The Primary Target of Nutritional Support: Body Composition or Muscle Function?

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In a 70-kg man, skeletal muscle accounts for 40–50% of the total body mass. A loss of the muscle mass due to the net breakdown of muscle proteins is a common feature of many acute and long-term illnesses. During the initial flow phase, patients with an acute critical illness (multiple trauma and sepsis) lose 1–2 kg muscle mass per day and up to half the muscle mass in periods of 1–2 weeks [1]. Many chronic diseases that impair the function of the lungs, liver, kidney and heart including cancer and AIDS (affecting multiple systems) are attended by a generally slower, gradual loss of muscle mass. A very slow, but in the end substantial, loss of muscle mass is also observed during aging (sarcopenia) [2]. The reduction in muscle mass in all these conditions is the major component of the reduction in lean body mass. Impairments are also seen in muscle function, with a reduction in strength and endurance capacity being most evident [2, 3]. This again limits the ability of the patients to walk and perform normal activities of daily living. In some of the chronic diseases, the reduction in muscle function forms a serious disability or even handicap that dramatically reduces their quality of life [3]. This limitation in physical performance and continuous subjective feelings of fatigue are experienced as the most distressing phenomenon of many acquired chronic diseases [3, 4]. In patients with multiple trauma and sepsis, the loss of muscle mass and functions leads to life-threatening complications (e.g. respiratory failure) and is a major cause of death [5].

In clinical nutrition practice, the traditional approach to try and combat excessive rates of muscle protein breakdown is to give the patient more
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energy (calories) or nutrition containing more protein (or amino acids). The assumption behind this strategy is that the primary cause of the reduction in muscle mass and the impairments in muscle function is to be sought in a nutritional deficiency or the reduced appetite of the patient. In some diseases this indeed forms (a minor) part of the problem. The traditional measure to follow the success of such nutritional interventions is an estimate of the body composition and the nitrogen balance method. A zero nitrogen balance is taken to indicate that, at the whole body level, no functional proteins are lost; a positive nitrogen balance or increase in lean body mass is taken to indicate that the patient is recovering and gaining muscle mass, strength and endurance again. However, we have to keep in mind that both methods are quantitative and do not provide information on the quality of the protein gains, which is the major determinant of organ functions.

Modern research approaches investigate adaptation at the molecular level in the muscle and have learned that not only the total amount of protein decreases during many of these diseases, but that there is also a major qualitative adaptation, which is in part common to all these acquired diseases and is in part specific. In this review, an overview will first be presented of the factors that control muscle mass, protein quality and muscle function in healthy subjects. This will be followed by an overview of the knowledge that we have today of the adaptations that occur in the muscles of patients and the consequences of the observed adaptations for muscle performance. These overviews will then lead to the conclusion that therapies that aim at restoring the muscle mass and at improving the physical ability of the patient in day-to-day life should be based on a better understanding of the disease-specific abnormalities that occur in muscle metabolism and physiology. The same conclusion holds for future attempts to define the optimal nutritional support that can be given to these patients during the various stages of their disease.

**Muscle Physiology in Healthy Subjects**

*Muscle Strength*

A muscle contraction is the final step in a command chain that extends from the higher centers of the central nervous system via the spinal cord and peripheral nerves to the muscle membrane [2]. Here an action potential is generated, which propagates into the sarcoplasmic reticulum, where calcium is released. The increase in cytosolic calcium leads to formation of cross-bridges between the thick protein filaments (myosin) and the thin actin filaments and leads to shortening of the myofibrils (the contractile elements of the myofibrils) and, therefore, a muscle contraction [2]. There are several potential reasons for a reduction in the ability of the muscle to generate force (strength) during acute and chronic diseases. The first is a substantial loss of the contractile proteins. The total content of actin and myosin determines
the number of myofibrils in the muscle fibers and the cross-sectional area of the fibers. A loss of actin and myosin will reduce the cross-sectional area of individual fibers and of the entire muscle and, as a consequence, the maximal force that can be produced by the muscle will be reduced, as it is proportional to the cross-sectional area [2]. A second potential reason for loss of contractility would be a reduction in the excitability of the muscle membrane (the ability to generate action potentials). The excitability of the muscle membrane depends on the resting membrane potential (RMP), which in turn depends on the distribution of electrolytes (potassium, sodium and chloride) across the membrane. A lower RMP will reduce the excitability [2]. A third potential reason would be changes in the composition of the myofibrils. Myofibrils not only consist of actin and myosin. There are many more proteins (e.g. titin, desmin, α-actinin, troponin, etc.) that play important roles in the spatial organization of the myofibrils and the mechanisms that lead to force production [2]. If disease processes lead to changes in the relative contribution of these protein constituents, then this also will have consequences for the maximal force production of the myofibrils.

**Muscle Endurance**

The most important aspect of muscle function in day-to-day life is not the maximal force that it can generate, but the ability to maintain the required power output (work rate) during repeated stimulations or prolonged exercise tasks. In muscle physiology this is called the endurance capacity. The endurance capacity is primarily determined by the number of mitochondria per unit mass of skeletal muscle [6]. A trained muscle contains 4- to 5-fold more mitochondria than the muscle from a healthy sedentary subject. The major advantage of the increased number of mitochondria is that the disturbance of the energy status will be smaller at a given absolute and relative (percent of maximum) work rate. A trained muscle is able to maintain higher concentrations of adenosine triphosphate (ATP) and creatine phosphate (CrP) and lower concentrations of adenosine monophosphate (AMP) and inorganic phosphate (Pi). This implies that fatigue, a critical fall in the energy status, which leads to failure to generate the work rate required for a specific task, can either be postponed or entirely be prevented. For the trained athlete, it means that he or she can run at a higher speed for a more prolonged period. In diseases or conditions in which the content of mitochondria decreases below a level, where the respiratory or posture muscles become fatigued, fatigue will have life-threatening consequences. A high mitochondrial content and smaller disturbances of the energy status also lead to lower rates of glycogen breakdown and glycolysis, as the enzymes involved in these processes are allosterically activated by increases in AMP and Pi during exercise [6]. Muscles with a low mitochondrial content, therefore, produce vast amounts of lactate and show a decrease in the muscle pH (an additional cause of fatigue) at very low work rates [7]. These metabolic factors again activate type-3 and
4 afferent nerve fibers in skeletal muscle, and via reflex mechanisms [for references see 6] this leads to increases in heart rate, arterial blood pressure, ventilation rate and the blood concentration of the catecholamines, which are all experienced as major increases in exercise stress. All patients with a low mitochondrial content, therefore, have major disadvantages and limitations in performing physical exercise.

Metabolic Consequences of Bed Rest and Long-Term Physical Inactivity

The adaptation of the muscle to bed rest at the molecular and metabolic level is fast and reversible. A 50% decrease in peripheral insulin-stimulated glucose utilization is already observed after as little as 72 hrs of bed rest [8]. A study by Saltin et al. [9] has shown that 20 days of bed rest leads to major changes in the cardiovascular response to exercise and a substantial reduction in the maximal blood flow through the exercising muscle. This period was too short though to lead to a significant decrease either in the muscle mass, capillary density or in the activity of a few mitochondrial enzymes [9]. However, patients with very low energy outputs in habitual activities due to physical limitations (neuromuscular diseases, tetraplegics), with several months of bed rest, and astronauts traveling through space in a weightless condition for several months generally have a substantial reduction both in muscle mass and in the density of the mitochondria in the muscle. Mitochondrial enzyme activities (reflection of the mitochondrial density) in these conditions may be as little as 10% of those in normal sedentary individuals [6, 7, 10]. Patients with chronic fatigue syndrome [4, 7, 11] also have such low mitochondrial contents and experience severe exercise disabilities. The symptoms that they report in day-to-day life (e.g. among others, dizziness, palpitations, muscular pains in the neck and shoulder region, orthostatic disturbances, subjective feelings of fatigue and weakness, headaches, tension and anxiety) occur in all subjects with extreme deconditioning and, therefore, have been suggested to be part of the physiology of people on the low end of the spectrum of physical activity [11].

The causes of the adaptations to bed rest and disuse seem to be the consequence of the lack of an adequate daily exercise stimulus. Many recent studies have shown that a disturbance in the cellular energy status (particularly increases in the AMP concentration [12]) and the recurrent increases in cytosolic Ca^{2+} during the contraction cycles [13] activate a number of regulatory pathways that lead to the increased expression of several so-called contraction-induced transcription factors. Some of these transcription factors control the expression of the mitochondrial oxidative enzymes and glucose transporter molecules, while others control fiber type or lead to muscle hypertrophy via an upregulation of the actin and myosin genes [12–17]. Such increases in the transcription rate and mRNA concentration of the relevant genes are most prominent in the first 4 hrs after exercise [16]. The time window with an increased transcription rate is likely to coincide with or be followed by a time window of increased translation (protein synthesis).
The insulin-like growth factors (IGF) seem to provide the signal for this increase in protein synthesis in the post-exercise period. Skeletal muscle is a major source of circulating IGF-1 with the production being increased by exercise [17, 18]. Skeletal muscle expresses two main IGF-1 isoforms. One of them is similar to the main liver IGF-1 and presumably has an endocrine action. The other muscle isoform probably has an autocrine/paracrine action and is called mechano-growth factor (MGF), as its production is increased by the mechanical activity of the muscle especially in response to stretch and overload [17, 18]. It has also been suggested that muscle during exercise is a major consumer of the circulating liver IGF-1. The temporary increases in transcription do lead to gradual increases in the relevant muscle proteins in subjects that perform exercise on a regular basis. Depending on the training intensity it takes several weeks or months of endurance training to achieve measurable increases in the activity of the mitochondrial oxidative enzymes and in the capillary density of the muscle fibers [19]. People who go from a normal sedentary state to a state of muscle disuse or bed rest seem to miss the repeated stimuli of the normal daily-living activities and gradually lose muscle mass and mitochondrial density. This among others is the case during aging [2]. Part of the reason for the loss of muscle mass and myofibrils in periods of disuse and denervation (see below) is also the upregulation of the ubiquitin-proteasome pathway [20], which is the main proteolytic system in muscle responsible for the breakdown of the myofibrillar proteins (actin and myosin). IGF-1 produced by the muscle during contractions not only stimulates protein synthesis, but also suppresses protein degradation.

**Neural Control of Muscle Gene Expression and Effects of Denervation**

It has been known since the late 1960s that cross-innervation of a fast and a slow muscle in experimental animals, connecting the nerve of the fast muscle to the slow muscle and vice versa, can completely change the protein package and biochemical characteristics [21, 22]. The slow muscle in a period of a few weeks becomes a fast muscle and vice versa. Many studies have since been published, which clearly show that the information that arrives via the nerve at the motor-endplate of a muscle fiber determines which proteins come to be expressed in that muscle fiber. Chronic low frequency electrical stimulation has been used for over 30 years to change expression profiles in the muscle of animal models and has taught us a lot about the plasticity (ability to change protein package and contractile characteristics) of the muscle and its control by the neural input [23]. It has been suggested that not only the firing pattern of the motoneurons, but also chemicals present in the axoplasmic flow, and growth factors (e.g. neuregulin) released by the motor endplates control gene expression in the muscle [23, 24]. Denervation leads to muscle atrophy (loss of myofibrils) both of type-1 and type-2 fibers. Furthermore, the difference between fast and slow fibers disappears as the fast fibers express more of the slow isoforms of the myofibrillar proteins and the slow fibers more of...
the fast isoforms [25]. Major changes also occur in the level of MyoD and myogenin, transcription factors that are known to regulate the expression of muscle-specific genes during muscle cell differentiation [14, 25, 26].

**Mechanism Causing Loss of Muscle Mass and Contractility in Critically Ill Patients**

Nitrogen losses in patients with an acute critical illness (sepsis and multiple trauma) indicate that 1–2 kg of muscle (or lean body) mass can be lost per day in the initial flow phase [1]. This implies that half the muscle mass can be lost in a 1- to 2-week period after a severe trauma [1]. Histological studies [27] revealed that muscle atrophy is the main cause of the rapid reduction in the muscle mass during that period with substantial reductions in the cross-sectional area of both type-1 and type-2 fibers. In some patients extensive necrosis was seen and will also contribute to the reduction in muscle mass [27]. Although it is difficult to make muscle force measurement in intensive care unit (ICU) patients, many observations suggest that the contractility of the remaining muscle mass is substantially reduced [5]. Many patients require mechanical ventilation due to contraction failure of the respiratory muscles. Many patients are also not able to generate voluntary contractions in the arm and leg muscles. In a rat model of critical illness in situ electrical stimulation of an isolated muscle via the innervating nerve revealed that the force loss was 4-fold larger than could be accounted for by the reduction in muscle cross-sectional area [28]. This must mean that the excitability of the muscle and/or of the nerve was reduced.

A potential mechanism that could lead to a reduced contractility during sepsis and critical illness is an impairment of the muscle to maintain an adequate energy store (ATP and CrP concentration). This has primarily been investigated in animal models with some studies rejecting this possibility [29] and others reporting decreased energy stores both at rest and after in situ electrical stimulation [28]. In the terminal end stage of critical illness, decreased energy stores (both ATP and CrP) have also been observed in biopsies taken from resting human muscles [30].

The RMP of the muscle was reduced by 25% (range 10–50%) in critically ill ICU patients [31]. This decrease in RMP was caused by a marked increase in the intramuscular sodium and chloride concentrations and a decrease in potassium [31, 32]. Such reductions in muscle RMP will contribute to the loss of contractility both in the acute phase of sepsis and after prolonged critical illness (Fig. 1). The mechanisms leading to this decrease in the muscle RMP are not understood in detail, but the high circulating concentrations of cytokines seem to play a role in it. Studies in animals have shown that infusion of human recombinant tumor necrosis factor (TNF-α) [33] and injections of
endotoxin [34] within 1 hr lead to marked (10–40%) reductions in the RMP and reduced force development upon electrical stimulation of the muscles.

Studies of animal models of sepsis and endotoxemia have also shown that free intracellular calcium is 2-fold higher in aortic smooth muscle cells [35]. Such rises, when present in skeletal muscle, heart and smooth muscle cells of the vascular wall and gastrointestinal tract, will also reduce the contractility (Fig. 1) of these cells and may thus form the basis for the hypovolemia of septic shock and for the paralysis seen in the gastrointestinal tract and in the peripheral and ventilatory skeletal muscles in critically ill patients.

Electrophysiological studies [36–38] have shown that the amplitude of the action potential of the innervating nerve is also reduced in many long-term critically ill patients as a consequence of axonal degeneration of the peripheral nerves. This polyneuropathy is another potential cause of the reduced contractility and weakness (Fig. 1).
Bed rest, contraction failure, and a reduction in the firing frequency of the innervating nerves, as explained in the previous section of this paper, will all contribute to the rapid muscle wasting that is seen in critically ill patients. The contraction induced anabolic signals at the transcription level, at the translation level (via IGF-1 and MGF) and reaching the muscle via the innervating nerve will all be reduced. A downregulation of the neuregulin release by the innervating nerve could also play a role in the glucose intolerance and insulin resistance of the muscle in critically ill patients [24]. A downregulation of neuregulin release may potentially also downregulate the number of acetylcholine receptors [24] and thus impair the neuromuscular transmission. In some patients abnormalities have also been observed in the size and structure of the motor endplates [39]. The functional denervation that occurs as a consequence of the polyneuropathy and impairments in neuromuscular transmission may also lead to a dedifferentiation of the muscle (reduced expression of muscle-specific genes). In line with this are the observations made recently by Larsson et al. [40] in the muscle of patients who had developed paralysis of spinal nerve-innervated muscles (acute tetraplegia), after treatment with nondepolarizing neuromuscular blocking agents and massive doses of corticosteroids. There was a general decrease in the content of the myofibrillar proteins, a very low myosin/actin protein ratio and absence of the myosin mRNA (in situ hybridization) in most of the muscle fibers. This also must imply that structural abnormalities occur in the myofibrillar contractile machinery in these patients, which may lead to a continued reduction in muscle force, even when the abilities of the nerve and muscle membrane to generate action potentials have been restored in the recovery period.

The ubiquitin-proteasome system is massively upregulated in traumatized patients and animal models [20]. In part, this may be achieved by mechanisms that operate during disuse and denervation, in part it also may be a consequence of factors that are specific for the critical illness (e.g. cytokines, the reduction in RMP, or the lack of the appropriate neural input). Obviously more research is required in this area. The reduction in muscle RMP will also reduce amino acid transport into the muscle, as many of the amino acid transporters that have been identified in muscle are dependent upon sodium cotransport and on the steepness of the sodium/potassium gradients [41, 42]. The lack of ability to build up normal amino acid gradients again may contribute to the observed imbalance between protein synthesis and degradation. This implies that protein balance can only be normalized after recovery of the RMP. Finally the increase in intracellular calcium will activate the calcium-activated proteases (calpains), phospholipases and endonucleases and may also contribute to muscular atrophy and cell death [35]. Suggestions have been made that increased rates of apoptosis may occur in lymphoid cells and in organ parenchyma during sepsis [43], but to date no reports have been published showing that early apoptosis may occur in muscle fibers and
Loss of the Endurance Capacity of the Muscle in Critically Ill Patients

Both in animal models [44] and in critically ill ICU patients [45] a major and rapid decrease was observed in the activity of several mitochondrial enzymes during the flow phase of critical illness. The activities of cytochrome C oxidase (a mitochondrial marker enzyme) in peripheral skeletal muscles decrease to very low levels within days after arrival at the ICU (Fig. 2). Substantial reductions were also seen in the oxidation rate of cytochrome C by muscle homogenates in the presence of succinate as substrate and smaller reductions were seen in citrate synthase activities (data not shown). The mechanism behind these reductions is not known, but is assumed to reflect a rapid decrease in the mitochondrial content of the muscle. This implies that the patients depend on glycolysis with lactate formation at very low workloads and that muscles fatigue rapidly during sustained contractions. The increased fatigability could also contribute to the respiratory failure, when the respiratory muscles would show a similar decrease. Most of the patients

![Graph showing decreases of cytochrome C oxidase activity in the anterior tibialis muscle of critically ill intensive care unit patients.](image)

**Fig. 2.** Decreases of cytochrome C oxidase activity in the anterior tibialis muscle of a variety of critically ill intensive care unit patients. For a detailed description of the patients see Helliwell *et al.* [27]. Unpublished data of Wagenmakers, Coakley and Campbell.
recovering from a critical illness experience severe exercise limitations and the stress of intense exercise (high heart rates and ventilation rates) at low exercise intensities encountered regularly in daily life for periods of up to 1 year after dismissal from the hospital. The physical limitations and symptoms that they experience in that period are very similar to those reported by chronic fatigue syndrome patients [4, 11]. It is not known whether the downregulation of the mitochondrial density persists during the recovery period, but it is clear that such a downregulation could explain most of the symptoms of these patients. The time course of the recovery of the RMP, and of the disappearance of the polyneuropathy and of the structural abnormalities in the myofibrils also should be investigated in order to understand the exercise limitations and design optimal therapeutic interventions.

Mechanisms Causing Loss of Muscle Mass and Function in Patients with Chronic Diseases

We are only just beginning to understand the mechanisms that lead to the loss of muscle mass and function in patients with chronic catabolic diseases such as cancer cachexia [46], chronic obstructive pulmonary disease (COPD) [47], chronic heart failure (CHF) [47], and chronic kidney failure [48]. A Medline search from 1966 until today gives 1,594 hits for fatigue and cancer; 75 hits for fatigue and lung disease, 435 hits for fatigue and heart failure, 84 hits for fatigue and liver disease, and 126 hits for fatigue and kidney failure. This is a clear expression of the fact that the physical limitations experienced by patients and the devastating influence of these limitations on the quality of life of the patients are well appreciated [3]. In spite of this, there is only a limited amount of publications that clearly describe the molecular changes that occur in the muscle of these patients and help us to understand the molecular basis of the exercise limitations. To the best of our knowledge simple questions, such as whether the force loss is in proportion to the reduction in muscle cross-sectional area or larger (pointing at excitation defects or an abnormal protein composition of the myofibrils), have not been answered. Today we do not know whether there is a decrease in the membrane potential of the resting muscles or the innervating nerves. This quite likely could be the case, as there are chronic inflammatory processes and increased circulatory cytokine levels [46–48] in most of these chronic diseases. We also know very little about the protein composition of the myofibrils, which could influence the force development (apart from some information on fiber type shifts; see below). The most detailed information is available on muscle biopsies from patients with COPD and CHF, and has been reviewed by Gosker et al. [47]. There are striking similarities between the two conditions. The concentration of the energy-rich phosphates is already lower in the resting muscles (both peripheral and respiratory) and also decreases faster during exercise according
to many $^{31}$P-MRS studies [for references see 47]. The mitochondrial content (oxidative capacity) of the peripheral muscles is reduced in both conditions, while the respiratory muscles show an increase in the mitochondrial content. This can explain the increased fatigability of the patients during daily-living activities, but also suggests that the respiratory muscles are protected against an increased fatigability by a mechanism that is not known today. In the peripheral muscles, there is a fiber type shift towards fast (glycolytic) type-2 fibers and in the respiratory muscles towards slow (oxidative) type-1 fibers [for further details and references see 47]. In predialytic patients with renal failure, only minimal shifts have been observed in muscle fiber types and mitochondrial enzyme activities [49], but we do not know what is happening in this respect in the muscle of patients with more severe renal failure on dialysis, with chronic liver failure and in the vast population of patients with cancer. Common to most of these catabolic conditions is an upregulation of the ubiquitin-proteasome pathway [20, 46, 48]. It is not known, though, to which extent this is due to bed rest and disuse or a nutritional depletion [20], or whether it is the consequence of disease-specific changes in the muscle.

**Potential Therapies and Nutritional Support**

Suggestions have been made that a reduced appetite leads to a nutritional depletion and acceleration of the loss of muscle mass and function in most of these diseases. However, the effect of hypercaloric nutrition on muscle performance and mass tends to be minimal. In COPD patients, it has been suggested that there may be an early response, especially on muscle performance, which could be related to improvements in the energy status of the muscle or to improvements of the muscle RMP [47]. In the long-term, increases in calorie intake or protein intake do not seem to counteract the reduction in muscle mass though and do not lead to further improvements in muscle function [47].

Exercise training programs of 6 weeks or more lead to clear increases in the oxidative capacity (measured as VO$_{2\text{max}}$ during incremental exercise) and endurance performance of patients with cancer fatigue [50], of cancer patients rehabilitating after high-dose chemotherapy [51], and of patients with COPD [47], CHF [47], liver disease [52] and kidney failure [53]. In several of these studies, substantial reductions were also seen in heart rate and lactate concentration at an equivalent submaximal work load. The quantitative improvements are large in many of these studies and suggest that many of the patients with, or recovering from chronic diseases, can efficiently be reconditioned with exercise, so that they can more easily perform activities of daily living. Regretfully these convincing scientific reports still seem to contrast today’s medical practice, in which bed rest still is regarded as optimal therapy by some of the treating physicians. Exercise training programs also reduce the psychologic distress experienced by cancer patients undergoing...
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chemotherapy [54]. Exercise programs also seem to be indicated to accelerate the reconditioning of patients recovering from a critical illness, but to date no such studies have been performed.

A potential new development in the clinical nutrition support that can be given to these patients seems to be the timed administration of oral amino acid-carbohydrate supplements during and immediately following exercise sessions. In healthy subjects it has been shown that exercise leads to a temporary increase in the protein synthesis rate of the muscle in the period following exercise [55–58]. Ingestion of amino acid-carbohydrate supplements, taken immediately before [58] or following the exercise [55–57], leads to a further increase in the muscle protein synthesis rate and a more positive protein balance (synthesis – degradation). This seems to suggest that ingestion of these supplements in long-term training studies should be able to increase the rate of muscle hypertrophy (strength training), or the rate at which increases occur in the oxidative capacity and mitochondrial density (endurance training). For patients with acute or chronic diseases, which severely limit their ability to perform exercise, it would be very important if the effect of the training sessions on the molecular adaptation in the muscle could be increased.

The reduction in muscle RMP that is seen in critically ill patients will also reduce the transport rate of creatine, carnitine, betaine and taurine from the blood into the muscle. The transport of these metabolites into the muscle also depends upon sodium cotransport and on the steepness of the sodium/potassium gradients [59, 60]. The massive creatinuria seen in trauma patients [61] seems to suggest that creatine is lost from the muscle, when the RMP falls. This may provide a reason to add creatine to the nutrition given to these patients. A loss of creatine will reduce the energy stores in the muscle and may lead both to impairments in contractility and in the endurance capacity [59]. Via effects on cell volume, creatine and other osmoregulators (taurine and betaine) have also been suggested to have anabolic effects in muscle [59]. A relative shortage of carnitine will reduce the rate of fatty acid oxidation in the muscle and could well be one of the causes of the excessive intramuscular lipid accumulation in the muscle of ICU patients [27]. Also in patients with liver disease and kidney failure, supplementation of creatine and carnitine should be considered as a major part of the biosynthesis of these metabolites normally occurring in these tissues [59, 60]. Creatine and carnitine and several of the intermediates in the biosynthetic route of these metabolites are water-soluble and, therefore, are removed from the body during dialysis. In patients with kidney failure, the use of recombinant human erythropoietin seems to be indicated, as it prevents the development of anemia, improves exercise capacity and reduces morbidity and mortality, when its use has been started before the onset of dialysis [62].

During critical illness, voluntary exercise will be impossible. In such cases some of the anabolic effects of exercise may be simulated by *in situ* electrical
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stimulation, e.g. of the respiratory muscles. Another possibility is the use of recombinant human IGF-1 to simulate the increase by exercise of the production of the muscle IGF-1 isoform and MGF. In recent studies the use of rhIGF-1 complexed with its principal binding protein, IGFBP-3, has been shown to attenuate muscle protein catabolism both in children and adults with severe burns [63, 64]. A positive nitrogen balance was also observed in chronic renal failure patients on maintenance dialysis, when they were treated with rhIGF-1 for 20 days [65]. Combinations of electrical stimulation with rhIGF-1 and timed amino acid-carbohydrate supplements may well be the most efficient way to rapidly increase the mass and improve the contractility of individual muscles or selected muscle groups.

Conclusions

In healthy subjects, a minimal amount of physical activity (muscle work) is required in order to maintain muscle mass and oxidative capacity (mitochondrial density). The exercise provides the metabolic, hormonal and neural signals that switch on a variety of contraction-induced genes that lead to temporary increases in protein synthesis and to net protein anabolism in the period following exercise. Disuse and bed rest lead to muscle atrophy and a reduction in the mitochondrial density. In patients with trauma and sepsis and in many chronic diseases, specific changes occur that lead to a further increase in the rate of muscle protein catabolism and a rapid loss of the oxidative capacity. In these disease states, decreases in the muscle RMP, a polyneuropathy, and changes in the functional organization of the myofibrils may also impair muscle function. Efficient therapeutic interventions and the optimal nutritional support should be based on a detailed knowledge of the underlying pathological mechanisms.

References

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**Discussion**

**Dr. Mokgokong:** You demonstrated the need for exercise very well. In the intensive care unit (ICU), setting practices can be instituted to encourage activity even in patients on long-term ventilation. In a condition like Guillain-Barré syndrome, where the problem is only with the nerves, the patient may need to be ventilated for a long time. You may then find that even when the condition improves, it may be difficult, because of the poor state of the muscles, to wean the patient off the ventilator. How can you keep the muscles of such a patient in good state? Does electrical stimulation have a role?

**Dr. Wagenmakers:** I think you have come up with a solution. Electrical stimulation should help, but it is very difficult at present to implement it in the clinical situation. In collaboration with technical universities we are starting work on means of stimulating more than one of the large muscle groups. If you can do that I think there will be great benefits for the patient – not only for muscle condition, but also for insulin sensitivity and the ability to use substrates. We already know from studies in patients with traumatic quadriplegia that they benefit greatly from exercise on special electrically driven bikes. This has been done at the Copenhagen muscle research center, and they have shown immense benefits in relation to the plasma concentration of metabolites. There is also a suggestion that the immune system improves.

**Dr. Labadarios:** There was a study a while ago in *Nutrition* [1], which showed that physiotherapy alone had a very significant effect in reducing catabolism. Maybe you could comment on that in relation to the timing of onset of physiotherapy?

**Dr. Wagenmakers:** Passive stretching of muscles is extremely helpful because it creates local anabolic signals in the muscle.
Dr. Becker: What is the percentage loss of muscle, or loss of strength, per day in a bed-ridden patient. If a patient is running on, say, 30% of ability and loses 1% of their strength per day, they might very quickly get to a point, where they don’t have the muscle strength to do anything. This concerns the point you made that you can lose up to 1.5 kg of muscle mass a day.

Dr. Wagenmakers: The loss of muscle mass is an important feature of the strength reduction in ICU patients, but it is not the most important factor. I believe the loss of the membrane potential is much more important.

Dr. Beaufrère: On average patients in ICU lose between 7 and 12 g nitrogen/day. That makes 60 g of protein, which is approximately 300 g of lean body mass/day. I would say that 1.5 kg/day of lean body mass loss would be the maximum value, and not all patients lose anything like that amount, would you agree?

Dr. Wagenmakers: I agree that 1.5 kg is the maximum.

Dr. Becker: The question of tyrosine bonding between muscle fibers was raised earlier. How will that influence the use of physiotherapy in older people?

Dr. Wagenmakers: My feeling is that even if you keep active until a very old age, you will not prevent all the negative effects of aging. There are some specific effects of aging that will lead to a slow loss of muscle function. But when you do exercise until a very old age, you can keep the turnover of the muscle proteins at a higher value, and I think the accumulation of proteins with that cross-link will also be reduced under those conditions. However, even when you are active until a very old age, there will be sarcopenia in comparison with younger individuals. So there are specific aging effects, but a lot can be prevented by regular exercise.

Dr. Leverve: I was impressed by your data on cytochrome oxidase activity in the ICU. The values obtained related to wet weight. Do you think there would still be the same difference if you corrected for edema?

Dr. Wagenmakers: There was not a lot of edema in these muscles, so what you see is the true decrease in mitochondrial content.

Dr. Leverve: Even after the first day there appeared to be a substantial decrease, which means this is a very fast mechanism.

Dr. Wagenmakers: No, it was on the 2nd or 3rd day, when the patients had passed the critical period, that the first biopsy was taken, so it is not until 2 or 3 days after the critical period that you start to see low values.

Dr. Leverve: The energy cost of maintaining a very negative membrane potential is high, so a slight decrease in this negativity will be an energy-saving process. Do you think that the change in muscle membrane potential in acutely ill patients could have an adaptive effect?

Dr. Wagenmakers: Maintenance of the sodium-potassium gradient is essential for cells and that is also why a major proportion of the resting energy expenditure goes into the maintenance of the muscle membrane potential. The muscle ought to maintain that membrane potential but it doesn’t, and that is why we see all these metabolic changes.

Dr. Soeters: Sodium-potassium ATPase is induced, so the pump is working harder to keep up the membrane potential in ICU patients. Thus the decrease in potential is countered by increased pumping, so you are using more energy.

Dr. Wagenmakers: That indicates that the muscle is doing everything it can to maintain the sodium-potassium gradient, but it is still failing.

Dr. Griffiths: I have a comment. I think Dr. Labadarios was alluding to a passive motion study, which I did some years ago [1]. That was in patients who had complete neuromuscular block, so the muscle was only having a rhythmic force applied to it. It was a small study, but it did suggest that the passive motion helped to preserve the
anatomical structure of the muscle and also reduced the protein loss without affecting synthesis.

I want to ask a question about the rate of wasting. I think that bed rest alone results in a much slower loss of muscle than in the situation in the ICU. The figures you were quoting, which came from some of our muscle data, were in the order of 2–4% a day, which is a colossal rate. I wonder how much of that is related to hypermetabolism. I recall a paper on the use of β-blockers in children [2], where nitrogen losses were reduced markedly by a reduction in the hypermetabolic state. I wonder whether these losses are related to an increased demand for fuel.

**Dr. Wagenmakers:** My personal feeling is that it is the cytokine effects that result in the greater muscle loss in ICU patients than in people on pure bed rest. I imagine that the use of β-blockers will reduce the turnover of adipose tissue. Adipose tissue releases resistin and tumor necrosis factor-α, so maybe there will be reduced concentrations of these cytokines with β-blocker treatment. My view is that the muscle loss isn’t related to changes in energy expenditure, but that is only speculation.

**Dr. Pichard:** When muscle undergoes atrophy during a period in the ICU, it is not vanishing; its substrate is used. If you decide to try to reduce this atrophy, you have to ensure that you are capable of providing the body with the appropriate substrate at that time. That’s going to be difficult, because nobody knows better how to provide the body with necessary substances than the body itself.

I have a practical question. We all know that mobilizing a patient is time-consuming and sometimes impracticable. My question reverts to the earlier discussion. Is there a place for electrical stimulation, and if so, how should we proceed, and when should it be employed?

**Dr. Wagenmakers:** About your comment, I am not sure whether the body always knows best, which fuel to use. For example, I don’t think that the insulin resistance that occurs is totally planned. This goes back to the question of whether it is the acute phase response that makes muscle mass disappear so rapidly.

In answer to your question about when we should start stimulating the muscles, I think we should try to recondition the ventilatory muscles as soon as possible. The longer you put a patient on the ventilator, the more these muscles will deteriorate and the more difficult it will be to wean the patient off the ventilator. With peripheral skeletal muscles, you can wait for a week or longer, before you start work to restore their function. I hope electrical stimulation may have a role in this, but it is very different from voluntary exercise in that it stimulates all the muscle fibers, so it is not a very physiologic way of stimulating the muscle. Therefore its future depends on whether we will be able to develop stimulation protocols that can mimic natural voluntary stimulation. The use of electrical stimulation can also be quite painful, so we will depend a lot on the abilities of electrophysiologists and technical experts to devise equipment that can provide a more natural stimulation protocol. If we achieve that, there is certainly a place for electrical stimulation in reconditioning muscles.

**Dr. Segal:** In this country, we have a 96-km annual road race with thousands of participants and a significant morbidity and even mortality – this year I think there were 2 deaths. At what stage does exercise actually become harmful?

**Dr. Wagenmakers:** Exercise becomes harmful, when you are doing more than your body is designed for. Some people can run many half marathons but not full marathons. When they try too hard, there is muscle damage and dramatically increased concentrations of cytokines in the blood. There is speculation that there is leakage of mucosal bacteria through the gut barrier, which can have dramatic effects. You will see fluid shifts, and some triathletes have an enormous gain of weight in the days following a triathlon. I don’t think that is a very healthy situation. However, it is certainly clear
that if you train very hard, you can do much more than someone who has not trained. The body will indicate when you have gone too far.

Ms. MacMahon: One of the things that your talk highlighted is that we shouldn’t just be concentrating on early nutritional intervention, but we should be looking at long-term nutritional intervention. Often once patients are out of their critically ill period, we think they are fine and we forget about them. In relation to long-term intervention in terms of building up and repairing the muscle damage, would you say that exercise is more important than nutrition? And looking at the nutritional side of things, if you are going to supplement with specific nutrients like creatine, zinc, and magnesium, are there certain levels of supplementation that we should be looking at? Also, if you are feeding patients in hospital and giving them supplements once they are out of the critically ill stage, should we be timing those supplements to follow physiotherapy or exercise, given that the nutrient uptake by muscle is better after exercise?

Dr. Wagenmakers: Those are a lot of practical questions that are very important, but I don’t think we have the scientific data to answer them. One of the points I was making is about the timing of administration of compounds that are taken up by transporters that depend on the sodium-potassium gradient: the greatest benefit will not be experienced until the gradient has been restored, so this means that we need to be able to measure the membrane gradient routinely, which we can’t do at present. Another example is creatine. I am sure that patients in ICUs lose a lot of creatine, because there is a great deal in their urine, but I don’t know of any studies in which people have used magnetic resonance spectroscopy to follow changes in creatine phosphate in ICU patients during their hospital stay and after discharge. These studies need to be done, before we can give practical advice.

Dr. Endres: You showed that mitochondria can adapt to physical activity, and we see that in palmitate oxidation and the cytochrome C oxidase activity. Is it theoretically possible to benefit the muscles by increasing cytochrome C oxidase activity or NADH activity, by adding cofactors such as riboflavin or thiamine?

Dr. Wagenmakers: It could be useful to supply the components to restore the respiratory chain during the recovery period, but there are no data to prove this.

Dr. Levereve: I don’t think supplementation with riboflavin would achieve anything, but riboflavin deficiency might have a very detrimental effect, so under the circumstances of a deficiency, its correction could be very helpful.

Dr. Wagenmakers: I can’t exclude the possibility that it might be helpful to add components of the respiratory chain, but I simply don’t know.

Dr. Levereve: In the case of riboflavin there are experimental data showing this clearly.

Dr. Endres: I know that Trijbels [Trijbels JMF, personal communication] and coworkers from Nijmegen showed that there was a partial deficiency of some enzymes in the respiratory chain that was clinically unconspicuous inapparent in adult patients doing treadmill exercise.

Dr. Heymsfield: There are two studies that have influenced my thinking on this subject. One of these involved banding the aorta in an animal model to produce left ventricular hypertrophy, and it was shown that if you also malnourish the animal the heart continues to hypertrophy [3]. This effect has also been shown in soleus muscle: you can induce a negative nitrogen balance for the whole body, but the muscle still hypertrophies when it is working [4]. Do the respiratory muscles continue to function normally, even though the person is in negative nitrogen balance, or are they impaired if you don’t provide nutritional support?

Dr. Wagenmakers: I don’t think that bed rest will ever lead to loss of ventilatory muscle function, however long it goes; also I don’t think respiratory muscle function is much affected in astronauts.
**Nutrition to Improve Muscle Function**

*Dr. Heymsfield:* This is a crucial question because it involves the issue of whether or not early nutrition support makes a difference. If these muscles continue to function reasonably well even in the phase of negative nitrogen balance, then maybe nutrition support really doesn’t help the particular functions that in the end determine outcome.

*Dr. Wagenmakers:* The beauty of the muscles of posture and the ventilatory muscles is that you are always using them, so they maintain the anabolic signals necessary to utilize amino acids to create new proteins. So as soon as you can make the respiratory muscle work and generate those anabolic signals, that is the time to provide appropriate nutritional support. But if these muscles are not being used, then I agree it probably doesn’t make sense to target them with nutritional therapy. They have to be in use to generate the local trophic factors necessary for them to take up amino acids.

*Dr. Mokgokong:* Does the brain provide anabolic signals?

*Dr. Wagenmakers:* We know that there are trophic molecules generated by nerve endings, but we know very little about how much they depend on the firing frequency of the nerve. I assume that the degree to which local trophic molecules are generated will depend on the total input coming from the brain to the muscle, and I can well imagine that you could get benefit from stimulating the brain magnetically, so that it produces signals that go to the muscles. Maybe it would be clinically possible to generate such neural traffic and I couldn’t exclude the possibility that it might benefit some patients. However, if the cord is transected and the path from the brain to the muscle is interrupted, then I don’t think there would be much benefit. I don’t believe these trophic factors exert their effects via the blood.

*Dr. Griffiths:* The pathology of the nerve is crucial in the critically ill. The process known as critical illness polyneuropathy is a distal neuropathic process that affects nerve endings. The relation of this to your talk is important, because clearly, if the nerve is damaged, you are not going to achieve any benefit from the trophic factors, or any recovery in the muscles. So when we are thinking about the muscle and its turnover and recovery, we have also to remember the pathology going on within the nerve itself.

*Dr. Wagenmakers:* I agree. If there is a neuropathy the muscle will not contract, so that is clearly quite important.

*Dr. Griffiths:* We also know that in the face of peripheral skeletal muscle wasting, cardiac muscle does not actually waste in the first 2 weeks of severe trauma or illness, because the increase in cardiac output is maintaining the stimulus.

*Dr. van der Merwe:* We used portal-systemic shunting in a model of hepatic osteodystrophy and showed that there was a marked decrease in muscle mass over a 16-week study period in the rat. When we reversed the shunt, the rats regained muscle mass and strength within 4 weeks, so it seems that local factors are important, as well as systemic factors.

*Dr. Wagenmakers:* I agree with you. I think cytokines play a major role in muscle wasting.

**References**