butterfield, L. Holloway, L. Gilliland, D. J. Baylink, R. L. Hintz, and B. M. Sherman. 1990. Effects of short term administration of recombinant human growth hormone to elderly people. *J. Clin. Endocrinol. Metab.* 70:519–527.
508. Taaffe, D. R., L. Pruitt, J. Reim, R. L. Hintz, G. Butterfield, A. R. Hoffman, and R. Marcus. 1994. Effect of recombinant human growth hormone *on* the muscle strength response to resistance exercise in elderly men. *J. Clin. Endocrinol. Metab.* 79:1361–1366.
509. Papadakis, M. A., D. Grady, D. Black, M. J. Tiemey, G. A. W. Gooding, M. Schambelan, and C. Grunfeld. 1996. Growth hormone replacement in healthy older men improves body composition but not functional ability. *Ann. Intern. Med.* 124:708–716.
510. Rudman, D., A. G. Feller, H. S. Nagraj, G. A. Gergaums, P. Y. Lalitha, A. F. Goldberg, R. A. Schlenker, L. Cohn, I. W. Rudman, and D. E. Matson. 1990. Effects of human growth hormone in men over 60 years old. *N. Engl. J. Med.* 323:1–6.
511. Schambelan, M., K. Mulligan, C. Grunfeld, E. S. Daar, A. LaMarca, D. P. Kotler, J. Wang, S. A. Bozzette, J. B. Breitmeyer, and the Serostim Study Group. 1996. Recombinant human growth hormone in patients with HIV-associated wasting. *Ann. Intern. Med.* 125:873-882.
512. Waters, D., J. Danska, K. Hardy, F. Koster, C. Qualls, D. Nickell, S. Nightingale, N. Gesundheit, D. Watson, and D. Schade. 1996. Recombinant human growth hormone, insulin-like growth factor 1, and combination therapy in AIDS-associated wasting. *Ann. Intern. Med.* 125:865–872.
513. Suchner, U., M. M. Rothkopf, G. Stanislaus, D. H. Elwyn, V. Kvetan, and J. Askanazi. 1990. Growth hormone and pulmonary disease. *Arch. Intern. Med.* 150:1225–1230.
514. Pichard, C., U. Kyle, J. C. Chevrolet, P. Jolliet, D. Slosman, N. Mensi, E. Temler, and B. Ricou. 1996. Lack of effects of recombinant growth hormone on muscle function in patients requiring prolonged mechanical ventilation: a prospective, randomized, controlled study. *Crit. Care Med.* 24403413.
515. Pape, G. S., M. Friedman, L. E. Underwood, and D. R. Clemmons. 1991. The effect of growth hormone on weight gain and pulmonary function in patients with chronic obstructive lung disease. *Chest 99:* 1495–1500.
516. Burdet, L., B. deMuralt, Y. Schutz, C. Pichard, and J.-W. Fitting. 1997. Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 156:1800–1806.
517. Rudman, D., and K. R. Shetty. 1994. Unanswered questions concerning the treatment of hyposomatotropism and hypogonadism in elderly men. *J. Am. Geriatr. Soc.* 42:522–527.
518. Borst, S. E., W. J. Millard, and D. T. Lowenthal. 1994. Growth hormone, exercise, and aging: the future of therapy for the frail elderly. *J. Am. Geriatr. Soc.* 42:528–535.
519. Mantzoros, C. S., and A. L. Moses. 1996. Whither recombinant human growth hormone? *Ann. Intern. Med.* 125:932–934.
520. Kenyon, A. T., K. Knowlton, I. Sandiford, F. C. Koch, and G. Lotwin. 1940. A comparative study of the metabolic effects of testosterone propionate in normal men and women and in eunuchoidism. *Endocrinology* 26:26–45.
521. Bhasin, S., T. W. Storer, N. Berman, K. E. Yarasheski, B. Clevenger, J. Phillips, W. P. Lee, T. Bunnell, and R. Casaburi. 1997. Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. *J. Clin. Endocrinol. Metab.* 82:407–413.
522. Sih, R., J. E. Morley, F. E. Kaiser, H. M. Perry, P. Patrick, and C. Ross. 1997. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J. Clin. Endocrinol.* 82:1661–1667.
523. Casaburi, R., T. Storer, and S. Bhasin. 1996. Testosterone effects on body composition and muscle performance. *In* S. Bhasin, H. Gabelnick, J. Spieler, R. D. Swerdloff, and C. Wang, editors. Androgens: Biology, Pharmacology and Clinical Applications. Wiley Liss, New York. 283-288.
524. Elashoff, J. D., A. D. Jacknow, S. G. Shain, and G. D. Braunstein. 1991. Effects of anabolic-androgenic steroids on muscular strength. *Ann. Intern. Med.* 115:387–393.
525. Bhasin, S., T. W. Storer, N. Berman, C. Callegari, B. Clevenger, J. Phillips, T. J. Bunnell, L. Tricker, and R. Casaburi. 1996. The effects of supraphysiological doses of testosterone on muscle size and strength in normal men. *N. Engl. J. Med.* 335:1–7.
526. Tenover, J. S. 1992. Effects of testosterone supplementation in the aging male. *J. Clin. Endocrinol. Metab.* 75:1092–1098.
527. Tenover, J. S. 1994. Androgen administration to aging men. *Endocrinol. Metab. Clin. North Am.* 23:877–892.
528. Bagatell, C. J., and W. J. Bremner. 1996. Adrogens in men: uses and abuses. *N. Engl. J. Med.* 334:707–714.
529. Ferreira, I. M., I. T. Verreschi, L. E. Nery, R. S. Goldstein, N. Zamel, D. Brooks, and J. R. Jardim. 1998. The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. *Chest* 114:19–28.
530. Choo, J. J., M. A. Horan, R. A. Little, and N. J. Rothwell. 1992. Anabolic effects of clenbuterol on skeletal muscle are mediated by β_2-

adrenoceptor activation. *Am. J. Physiol.* 263:E50–E56.
531. Zeman, R. J., R. Ludeman, T. G. Easton, and J. D. Etlinger. 1988. Slow to fast alterations in skeletal muscle fibres caused by clenbuterol, a B-receptor agonist. *Am. J. Physiol.* 254:E726–E732.
532. Moore, N. G., G. P. Pegg, and M. N. Sillence. 1994. Anabolic effects of the β_2-adrenoceptor agonist salmeterol are dependent on route of administration. *Am. J. Physiol.* 267:E475–E484.
533. Meeuwisse, W. H., D. C. McKenzie, S. R. Hopkins, and J. D. Road. 1992. The effect of salbutamol on performance in elite non-asthmatic athletes. *Med. Sci. Sports Exer.* 241161-1166.
534. Martineau, L., M. A. Horan, N. J. Rothwell, and R. A. Little. 1992. Salbutamol, a β-adrenoceptor agonist, increases muscle strength in young men. *Clin. Sci.* 83:615–621.
535. Maltin, C. A., M. I. Delday, J. S. Watson, S. D. Heys, I. M. Nevison, I. K. Ritchie, and P. H. Gibson. 1993. Clenbuterol, a β-adrenoceptor agonist, increases relative muscle strength in orthopaedic patients. *Clin. Sci.* 84:651–654.
536. Congleton, J., and M. F. Muers. 1998. Effect of regular use of high-dose nebulized β_2-agonists on resting energy expenditure, weight and handgrip strength in patients with chronic airflow limitation. *Chest* 113:1588–1594.
537. Breen, E. C., E. C. Johnson, H. Wagner, H. M. Tseng, L. A. Sung, and P. D. Wagner. 1996. Angiogenic growth factor mRNA responses in muscle to a single bout of exercise. *J. Appl. Physiol.* 81:355–361.
538. McPherron, A. C., A. M. Lawler, and S. J. Lee. 1997. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. *Nature* 387:83–90.
539. McPherron, A. C., and S. J. Lee. 1997. Double muscling in cattle due to mutations in the myostatin gene. *Proc. Natl. Acad. Sci. U.S.A.* 94: 12457-12461.
540. Kambadur, R., M. Sharma, T. P. L. Smith, and J. J. Bass. 1997. Mutations in myostatin (GDF8) in double-muscled Belgian blue and Piedmontese cattle. *Genome Res.* 7:910–916.
541. Reitz, B. A., J. W. Wallwork, S. A. Hunt, J. L. Pennock, M. E. Billingham, P. Oyer, E. B. Stinson, and N. E. Shumway. 1982. Heart lung transplantation: successful therapy for patients with pulmonary vascular disease. N. *Engl. J. Med.* 306:557–564.
542. Toronto Lung Transplant Group. 1986. Unilateral lung transplantation for pulmonary fibrosis. N. *Engl. J. Med.* 314:1140–1145.
543. Pasque, M. K., J. D. Cooper, L. R. Kaiser, D. A. Haydock, A. Triantafillou, and E. P. Trulock. 1990. Improved technique for bilateral lung transplantation: rationale and initial clinical experience. *Ann. Thorac. Surg.* 49:785–791.
544. Barr, M. L., F. A. Schenkel, R. G. Cohen, K. M. Chan, R. G. Barbers, C. C. Marboe, and V. A. Stames. 1995. Living-related lobar transplantation: recipient outcome and early rejection patterns. *Transplant. Proc.* 27:1995–1996.
545. Williams, T. J., R. F. Grossman, and J. R. Maurer. 1990. Long-term functional follow-up of lung transplant recipients. *Clin. Chest Med.* 11:347–358.
546. Theodore, J., A. T. Morris, C. M. Burke, A. R. Glanville, A. VanKessel, and J. C. Baldwin. 1987. Cardiopulmonary function at maximum tolerable work rate following human heart-lung transplantation. *Chest* 92:433–439.
547. Levy, R. D., P. Ernst, S. M. Levine, H. Shennib, A. Anzueto, C. L. Bryant, J. H. Calhoon, J. K. Trinkle, S. G. Jenkinson, and W. J. Gibbons. 1993. Exercise performance after lung transplantation. *J. Heart Lung Transplant.* 12:23–33.
548. Miyoshi, S., E. P. Trulock, H.-J. Schaefers, C.-M. Hsieh, G. A. Patterson, and J. D. Cooper. 1990. Cardiopulmonary exercise testing after single and double lung transplantation. *Chest* 97:1130–1136.
549. Williams, T. J., G. A. Patterson, P. A. McClean, N. Zamel, and J. Maurer. 1992. Maximal exercise testing in single and double lung transplant recipients. *Am. Rev. Respir. Dis.* 145:101–105.
550. Williams, T. J., M. Howard, J. Roget, and D. S. Esmore. 1992. Exercise capacity after combined heart-lung transplantation. *Transplant. Proc.* 24:2018.
551. Nixon, P. A., F. J. Fricker, B. E. Noyes, S. A. Webber, D. M. Orenstein, and J. M. Armitage. 1995. Exercise testing in pediatric heart, heart-lung and lung transplant recipients. *Chest* 107:1328–1335.
552. Kimoff, R. J., T. H. Cheong, M. G. Cosio, A. Guerraty, and R. D. Levy. 1990. Pulmonary denervation in humans. *Am. Rev. Respir. Dis.* 142: 1034-1040.
553. Sciurba, F. C., G. R. Owens, M. H. Sanders, B. P. Griffiths, R. L. Hardesty, I. L. Paradis, and J. P. Costantino. 1988. Evidence of altered pattern of breathing during exercise in recipients of heart-lung transplants. N. *Engl. J. Med.* 319:1186–1192.
554. Gibbons, W. J., S. M. Levine, C. L. Bryan, J. Segarra, J. H. Calhoon, J. K. Trinkle, and S. G. Jenkinson. 1991. Cardiopulmonary exercise responses after single lung transplantation for severe obstructive lung disease. *Chest* 100:106–111.
555. Orens, J. B., F. S. Becker, J. P. Lynch, 3, P. J. Christensen, G. M. Deeb, and F. J. Martinez. 1995. Cardiopulmonary exercise testing following allogeneic lung transplantation for different underlying disease states. *Chest* 107:144–149.
556. Ross, D. J., P. F. Walters, Z. Mohenifar, M. J. Belman, R. M. Kass, and S. K. Koerner. 1993. Hemodynamic responses to exercise after lung transplantation. *Chest* 103:46–53.
557. Morton, J. M., E. A. Side, G. I. Snell, E. H. Walters, and T. J. Williams. 1997. Maximal oxygen uptake continues to improve beyond three years post lung transplantation (abstract). *Am. J. Respir. Crit. Care Med.* 155(4, Part 2):A382.
558. Stiebellehner, L., M. Quittan, A. End, M. Grimm, G. Wiesselthaler, W. Klepetko, P. Haber, and 0. C. Burghuber. 1998. Aerobic endurance training improves exercise performance in lung transplant recipients. *Chest* 113:906–912.
559. Martinez, F. J., J. B. Orens, R. I. Whyte, L. Graf, F. S. Becker, and J. P. Lynch, 3. 1996. Lung mechanics and dyspnea after lung transplantation for chronic airflow obstruction. *Am. J. Respir. Crit. Care Med.* 153:1536–1543.
560. Jensen, R. L., F. G. Yanowitz, and R. 0. Crapo. 1991. Exercise hemodynamics and oxygen delivery measurement in heart transplant patients. *Am. J. Cardiol.* 68:129–133.
561. Maurer, J. R., and S. Tewari. 1997. Nonpulmonary medical complications in the intermediate and long term survivor. *Clin. Chest Med.* 18:367–382.
562. Williams, T. J., X. N. Wang, M. F. Carey, M. J. McKenna, J. L. Li, S. F. Fraser, E. A. Side, G. I. Snell, and E. H. Walters. 1996. Low mitochondrial ATP production rate in human skeletal muscle post lung transplant (abstract). *Am. J. Respir. Crit. Care Med.* 153(4, Part 2): A828.
563. Li, J. L., M. J. McKenna, X. N. Wang, S. F. Fraser, M. F. Carey, E. A. Side, G. I. Snell, E. H. Walters, and T. J. Williams. 1996. Low skeletal muscle sarcoplasmic reticulum calcium release post lung transplant (abstract). *Am. J. Respir. Crit. Care Med.* 153(4, Part 2):A828.
564. Hall, M. J., G. I. Snell, E. A. Side, D. S. Esmore, E. H. Walters, and T. J. Williams. 1994. Exercise, potassium and muscle deconditioning post thoracic transplantation. *J. Appl. Physiol.* 77:2784–2790.
565. Williams, T. J., S. F. Fraser, M. J. McKenna, J. L. Li, X. N. Wang, M. F. Carey, E. A. Side, G. I. Snell, and E. H. Walters. 1996. Skeletal muscle sodium/potassium pump activity is normal post lung transplant (abstract). *Am. J. Respir. Crit. Care Med.* 153(4, Part 2):A828.
566. de Meer, K., J. A. L. Jeneson, V. A. M. Gulmans, J. van der Laag, and R. Berger. 1995. Efficiency of oxidative work performance of skeletal muscle in patients with cystic fibrosis. *Thorax* 50:980–983.
567. Hokanson, J. F., J. R. Mercier, and G. A. Brooks. 1995. Cyclosporin A decreases rat skeletal muscle mitochondrial respiration *in vitro*. *Am. J. Respir. Crit. Care Med.* 151:1848–1851.
568. Mercier, J. R., J. F. Hokanson, and G. A. Brooks. 1995. Effects of cyclosporin A on skeletal muscle mitochondrial respiration and endurance times in rats. *Am. J. Respir. Crit. Care Med.* 151:1848–1851.
569. Head, J. R., and E. E. Avery. 1949. Intra-cavitary suction (Monaldi) in the treatment of emphysematous bullae and blebs. *J. Thorac. Surg.* 18:761–776.
570. Cooper, J. D., E. P. Trulock, A. N. Triantafillou, G. A. Patterson, M. S. Pohl, P. A. Deloney, R. S. Sundaresan, and C. L. Roper. 1995. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. *J. Thorac. Cardiovasc. Surg.* 109:106–119.
571. Cooper, J. D., G. A. Patterson, R. S. Sundaresan, E. P. Trulock, R. D. Yusen, M. S. Pohl, and S. S. Lefrak. 1996. Results of 150 consecutive bilateral lung volume reduction procedures in patients with severe emphysema. *J. Thorac. Cardiovasc. Surg.* 112:1319–1330.
572. Benditt, J. O., S. Lewis, D. E. Wood, L. Kliia, and R. K. Albert. 1997. Lung volume reduction surgery improves maximal O_2 consumption, maximal minute ventilation, O_2 pulse, and dead space-to-tidal volume ratio during cycle ergometry. *Am. J. Respir. Crit. Care Med. 156:* 561-566.
573. Sciurba, F. C., R. M. Rodgers, R. J. Keenan, W. A. Slivka, J. E. Gorcsan, P. F. Ferson, M. Holbert, M. L. Brown, and R. J. Landreneau. 1996. Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. N. *Engl. J. Med. 334:* 1095-1099.
574. Benditt, J. O., D. E. Wood, F. D. McCool, S. Lewis, and R. K. Albert. 1997. Changes in breathing and ventilatory muscle recruitment pat-

terns induced by lung volume reduction surgery. *Am. J. Respir. Crit. Care Med.* 155:279–284.

575. **Bloch,** K. E., Y. Li, J. Zhang, R. Bigisser, V. Kaplan, W. Weder, and E. W. **Russi.** 1997. Effect of surgical lung volume reduction on breathing pattern in severe pulmonary emphysema. *Am. J. Respir. Crit. Care Med.* 156:553–560.

576. **Celli,** B. R., M. M. Deoca, R. Mendez, and J. Stetz. 1997. Lung volume reduction surgery in severe COPD decreases central drive and ventilatory response to CO_2. Chest 112:902–906.

577. Sciurba, F. C. 1997. Early and long-term outcomes following lung volume reduction surgery. *Clin. Chest Med.* 18:259–276.