Renin-Angiotensin Mechanism.

R

Radiation-Induced Normal Tissue Injury

Radiation induces a complex tissue-specific response cascade at the molecular, cellular and tissue level involving DNA damage response, cell cycle arrest, induction of apoptosis, loss of reproductive capacity, premature senescence, cytokine cascades, tissue remodeling, etc. Predictive in vitro assays try to target different variables known to determine normal tissue reactions.

Raise

► Promotion of and Adherence to Physical Activity

RANK Ligand

Is a protein found on the surface of osteoblasts that is necessary for the stimulation of osteoclast development and maturation through its binding with RANK (Receptor Activator of Nuclear Factor κB) present on the surface of osteoclasts. Inhibition of RANK-L reduces osteoclast development/maturation.

Rate of Force Development (RFD)

The rate at which force develop at maximal effort (Newton $\cdot$ sec^{-1}).

Reaction Time

The time that elapses between a person being stimulated to move (receiving a stimulus) and initiating a movement in response.

Reactive Nitrogen Species (RNS)

Highly reactive molecules where the reactive center is nitrogen.

Cross-References

► Redox Status

Reactive Oxygen Species (ROS)

Highly reactive chemicals, containing oxygen, that interact with other molecules and produce damage. ROS is a general term that refers to oxygen-centered free radicals but also to non-radical but reactive derivatives of oxygen such as hydrogen peroxide.

Reactive Strength

Reactive Strength can be defined as the ability of the neuromuscular to tolerate a relatively high stretch load and effectively change movement from rapid eccentric to rapid concentric.

Reactive Training

► Plyometric Training

Receptor Activator of Nuclear Factor Kappa Beta Ligand (RANKL)

A compound released from osteoblasts that binds to its receptor (RANK) on the surface of osteoclasts. This activates osteoclasts and eventually bone resorption.

Frank C. Mooren (ed.), *Encyclopedia of Exercise Medicine in Health and Disease*, DOI 10.1007/978-3-540-29807-6,

Receptor Density

The concentration of a specific molecule(s), often on the outer surface of a cell, which binds a specific ligand such as a hormone or growth factor.

Receptors

Receptors are specific areas of the cell membrane, which can be activated by hormones and transmitter substances. Receptors pass through the membrane and may activate intracellular signaling systems. There are many types of receptors. Epinephrine and norepinephrine are acting on two different types of receptors called α-adrenergic receptors (or α-adrenoceptors) or on β-adrenoceptors. There are several subtypes. Activation of so-called α_1-adrenoceptors increases the intracellular concentration of Ca^{++} and smooth cells will contract. Activation of β-adrenoceptors increases c-AMP inside cells and this may result in various responses dependent on the subtype of the receptor.

Recombinant Human EPO

The renal hormone erythropoietin (EPO) is necessary for red blood cell production. Because EPO deficiency leads to anemia, patients with chronic kidney disease are substituted with genetically engineered "Erythropoiesis Stimulating Agents" (ESA), that is, recombinant human EPO (rHuEPO) or analogs thereof. In addition, ESAs are administered to cancer patients with symptomatic anemia receiving chemotherapy. rHuEPO is produced in cultures of cells transfected with either the human *EPO* gene or *EPO* cDNA (the coding sequence of the gene) linked to an expression vector (recombinant DNA), which are integrated into the genome of the host cells and stably expressed over time. Mammalian host cells must be used for the manufacture because of the complex structure of EPO, which is a glycoprotein composed of 165 amino acids and 4 glycans (carbohydrate side chains). The World Health Organization (WHO) has implemented the following international nonproprietary names (INNs) for the ESAs: Eukaryotic cell-derived rHuEPOs, whose peptide core is identical with that of human urinary EPO is termed "Epoetin." Changes in the amino acid sequence are indicated by a different prefix (e.g., "Darbepoetin"). Analogs of a given EPO-type substance with an altered glycosylation pattern due to production in a different host cell system are classified by a Greek letter added to the name (alpha, beta, etc.). The three tetra-antennary N-linked (at the asparagines 24, 38, and 83) and the one small O-linked (at serine 126) glycans of the Epoetins as well as those of endogenous EPO are heterogenous, yielding several EPO isoforms that can be separated by electrophoresis, isoelectric focusing (IEF), mass spectrometry, and NMR spectroscopy. Chinese hamster ovary (CHO) cells are most commonly used for the large-scale pharmaceutical manufacture of ESAs. CHO cell-derived rHuEPOs (Epoetin alfa and Epoetin beta) have been used as anti-anemic agents for >20 years. Since the patents for the originator products have expired recently in the EU and elsewhere, other manufacturers than the inventors have launched copied products ("Biosimilars," "Follow-on Biologics"). These are marketed under the INNs Epoetin alfa (like the reference product) or Epoetin zeta. In addition, an Epoetin omega (manufactured in baby hamster kidney cells [BHK]) and an Epoetin delta (manufactured in human fibrosarcoma cells) were at times used clinically in some countries. The half-life of intravenously (i.v.) administered Epoetins is 6–8 h. Darbepoetin alfa is a mutated hyperglycosylated rHuEPO analog with an i.v. half-life of 1 day. Methoxypolyethylene-coupled Epoetin beta (methoxyPEG-EPO) has a half-life of 5–6 days.

Recovery Oxygen Uptake

► Excess Postexercise Oxygen Consumption

Red Blood Cell Capillary Transit Time

The time it takes for red blood cells to traverse completely the length of the capillary or capillary segments from arteriole to venule.

Red Blood Cell Rheological Properties

► Blood Rheology

Redox Homeostasis

► Redox Status

Redox Signaling

Gene expression controlled by redox-sensitive mechanisms of signal transduction.

Redox Status

Pedro Tauler Riera
Departament de Biologia Fonamental i Ciències de la Salut, Universitat de les Illes Balears, Palma de Mallorca, Spain

Synonyms

Oxidant/antioxidant homeostasis; Oxidative status; Redox homeostasis

Definition

The redox status could be defined as the balance between ► oxidants (or pro-oxidants) and ► antioxidants (Fig. 1). Oxidants, including ► free radicals and other reactive species, are continuously produced in the cell. As it is impossible to completely prevent oxidant production, several antioxidant systems have evolved in the cell. In order to maintain a healthy status, oxidants and antioxidants should be in equilibrium. However, this equilibrium is very difficult to maintain in the cell. When this equilibrium between oxidant and antioxidant is disrupted, tilting the equilibrium toward an oxidized state, ► oxidative stress is produced. Oxidative stress is involved in the physiopathology of several diseases, including cardiovascular disease, cancer, diabetes, and many others.

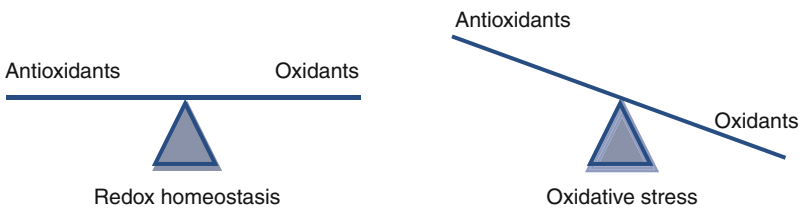
Basic Mechanisms

As a consequence of the previous definition, it can be considered that two opposite mechanisms are involved in the redox status molecular mechanism: the mechanisms leading to the production of oxidants and the mechanism of antioxidants.

Oxidants and Its Production

The most important oxidants to be considered are the free radicals and related species. Free radicals (chemical species with one unpaired electron) can be generated as products of homolytic, heterolytic, or redox reactions, producing either charged or uncharged radical species. ► Reactive oxygen species (ROS) is a general term that refers to not only oxygen-centered free radicals but also includes non-radical but reactive derivatives of oxygen, especially hydrogen peroxide. Similarly, the term "reactive nitrogen species (RNS)" refers to nitrogen radicals as well as other reactive molecules where the reactive center is nitrogen. The primary free radicals generated in cells are superoxide ($O^{2\bullet-}$) and nitric oxide (NO).

Molecular oxygen in the ground state contains two unpaired electrons in the outer shell. Since the two single electrons have the same spin, oxygen can only react with one electron at a time and therefore, it is not very reactive with the two electrons in a chemical bond. If one of the two unpaired electrons is excited and changes its spin, the resulting species (known as singlet oxygen) becomes a powerful oxidant as the two electrons with opposing spins can quickly react with other pairs of electrons, especially double bonds. As indicated previously, superoxide anion, the product of a one-electron reduction of oxygen and a relatively stable radical, is the precursor of most ROS and a mediator in oxidative chain reactions. Dismutation of superoxide anion produces hydrogen peroxide (H_2O_2). Hydrogen peroxide can be homolytically cleaved (partially reduced) in a Fenton reaction by transition metals, to form the highly reactive hydroxyl radical, one of the strongest oxidant produced by biological systems.



Redox Status. Fig. 1 Schematic representation of the redox homeostasis (balanced) versus oxidative stress (unbalanced)

The transition metals catalyzing this reaction may be re-reduced by superoxide anion, propagating this process. In addition, superoxide anion may react with other radicals including nitric oxide (NO), in a reaction controlled by the rate of diffusion of both radicals, to form peroxynitrite and subsequently other RNS. The main product, peroxynitrite, is also a very powerful oxidant. The oxidants derived from NO are the ones referred to as RNS.

There are many cellular sources of free radicals. Many are produced by normal ongoing metabolism, especially from the electron transport system in the mitochondria and from a number of normally functioning enzymes such as xanthine oxidase, cytochrome p450, monoamine oxidase, and nitric oxide synthase.

The main sources of superoxide anion, as the primary ROS produced, are the following ones [1, 2]:

- *Mitochondria.* It is widely believed that one of the forms of radical is due to a "leak" in the mitochondrial electron transport chain. Even during basal metabolism (in a resting state) unwanted side reactions occurring in the electron transport chain can lead to production of superoxide anion. Mitochondria have generally been cited as the predominant source of ROS in muscle cells, and many authors have reiterated early reports that 2–5% of the total oxygen consumed by mitochondria may undergo one electron reduction with the generation of superoxide [2]. During exercise it has been assumed that mitochondria are also the main source of ROS.
- *Xanthine oxidase.* This enzyme is found in two different forms: xanthine deshydrogenase (XDH) and xanthine oxidase (XO). Under normal physiological conditions, XDH is the dominant form of the enzyme, and oxidizes both hypoxanthine and xanthine (to uric acid) in a process that, in addition, reduces NAD^+ to NADH. On the other hand, XO catalyzes the same transformation but using oxygen, instead of NAD^+, as electron acceptor and, thus, producing superoxide anion.
- *Neutrophils and other phagocytes.* As a consequence of their functions, neutrophils and other phagocytic cells produce large amounts of free radicals by a mechanism known as ►oxidative burst, enhancing oxidative stress.

On the other hand, NO is a vasodilator resulting from the breakdown of arginine to citrulline, in a reaction catalyzed by a family of NADPH-dependent enzymes called nitric oxide synthases in many cell types. Synthesis occurs through several types of nitric oxide synthases (NOS). Nitric oxide synthases convert L-arginine into NO and L-citrulline utilizing NADPH.

As it has been indicated previously, when free radical production increases, oxidative stress is produced. Under these conditions, free radicals are capable to oxidize some biological essential molecules such as proteins, nucleic acids, and lipids, affecting the integrity and functionality of the cell. In order to counteract the effects of oxidative stress, the organism disposes of a complex system of antioxidants.

Antioxidants and Antioxidant Mechanisms

In order to maintain low levels of oxidants, both enzymatic and ►nonenzymatic antioxidants are present in cellular and extracellular compartments.

Principal ►antioxidant enzymes include superoxide dismutase, glutathione peroxidase, and catalase [1]. Additional antioxidant enzymes such as peroxiredoxin, glutaredoxin, and thioredoxin reductase also contribute to cellular protection against oxidation. Superoxide dismutase (SOD) supposes the first line of defense against superoxide anion as SOD dismutates superoxide anion to form hydrogen peroxide and oxygen. Three isoforms of SOD can be found in mammals, with a different distribution, requiring all transition metal in the active site to accomplish the catalytic breakdown of the superoxide anion. Glutathione peroxidase is a selenoprotein which catalyzes the reduction of hydrogen peroxide and other hydroperoxides to water and alcohol, respectively, using reduced glutathione (GSH) as the electron donor. When GSH is the electron donor, it donates a pair of hydrogen ions and GSH is oxidized to glutathione disulfide (GSSG). The reduction of GSSG back to GSH is accomplished by glutathione reductase, a flavin containing enzyme whereby NADPH provides the reducing power. Catalase catalyzes also the breakdown of hydrogen peroxide into water and oxygen. Iron is a required cofactor attached to the active site of catalase. The main differences between glutathione peroxidase and catalase are a much lower catalase affinity for hydrogen peroxide and the consumption of glutathione in glutathione peroxidase activity.

Nonenzymatic antioxidants can be classified in endogenous antioxidants and dietary antioxidants. Endogenous antioxidants are synthesized in the organism. Some of the endogenous antioxidants are glutathione, uric acid, and coenzyme Q10. Glutathione is a tripeptide and is the most abundant nonprotein thiol in cells. Glutathione is primarily a cellular antioxidant and it is found in low concentrations in circulation. In addition to its role as a substrate of glutathione peroxidase, GSH can directly react with a variety of radicals by donating a hydrogen atom. Furthermore, GSH is also involved in reducing other antioxidants such as vitamins E and C. Uric acid (and/or urate)

is a by-product of purine metabolism and is considered the main, in terms of concentration, antioxidant in human fluids, especially in plasma. As an antioxidant, urate is able to protect against oxidative damage by acting as an electron donor, neutralizing several free radicals. Furthermore, urate is also able to chelate metal ions such as iron and copper and prevent them from catalyzing hydroxyl radicals via the Fenton reaction. Finally, and among endogenous antioxidants, coenzyme Q10 could be also highlighted. Coenzyme Q10 (ubiquinone) is synthesized in cells and is essential in mitochondrial electron transport and is also located in cell membranes. Its antioxidant capacity has been clearly demonstrated in vitro, but remains uncertain in vivo [2].

Numerous dietary antioxidants also contribute to cellular protection against free radicals. Dietary antioxidants include vitamin C, vitamin E, and carotenoids. Vitamin C (ascorbic acid) is a hydrophilic antioxidant that functions in aqueous environments such as plasma and the cellular cytosol. Vitamin C can directly scavenge several radicals and, also, plays an important role in the recycling of vitamin E. Vitamin C can be mainly obtained from several fresh fruits such as strawberries, kiwis, and oranges. On the other hand, vitamin E and carotenes are hydrophobic antioxidants. Vitamin E is one of the most widely distributed antioxidants in nature, and it is the primary ► chain-breaking antioxidant in cell membranes. It has been suggested that vitamin E has, in addition to its antioxidant activity, more beneficial cellular functions. Similar to vitamin E, carotenes are lipid-soluble antioxidants located primarily in the membranes of tissues. The antioxidant properties of carotenes come from their structural arrangement consisting of long chains of conjugated double bonds; this arrangement permits the scavenging of several ROS.

Exercise Intervention

The beneficial effects of regular, non-exhaustive physical exercise have been known for a long time. Exercise is part of the treatment of common diseases such as diabetes mellitus or coronary heart disease. It improves plasma lipid profile, increases bone density, and helps in weight loss. However, it has been suggested that the beneficial effects of exercise are lost with exhaustion and with lack of training. In this sense, it has become clear that the prolonged and intense exercise, exhaustive exercise, induces high free-radical production and generates oxidative stress, leading to oxidative damage to main cellular components [3]. During the last years, general knowledge about the biological implications of exercise-induced oxidative stress has expanded rapidly. While the roles and importance of free radicals in normal physiology, disease pathology, and even in aging continue to be studied and debated, free radicals are widely thought to be essential in effecting both the damage and the adaptation that accompany acute as well as continuous physical activity. In spite of recent controversial results, the mitochondrial respiratory chain, the enzyme xanthine oxidase, and the activated neutrophils are considered the main sources of free radicals during exercise [3, 4].

The occurrence of oxidative stress and oxidative damage during exhaustive exercise opened up the possibility to prevent oxidative damage by administrating antioxidants supplements. In fact, not all, but several studies have shown beneficial effects of antioxidant supplementations preventing oxidative damage. However, nowadays it is believed that while high levels of free radicals induce oxidative damage to all cellular components, low-to-moderate levels of oxidants play multiple ► regulatory roles in cells such as the control of gene expression, regulation of cell signaling pathways, modulation of skeletal muscle force production, and adaptation to exercise. In fact, it has been shown that training induces adaptations of antioxidant defenses to oxidative stress, producing low levels of oxidative damage. Thus, the prevention of ROS formation or the use of high antioxidant doses could lead, among others, to a lack of adaptation to exercise and even to the prevention of health-promoting effects of exercise [5].

Cross-References

► Nitric Oxide
► Oxidative Stress

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Reduced Force Production Capacity

► Fatigue

Regeneration

Repair of a destructed cell, tissue or organ.

Cross-References

► Overtraining Syndrome
► Overtraining-Biochemical Markers

Regimen

The specification of the changes in behavior or lifestyle, usually provided by a physician or some professional external agent.

Regimen Adherence

► Behavior Change

Regimen Compliance

► Behavior Change

Registered Dietitian (RD)

A trained professional who has had the appropriate university training in the field of nutrition, and then who has applied to and been accepted to an accredited dietetic internship that will focus on practical training in the field of dietetics and nutrition. The RD has passed a national board examination and maintains his/her RD status by obtaining a certain number of continuing education credits over a 5-year period.

Regulatory Light Chain Phosphorylation

There are two kinds of light chain attached to each myosin head: essential and regulatory. As indicated above, the essential and regulatory light chains have fiber-type specific isoforms. The regulatory light chains are relatively unphosphorylated in the resting state, but become phosphorylated by activation of the enzyme myosin light chain kinase. This enzyme is activated by the calcium-calmodulin complex. When the muscle is activated, calcium concentration increases and some of the calcium will bind transiently to calmodulin. ATP serves as the source for the phosphate group, and MLCK transfers the terminal phosphate of ATP to the regulatory light chain. There is a single phosphorylatable site on the regulatory light chain of skeletal muscle. Phosphorylation gives the light chain a more negative charge, and increases the mobility of the myosin head. This means that in the dephosphorylated state, the myosin head tends to stay close against the backbone of the myosin filament. Phosphorylation allows the head to swing away from the filament backbone and increases the likelihood that the myosin head will interact with actin. Phosphorylation essentially increases the probability of myosin binding to actin and therefore it increases the rate of force development. Dephosphorylation of the regulatory light chains is achieved by another enzyme, myosin light chain phosphatase. This enzyme is assumed to be unregulated, so it functions at a rate that corresponds to the relative concentration of phosphorylated light chains. In the absence of contractile activity, the regulatory light chains will return to the rested state in about 5–6 min.

Regulatory Roles

ROS play cellular regulatory roles. In the last years some researchers have suggested that ROS (and other reactive species) are essential regulating the expression of several genes. These regulatory roles can be observed in very different physiological aspects such as the mitochondrial biogenesis, muscle glucose uptake, and many others. Taking into account these observations, it has been suggested that a certain level of reactive species is essential and, thus, massive antioxidant supplementations should be avoided.

Rehabilitation

The use of all means aimed at reducing the impact of disabling and handicapping conditions and at enabling people with disabilities to achieve optimal social integration.

Rehabilitation Therapy in COPD

► Chronic Obstructive Pulmonary Disease

Rehabilitation, Cardiac

Maurizio Volterrani[1], Ferdinando Iellamo[2]
[1]UO di Riabilitazione Cardiologica, IRCCS San Raffaele Pisana, Rome, Italy
[2]Internal Medicine, University Tor Vergata, Rome, Italy

Synonyms

Cardiac rehab; Cardiac rehabilitation

Definition

The US Public Health Service defines Cardiac Rehabilitation (CR) as "Cardiac rehabilitation services are comprehensive, long-term programs involving medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling. These programs are designed to limit the physiological and psychological effects of cardiac illness, reduce the risk of sudden death or re-infarction, control cardiac symptoms, stabilize or reverse the atherosclerotic process, and enhance the psychological and vocational status of the individual patient" [1].

Cardiac rehabilitation is overseen by a specialized team of doctors, nurses, and other health care professionals. Members of the cardiac rehabilitation team may include a dietician or nutritionist, physical therapist, exercise physiologist, psychologist, occupational therapist, and social worker.

CR is highly recommended by the European Society of Cardiology, the American Heart Association, and the American College of Cardiology [2, 3]. The core component of CR programs is physical exercise.

CR programs involve both ambulatory and residential programs, according to national Health Care Systems.

Eligible Patients

Patients who are considered eligible for Cardiac Rehabilitation include those who have experienced one or more of the following conditions:

- Myocardial Infartion (MI)
- Coronary Artery Bypass Grafting (CABG)
- Percutaneous coronary interventions
- Stable angina
- Heart valve surgical repair or replacement
- Heart or heart/lung transplantation
- Stable Heart Failure

The benefits of CR apply equally to both men and women, with similar improvements in functional capacity in elderly as in younger patients.

Pathogenetic Mechanisms

The mechanisms responsible for the beneficial effects of exercise in the framework of CR are not completely defined, but it is very likely that several interwined mechanisms contribute [4].

Epidemiological and experimental studies have identified multiple biological mechanisms that help to explain the effects of exercise training in secondary prevention of cardiovascular disease.

These mechanisms include:

- Antiatherogenic effects
- Antithrombotic effects
- Endothelial function alteration
- Autonomic functional changes
- Anti-ischemic effects
- Antiarrhythmic effects

Increased flow-mediated shear stress on arterial walls during exercise results in improved endothelial function, which is associated with enhanced synthesis and release of nitric oxide, which is responsible for endothelium-dependent vasodilatation and inhibition of multiple processes involved in atherogenesis and thrombosis. Chronic inflammation plays a major role in the pathogenesis of atherosclerotic lesions. Aerobic exercise training is associated with reduced plasma levels of C-reactive protein, a nonspecific biomarker of ► inflammation, which suggests that exercise training has also anti-inflammatory effects. Furthermore, exercise training has favorable effects on hemostasis, which can reduce the risk of a thrombotic occlusion of a coronary artery after the disruption of a vulnerable plaque. These antithrombotic effects include increased plasma volume, reduced blood viscosity, decreased platelet aggregation, and enhanced thrombolytic ability. Endurance exercise also can promote decreases in blood pressure and serum triglycerides, increases in high-density lipoprotein cholesterol, and improvements in insulin sensitivity and glucose homeostasis. All these beneficial effects translate in anti-ischemic effects.

Aerobic exercise training may decrease the risk of life-threshold arrhythmias and sudden cardiac death, by reducing sympathetic and enhancing parasympathetic (vagal) cardiac control, as indicated by increased heart rate

variability and increased baroreceptor reflex sensitivity, two clinical indexes of the vagal control of the sinoatrial node linked to a greater risk of ventricular fibrillation.

Exercise Intervention

Cardiac rehabilitation programs are generally divided into three main phases:

1. Inpatient CR (also known as Phase 1 CR): a program that delivers preventive and rehabilitative services to hospitalized patients following an index cardiovascular event.
2. Early outpatient CR (also known as Phase 2 CR): a program that delivers preventive and rehabilitative services to patients in the inpatient/outpatient setting early after a cardiovascular event, generally within the first 3–6 months after the event but continuing for as much as 1 year after the event.
3. Long-term outpatient CR (also known as Phase 3 or Phase 4 CR): a program that provides longer-term delivery of preventive and rehabilitative services for patients in the outpatient setting to be continued all-lifelong.

Phase 1

This program begins while patients are still in the hospital. Phase 1 includes education regarding the disease and the recovery process, personal encouragement, and inclusion of family members in classroom group meetings. Range-of-motion exercises can be initiated within the first 24–48 h. Patients should, at the beginning, try to sit up, stand, and walk in their room. Subsequently, they should start to walk in the hallway at least twice daily for certain specific distances or as tolerated. Standing heart rate and blood pressure should be obtained followed by 5 min of warm-up or stretching. Walking, often with assistance, is resumed, with a target heart rate of less than 20 beats above the resting heart rate. Starting with 5–10 min of walking each day, exercise time gradually can be increased to up to 30 min daily.

Phase 2

This phase starts 2–6 weeks after the index cardiovascular event. This phase is mainly centered on supervised exercise training programs.

In this phase, exercise prescription is based on the results of a symptoms-limited exercise test, with detection of patient's peak heart rate (HR). Exercise test often includes monitoring of gas exchanges (i.e., cardiopulmonary exercise test) for objectively measuring functional capacity through evaluation of maximal oxygen consumption (► maximum O_2 uptake) and other relevant physiological parameters, such as ventilatory efficiency (e.g., VE/VCO_2 slope). Cardiopulmonary exercise test is mainly helpful in the functional evaluation of patients with stable chronic heart failure.

In this phase of CR, exercise training sessions are supervised. Initially, continuous ECG monitoring is recommended for most patients.

Exercise sessions should begin with 10 min of warm-up, during which light calisthenics and muscular stretching are performed to avoid muscle injury and to bring about a graded increase in heart rate. This warm-up period is followed by 30–40 min of aerobic exercise (e.g., walking, jogging, bicycling) and a final 10 min of cool-down period involving muscular stretching. The cool-down period is very important. Gradual cool-down prevents ventricular arrhythmias, which may occur in patients with coronary disease on abrupt cessation of exercise, particularly in elderly patients.

Exercise intensity is targeted to progressively achieve 75% and then 85% of peak HR attained at the initial exercise test or to 65–75% in older individuals. A follow-up exercise test should be performed at 4–8 weeks after the patient starts the program, and the result should be used to reset the exercise training program.

Aerobic endurance exercise appears to be the most effective in secondary prevention. Any aerobic activity seems to work, including walking, jogging, or cycling, although cycling seems the most effective. Moderate-to-vigorous intensity exercise seems to be the most effective. The physical training process should contemplate an increase in the number and duration of sessions and only later their intensity.

Aerobic exercise training would be effective both in the form of continuous moderate training and in the form of interval training, which alternates brief bouts of high-intensity exercise, for example, 90% HRmax, with bouts of less-intensive exercise.

Resistance exercises, such as chest press, leg press, leg extension, leg curls, triceps extension, biceps curl, shoulder press, etc. are also recommended, when not contraindicated (e.g., early after CABG, hypertensive response to exercise). Resistance exercises have been shown to increase muscular strength, power, and mass and to ameliorate lipid and glucose metabolism, being simultaneously safely. They also enhance independence, and quality of life while reducing disability in persons with and without cardiovascular disease, which is mostly important in the elderly [5].

Usually, they consist in one set of 8–15 repetitions at an intensity equal to 40% of one repetition maximum, and

involving 8–10 major muscle group in sequence. The recommended frequency is 2 days per week

Phase 2 CR typically envisages 3 weekly exercise sessions in an outpatient setting and may last 3–6 months.

In the inpatient setting, 2 daily exercise training sessions for 6 days a week for a shorter duration are foreseen, according to National Health Care Systems and local practice.

Phase 3

Phase 3 of cardiac rehabilitation is a maintenance program designed to continue for the patient's lifetime. Present guidelines recommend ► physical activity for all or most of the days. The amount of physical activity should be at least for 150 min/week of moderate intensity aerobic exercise or 75 min/week of vigorous intensity aerobic exercise. Patients usually need to allow 30–60 min for each session, which includes a warm-up of at least 10 min, which can be even interspersed throughout the whole day [6].

Activities consist of the type of exercises the patient enjoys, such as walking, bicycling, or jogging, with 2 weekly sessions of resistance exercise. The main goal of phase 3 is to promote habits that lead to a healthy and satisfying lifestyle.

Phase 3 programs do not usually require medical supervision. In fact, most patients participate in "phase 3" equivalent exercises at the exercise facilities in the community.

Periodic assessments of patient's clinical status for redefining physical activity programs are, however, recommended.

Safety

Supervised exercise training programs are extremely safety. Randomized, controlled trials have shown no significant difference in morbidity or mortality in rehabilitation compared with control patient groups.

Cardiac rehabilitation is not only clinically effective, but is cost-effective as well. Cardiac rehabilitation compares favorably with other medical interventions performed commonly in patients with coronary heart disease.

Contraindications to CR

Exercise-based CR is contraindicated in patients with the following conditions:

Severe residual angina
Uncompensated heart failure
Uncontrolled arrhythmias
Severe ischemia, LV dysfunction, or arrhythmia during exercise testing
Poorly controlled hypertension
Hypertensive or any hypotensive systolic blood pressure response to exercise
Unstable concomitant medical problems (e.g., not controlled diabetes, ongoing febrile illness, etc.)

Therapeutical Consequences of CR

The aim of CR is to improve functional capacity, and hence exercise tolerance, recovery, and well-being.

CR is associated with reductions in submaximal heart rate, systolic blood pressure, and rate-pressure product, thereby decreasing myocardial oxygen requirements during activities of daily living. In addition, improvement in cardiorespiratory endurance is associated with a significant reduction in subsequent cardiovascular fatal and nonfatal events, independent of other risk factors.

Expected and actual consequences of CR are: (1) improved clinical stability and symptoms control to allow patients to resume their customary activities, (2) life-style changes, including smoking cessation and changes in dietary habits, leading to a better health behavior, (3) improvements of CV risk factors and reduced overall cardiovascular risk through the mechanisms illustrated above, all leading to an improved prognosis.

These beneficial effects, however, do not persist long-term after completion of cardiac rehabilitation without a long-term maintenance program. Therefore, exercise training must be maintained all-lifelong to sustain the benefits it induces.

Cross-References

► Arteriosclerosis

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Rehydration

Gain of body water following body water loss.

Cross-References

► Fluid Replacement

Renal Medullary Carcinoma

It is a rare type of cancer that affects the kidney. It tends to be aggressive, difficult to treat, and is often metastatic at the time of diagnosis.

Renin

An aspartyl-protease mainly produced and released into circulation by juxtaglomerular epithelioid cells, located in the walls of renal afferent arterioles at the entrance of the glomerular capillary network. Renin acts on angiotensinogen, an α2-globulin produced by the liver, forming angiotensin I.

Renin-Angiotensin Mechanism

Francesco Fallo, Andrea Ermolao
Department of Medical and Surgical Sciences, University of Padova, Padova, Italy

Synonyms

Hormones regulating vascular tone and body fluids; Renin-angiotensin system

Definition

The ► renin-angiotensin system plays a primary role in regulating the physiological response and adaptation of fluid-electrolyte balance and cardiovascular activity to exercise in man through vasoconstriction and aldosterone production. Recent advances have suggested the existence of local renin-angiotensin systems (i.e., muscle, heart, and kidneys) as regulators of chronic tissue effects. A role of gene variants of the ► angiotensin-converting enzyme (ACE) in determining human athletic performance has been recently indicated.

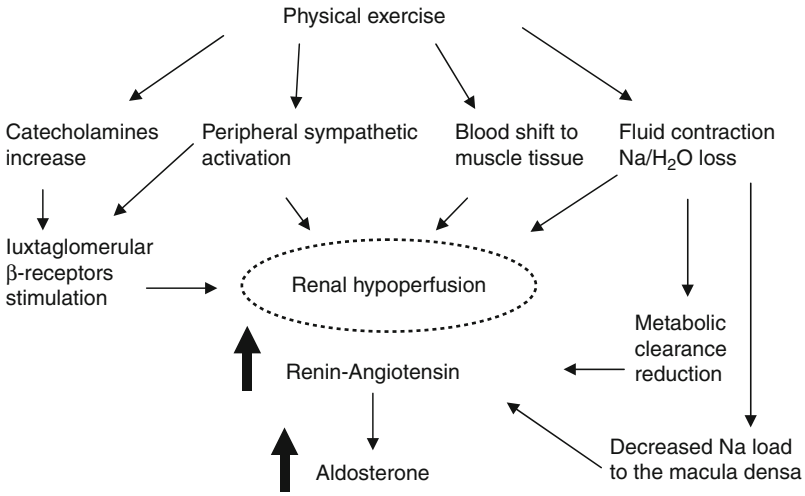
Basic Mechanisms

The renin-angiotensin system regulates sodium-fluid balance and arterial pressure. ► Renin is an aspartyl-protease secreted into circulation by juxtaglomerular epithelioid cells, after conversion from its inactive form (i.e., prorenin). The main signals to the juxtaglomerular cells causing renin secretion are the decreased tension of the renal afferent arteriolar wall (vascular baroceptor), the fall in the NaCl load to the macula densa, and the stimulation of juxtaglomerular β-adrenoceptors. In plasma, renin hydrolizes the α2-globulin ► angiotensinogen, synthesized by liver, to the decapeptide ► angiotensin I, quickly converted by ACE (produced by the lung) into the active octapeptide ► angiotensin II. The ACE is also present on the membrane of vascular endothelial cells in various organs, including muscle, and catalyzes the inactivation of vasodilator bradykinin. Angiotensin II interacts with two membrane receptors (AT1, AT2) of target organs, primarily increasing vascular tone and stimulating aldosterone secretion from the adrenal zona glomerulosa. Aldosterone potentiates the activity of the ► Na/K pump in the kidney distal tubular cells, leading to sodium retention and potassium excretion. Positive sodium balance causes body fluid repletion, which reduces renin secretion *via* a negative feedback.

Exercise Intervention

Effect of Physical Exercise on Renin-Angiotensin System

Renal hypoperfusion is considered the physiological mechanism of renin-angiotensin system activation during physical exercise in man (1–3) (Fig. 1). However, other factors may be present and the actual signal to the juxtaglomerular cells for renin secretion has still to be clarified. In this regard, current hypotheses can be summarized: (1) Exercise, if heavy and in a hot environment, leads to an important loss of sodium and water with sweating; this induces extracellular fluid restriction and



Renin-Angiotensin Mechanism. Fig. 1 Effect of exercise on the renin-angiotensin system

thereby decreases renal perfusion. Exercise also causes a blood shift toward the active muscles tissue, as well as a possible reduction in plasma volume in running and cycling. Both these conditions can further reduce renal perfusion. Finally, sodium loss decreases sodium filtration by glomeruli and the NaCl load to the macula densa, with a direct renin stimulating effect. (2) Physical activity enhances renal sympathetic tone and directly increases renin secretion by activating β-adrenoceptors on juxtaglomerular cells. Increased sympathetic activity, by vasoconstriction of glomerular afferent arteriolae, causes renal hypoperfusion and renin stimulation. Moreover, circulating catecholamines are increased by physical stress, stimulating β-adrenoceptors at vessel and juxtaglomerular cells site. The activation of adrenergic system seems mainly involved in response to isometric exercise, where the hemodynamic change is seen as the elevation in peripheral vascular resistance elicited from reflex by afferent impulses originating in the exercising muscle. (3) During exercise, blood redistribution from splanchnic to muscular circulation decreases hepatic blood flow, reducing metabolic clearance of renin.

Since angiotensin II is the primary regulator of aldosterone production, the activation of renin-angiotensin system during various types of exercise has been shown to parallel that of aldosterone. However, a lower increase of angiotensin II compared to that of aldosterone has been observed in high-intensity exercise, suggesting a role of metabolic acidosis in angiotensin II degradation or a delayed response of adrenal zona glomerulosa to acute angiotensin II stimulation. Moreover, ACE-inhibitor captopril, which blocks angiotensin II formation, has no effect on aldosterone response to maximal exercise. Dissociation between renin response and aldosterone response to exercise has been attributed to the effect of ACTH or other possible factors (hydrogen ions and potassium) on aldosterone secretion.

Recent data indicate the existence of a skeletal muscle renin-angiotensin system (4), with local angiotensin II production resulting from a combination of in situ synthesis and of uptake from circulation of all renin-angiotensin system components. Current studies have shown the presence of only AT1 receptors in human skeletal muscle. Increased local ACE and angiotensin II seem to be related to greater strength gains, perhaps *via* muscle hypertrophy, whereas lower ACE levels and reduced bradykinin degradation are linked to enhanced endurance performance. Angiotensin II regulates muscle performance acting at different sites, shown in Table 1.

Conditions Affecting the Renin-Angiotensin System Response to Exercise

Genotype

An insertion (I)/deletion (D) polymorphism of the ACE gene has been proposed as a potential marker of differential response to exercise (5). The I/D polymorphism is responsible for half the variation in ACE enzyme activity, with a progressive increase of its activity from the homozygote genotype II, to the homozygote DD. Angiotensin II has effects which might alter performance. In fact, angiotensin II acts as a growth factor on cardiomyocytes, while in animal models ACE inhibition has been shown to attenuate overload-induced skeletal muscle hypertrophy.

Renin-Angiotensin Mechanism. Table 1 Sites of angiotensin II-related mechanisms regulating muscle performance

• Vascular system Increases capillary density in skeletal muscles (AT1 receptors)
• Nervous system Increases norepinephrine and epinephrine release from sympathetic and central nervous system
• Skeletal muscle Directly induces hypertrophy Redirects blood flow to type 2 fibers
• Smooth muscle Modifies vascular smooth muscle cell tone in skeletal muscle

Alternatively, such effects may be mediated through the potent kininase activity of ACE. Bradykinin can alter energy metabolism, reduce lactate concentrations, and change glucose and free fatty acids availability. Current studies suggest that ACE II genotype may be related to a better performance in aerobic endurance of medium duration, while ACE DD genotype seems to have a positive influence on shorter performance at higher-intensity activities. A higher metabolic efficiency, that is, a lower ratio between muscle work performed and energy expenditure, has also been linked to reduced renin-angiotensin system activity (ACE II genotype). At variance, ACE DD genotype is associated to greater muscle size and strength at baseline and after resistance training. Much remains to be learned about the role of other genes in regulating muscle performance during exercise.

Age/Gender/Posture/Daytime/Menstrual Status

Resting levels of renin and aldosterone decrease with age, while no differences in renin and aldosterone response have been observed between males and females after maximal exercise. Exercising at moderate intensity (40–50% of $V0_{2max}$) in a supine position induces a lower increase in renin and aldosterone with respect to the normal upright position. The time of the day does not affect aldosterone response to exercise (60% of $V0_{2max}$), while renin response is markedly higher in the afternoon than in the early morning. In eumenorrheic athletes, pre-exercise levels of renin and aldosterone are significantly higher during the midluteal phase than in the follicular phase of the menstrual cycle. While renin elevation is similar in both these menstrual phases during submaximal exercise, aldosterone response is greater during the midluteal than during the follicular phase. Higher resting and postexercise levels of aldosterone may be due to elevated progesterone levels, leading to a lower sodium-to-potassium ratio and decreased losses of sodium and potassium in sweat.

Thermal Stress/Salt-Water Balance

After prolonged exposure to thermal stress, a reduction in sweat sodium output occurs as a consequence of a concomitant increase in renin and aldosterone at rest. During intense and prolonged exercise as well as during moderate exercise in the heat or in a dehydrated condition, a paradoxical reduction in renal concentrating ability has been demonstrated in spite of a higher stimulation of either renin-angiotensin system activity or vasopressin secretion. The sympathoadrenal system seems to play a major role in this phenomenon. Salt intake can influence renin response to exercise. Indeed, while short-term exercise induces comparable increments of renin during normal and high sodium diet, in the salt-loaded state no renin increase was observed during long-term exercise.

Altitude

A review of the studies carried out at high altitude suggests a decrease in resting renin and aldosterone levels during acute exposure (−9% and −29%, respectively), and a further decline (−10% for both hormones) from acute to chronic exposure. The mechanisms responsible for this reduction are still unknown, although the suppression of plasma renin activity may be related to the increase of atrial natriuretic peptide with acute altitude exposure and/or to stimulation of an intrarenal baroreceptor, due to increased renal perfusion following chronic altitude exposure. On the other hand, the decrease of aldosterone during acute or chronic hypobaric hypoxia is probably due to the reduced renin values, although a decrease in plasma potassium and ACTH may play a role. Finally, the production of angiotensin II as well as ACE activity do not appear to be inhibited by hypoxia. After exercise, renin response seems to be similar to that observed at sea level, and there is a general agreement about a slightly reduced aldosterone response to exercise during both acute and chronic high altitude exposure. Dissociation between renin and aldosterone response during exposure to high altitude disappears with time, probably indicating the presence of an adaptation mechanism. During high altitude exposure, the reduced aldosterone response to angiotensin II may contribute to the increased diuresis and natriuresis, thus preventing pulmonary and brain edema seen in "► acute mountain sickness." Resulting hemoconcentration can also be beneficial for increasing hemoglobin and oxygen transport.

Training Level/Type of Exercise

There is no evidence in humans that training can influence resting renin and aldosterone levels. A lower increase in renin and aldosterone after exercise has been reported in well-trained than in untrained subjects; however, there are also reports indicating normal response of renin and aldosterone, when hormone values are adjusted for confounding variables, such as age, sex, body weight, etc. In male runners participating in a single or a stage long-distance running race, aldosterone levels increase, returning to normal after the end of the competition. Increases in renin and aldosterone after maximal exercise during swimming are lower than those observed during running, probably because of the different hemodynamic conditions, since the body fluid shift induced by the supine position and water pressure may decrease renin response to exercise. Other studies confirm lower resting renin and aldosterone levels after water immersion, while do not report modifications of these hormones after submaximal or maximal exercise during swimming.

Conclusions

The modification of renin-angiotensin system during physical exercise probably represents the homeostatic response of the human body to a new biological condition. This adaptation leads to the maintenance of an adequate water and electrolyte balance as well as of cardiovascular function. With cessation of exercise, hormones return to normal levels, and no relationship has been demonstrated between physical activity and persistent endocrine alterations. However, the behavior of this hormonal system during recovery from various modes and duration of exercise requires further study. New mechanisms of renin-angiotensin system regulation, that is, changes in receptor number and sensitivity to angiotensin II and aldosterone, and the possible influence of different genotypes should also be evaluated further.

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Renin-Angiotensin System

A system regulating sodium-fluid balance and arterial pressure of interacting components that include renin, angiotensinogen, angiotensin-converting enzyme, angiotensin I, angiotensin II.

Cross-References

► Renin-Angiotensin Mechanism

Repeated Bout Effect

Muscle adaptation occurs following an initial bout of damaging exercise so that future performances of similar exercise cause an attenuated damage response.

Repeated Sprint Ability

It is the ability to reiterate maximal short-term (2–6 s or 20–40 m) sprint with different exercise modes (line, slalom, and shuttle running) with brief and consequently incomplete recovery time (20–30 s). This ability known as RSA has been considered to be a team-sport specific fitness determinant for success.

Reperfusion

Restoration of blood flow through tissue after a period of ischemia, causing oxidative stress and inflammation.

Reproductive Cycle

► Menstrual Cycle

Required Nutrients

► Micronutrients

Resistance Training

William J. Kraemer[1], Nicholas A. Ratamess[2]
[1]Department of Kinesiology, University of Connecticut Human Performance Laboratory, Storrs, CT, USA
[2]Department of Health and Exercise Science, The College of New Jersey, Ewing, NJ, USA

Synonyms

Strength training; Weight lifting; Weight training

Definition

► Resistance training includes several modalities of exercise designed to overload the human body. The objective is to repeatedly contract skeletal muscles at intensities greater than one is normally accustomed to. Metabolic, neural, muscular, connective tissue, endocrine, and cardiovascular changes take place that contribute to increases in muscular strength, power and speed, hypertrophy, endurance, motor performance, balance, and coordination [1, 2]. The resultant effect can be improved performance for athletic populations and/or improved quality of life or ability to perform activities of daily living in older or clinical populations [3]. The source of resistance varies but may include one's body weight, manual (self-applied or partner) resistance, stretchable bands/tubing, sport-specific devices, free weights (barbells, dumbbells, kettle bells, and associated equipment), machines, medicine balls, balance equipment (stability balls, BOSU™ balls, wobble boards), and special implements (chains, sand bags, kegs, sledge hammers, and strength competition equipment).

Characteristics

The resistance training program is the critical element to subsequent ► physiologic adaptation. Programs can be systematically altered to target specific components of fitness. The ► acute program variables include muscle actions used, intensity, volume (total number of sets and repetitions), exercises selected and workout structure (the number of muscle groups trained), exercise sequence, rest intervals between sets and exercises, repetition velocity, and training frequency [1, 2]. Manipulation of the acute program variables targets increases in muscle strength, power, endurance, and hypertrophy. Guidelines for resistance training program design have been developed by the American College of Sports Medicine and endorsed by the National Strength and Conditioning Association [2]. Table 1 summarizes these recommendations [2].

Resistance training programs depend on several factors including the individual's goals, strengths and weaknesses, training status, injury or health concerns, equipment availability, and the specific needs of the activity the individual is training for [1, 4]. Training status reflects a continuum of adaptations such that the level of fitness, training experience, and genetic endowment each make a significant contribution. Untrained individuals have a large window of adaptation and respond favorably to most training programs. However, trained individuals show slower rates of improvement so program design needs to become more sophisticated in order to produce further positive adaptations [1–3]. Although general programs are effective initially, greater specialization is needed as the individual increases muscular fitness [1].

Table 1 provides a framework for program design. Any resistance training program can be effective so long as it includes recommended training strategies and adheres to the three basic tenets of progression: ► progressive overload, ► specificity, and ► variation [2]. Progressive overload entails the gradual increase of stress placed upon the body during training, e.g., lifting more weight or performing more repetitions with a standard resistance. The human body will only adapt if it is consistently required to exert greater force, power, or endurance to meet higher physiological demands. The overload must surpass the individual's current threshold level for adaptation. Specificity involves designing programs specific to needs. All training adaptations are specific to the stimulus, i.e., the muscle actions involved, speed of movement, range of motion, muscle groups trained and movement patterns, energy systems involved, and intensity and volume of training. Although there are some carryover effects, the most effective programs are designed to meet individual needs. *Variation* increases the number of stimuli encountered during training. It requires alterations in one or more program variables over time. Studies have shown that systematically varying volume and intensity (periodization) is most effective for long-term fitness improvements compared to non-varied programs [1, 2, 4].

► Periodized resistance training involves planned manipulation of the program variables in a systematic manner. This is most commonly implemented by use of specific training cycles. Cycles target few fitness components and allow improvement by specialized training as it becomes more difficult to simultaneously improve several fitness variables at once with advanced training (as is the case in untrained or moderately trained populations). One commonly studied periodization scheme is the ► classic model. It is characterized by high initial training

Resistance Training. Table 1 Resistance training guidelines

Variable	Strength	Hypertrophy	Power	Endurance
Muscle action	CON, ECC, and ISOM	CON, ECC, and ISOM	CON, ECC, and ISOM	CON, ECC, and ISOM
Intensity	60–70% 1RM (NOV, INT)	70–85% 1RM (NOV and INT)	Similar to strength training to increase force component	60–70% 1RM (NOV, INT)
	80–100% 1RM periodized (ADV)	70–100% 1RM periodized (ADV)	Light-to-moderate (30–60% 1RM for UB, 0–60% 1RM for LB exercises) to increase velocity component (NOV, INT, and ADV)	50–80% 1RM periodized (ADV)
Volume	1–3 sets per exercise for 8–12 reps (NOV)	1–3 sets per exercise for 8–12 reps (NOV and INT)	1–3 sets per exercise for 3–6 reps (NOV, INT)	1–3 sets per exercise for 8–12 reps (NOV)
	Multiple sets per exercise (INT, ADV) periodized matching changes in intensity for 1–10 reps	3–6 sets per exercise for 1–12 reps periodized with emphasis in 6–12 rep range (ADV)	3−6 sets of 1–6 reps (ADV)	Multiple sets per exercise (INT, ADV) periodized matching changes in intensity for 10–25 reps or more
Exercise selection	UL and BL single- and multiple-joint exercises with emphasis on multiple-joint exercises (NOV, INT, ADV)	UL and BL single- and multiple-joint free weight and machine exercises (NOV, INT, and ADV)	Multiple-joint exercises (NOV, INT, and ADV)	UL and BL single- and multiple-joint free weight and machine exercises (NOV, INT, and ADV)
	Free weight and machine exercises with emphasis on free weights in ADV training			
Workout structure	Total body or UB/LB split	Total body, UB/LB split, or muscle group split routines	Total body or UB/LB split	Total body, UB/LB split, or muscle group split routines
Exercise order	Large muscle group exercises before small, multiple-joint exercises before single-joint, higher-intensity exercises before lower-intensity, rotation of UB and LB or opposing exercises for NOV, INT, and ADV	Similar to strength training	Similar to strength training	Numerous sequencing strategies may be used to induce fatigue (NOV, INT, and ADV)
Rest intervals	2–3 min for core exercises (NOV, INT, and ADV)	1–2 min (NOV, INT)	2–3 min for core exercises (NOV, INT, and ADV)	1–2 min for high reps (15–20 or more) $<$ 1 min for moderate reps (10–15)
	Assistance exercises – 1–2 min (NOV, INT, and ADV)	2–3 min for heavy sets, 1–2 min or less for low-to-moderate intensity sets (ADV)	Assistance exercises – 1–2 min (NOV, INT, and ADV)	Circuit training – time needed to get from one station to another (NOV, INT, and ADV)

Resistance Training. Table 1 (Continued)

Variable	Strength	Hypertrophy	Power	Endurance
Lifting velocity	Slow (2–3 s)-to-moderate (1–2:1–2) (NOV)	Slow-to-moderate (NOV, INT)	Fast (NOV, INT, and ADV)	Slow for moderate number of reps (10–15)
	Moderate (INT) continuum of velocities from unintentionally slow-to-fast (<1:1) (ADV)	Slow-to-fast depending on goals of set (ADV)		Moderate-to-fast for high reps (15–25 or more) (NOV, INT, and ADV)
Frequency	2–3 days/week (NOV)	2–3 days/week (NOV)	2–3 days/week (NOV)	2–3 days/week (NOV)
	3–4 days/week (INT)	3–4 days/week (INT)	3–4 days/week (INT)	3–4 days/week (INT)
	4–6 days/week (ADV)	4–6 days/week (ADV)	4–5 days/week (ADV)	4–6 days/week (ADV)

CON concentric muscle action, *ECC* eccentric muscle action, *ISOM* isometric muscle action, *NOV* novice, *INT* intermediate, *ADV* advanced, *1RM* one repetition-maximum, *UL* unilateral, *BL* bilateral, *UB* upper body, *LB* lower body

volume and low-to-moderate intensity. As training progresses, volume decreases and intensity increases in order to maximize strength, power, or both. Each training phase is designed to emphasize a particular component, e.g., hypertrophy, strength, and power. The classic model of periodization has been shown to be superior for increasing maximal strength, cycling power, motor performance, and jumping ability [1, 2]. However, muscular endurance is more specifically trained using the opposite approach. ► Reverse periodization is the opposite of the classical model in that intensity is highest and volume is lowest initially. Each subsequent phase comprises a reduction in intensity with concomitant increase in volume. This model has been shown to be superior for endurance enhancement compared to nonperiodized and classic models [2]. A third paradigm is the ► nonlinear (undulating) model**.** The undulating model allows variation in intensity and volume within each weekly or biweekly cycle by rotating different protocols. One workout may be dedicated to a trainable characteristic, e.g., strength, power, local muscular endurance. The loading schemes for core exercises may be heavy, moderate, and light rotated from one workout to the next. This model compares favorably with the classic model and one study found it to be superior for increasing maximal strength [1, 2].

Measurements/Diagnostics

Testing is a critical element to resistance training. Testing serves many purposes including identifying an individual's strengths and weaknesses, training loads, and is used to evaluate progress. Identifying strengths and weaknesses directs the trainer toward selecting exercises, intensity, and volume aimed at improving the weaknesses to increase muscle balance, performance, and reduce the risk of injury [5]. Testing determines maximal strength levels for an exercise. Thus, a relative percent (e.g., 70%) can be prescribed as exercise intensity. The trainer simply calculates the training load by multiplying the maximal value by the decimal of the percent. Testing is critical for assessing progress. This can be in the form of a maximal strength test or by measuring the maximal number of repetitions performed at a given load.

Strength testing comes in various forms depending on the type of strength measured, e.g., dynamic concentric and eccentric, isometric, or isokinetic muscle strength. The gold standard of dynamic strength testing is the ► one repetition-maximum (1RM) which can be performed with free weights and machines. The 1RM is the maximal amount of weight that can be lifted once for a specific exercise (usually for multiple-joint exercises like the squat, bench press, and dead lift). High test-retest reliabilities have been shown for 1RM testing [5]. Isometric tests are performed at a static position. Force and torque vary throughout joint range of motion so precise standardization is required. Some devices used include the hip and back dynamometer and handgrip dynamometer (grip strength) in addition to strain gauges used in laboratory settings. Although peak force is often measured, rate of isometric force development and fatigue index can also be measured [4, 5]. Isokinetic strength testing can be performed with a dynamometer that maintains the lever arm at a constant angular velocity. This type of strength evaluation accounts for concentric and eccentric movement velocity but the cost can be prohibitive. Testing

should match the training velocity and/or include a spectrum of slow (< 90°/s), moderate (100–180°/s), and fast (>200°/s) velocities. Test-retest reliability for isokinetic testing is high when position is standardized, equipment is calibrated, and maximal effort is given by the individual [4, 5].

Cross-References

► AIDS, Exercise
► Strength Training, Health Benefits of

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Resistance Training, Children

Avery Faigenbaum
Department of Health and Exercise Science, The College of New Jersey, Ewing, NJ, USA

Synonyms

Strength training; Weight training

Definition

► Resistance training is defined as a specialized method of conditioning that involves the progressive use of a wide range of resistive loads and a variety of training modalities including free weights (barbells and dumbbells), weight machines, medicine balls, elastic bands, and body weight that are specifically designed to enhance health, fitness, and sports performance. Resistance training should be distinguished from the competitive sports of weightlifting and powerlifting. The term children refers to boys and girls who have not yet developed secondary sex characteristics (Tanner stages 1 and 2 of sexual maturation; approximately up to age 11 in girls and 13 in boys). This period of development is often referred to as ► preadolescence. The term ► adolescence refers to the period of time between childhood and adulthood.

Characteristics

There is growing interest from the general public, sport organizations, and the scientific community regarding resistance training for children. Key areas of concern relate to the trainability of muscle strength in children, the relative safety of resistance exercise for younger populations, and the potential benefits associated with regular resistance training. Although some observers once considered resistance exercise unsafe and potentially injurious to the developing musculoskeletal system, research regarding the effects of resistance training on children has increased over the past two decades and the qualified acceptance of youth resistance training by medical and fitness organizations has become widespread [1–3].

Effectiveness of Resistance Training

During preadolescence, many physiological changes related to growth and development occur at a rapid rate. Thus, it can be expected that healthy children will show noticeable gains in height, weight, and measures of physical fitness during the developmental years. For example, muscular strength normally increases from childhood through the early adolescent years, at which time there is a marked acceleration in strength in boys and a general plateau in strength in girls. For this reason, strength changes from a low volume (sets x repetitions x load), short-duration resistance training program may not be distinguishable from gains due to normal growth and development. This is an important consideration when evaluating research studies that failed to demonstrate strength gains in youth following a resistance training program.

A compelling body of scientific evidence indicates that children can significantly increase their muscle strength above and beyond growth and development providing that the resistance training program is of sufficient duration, intensity, and volume. Boys and girls have benefited from this type of exercise and a wide variety of resistance training programs from single set workouts on weight machines to advanced multi-set protocols with free weights have proven to be efficacious [4]. On average, strength gains of roughly 30% are typically observed following short-term (8–20 weeks) youth resistance training programs.

Mechanisms of Strength Development

It appears that training-induced strength gains during preadolescence are more related to neuromuscular mechanisms than to morphological factors. Neuromuscular adaptations including increases in motor unit activation and changes in motor unit coordination, recruitment and firing are primarily responsible for training-induced strength gains during preadolescence [1]. Improvements in motor skill performance and the coordination of the involved muscle groups may also play a role in training-induced strength gains during preadolescence. Without adequate levels of circulating androgens to stimulate increases in muscle size, children appear to experience more difficulty increasing their muscle mass consequent to a resistance training program as compared to older populations. During and after puberty, gains in muscle strength following resistance training may be associated with changes in the cross-sectional area of muscle in males since testosterone and other hormonal influences on muscle hypertrophy would be operant. Smaller amounts of testosterone in females limit the magnitude of training-induced gains in muscle hypertrophy.

Risks and Concerns

Resistance training was not always recommended for children due to the presumed high risk of injury associated with this type of exercise as well as the alleged lack of any training-induced benefit. In the vast majority of published studies, no overt clinical injuries have been reported-during youth resistance training research programs [5]. Scientific findings suggest that youth resistance training is relatively safe, provided the programs are characterized by qualified supervision, safe equipment, and strict adherence to age-appropriate training guidelines.

Although the risk of injury associated with youth resistance training is relatively low, a traditional area of concern in children is the potential for training-induced damage to the ► growth cartilage. Since growth cartilage is the weak link in the young skeleton, it is more easily damaged by repetitive microtrauma. While injury to the growth cartilage was noted in a few retrospective case reports, most of these injuries were due to improper lifting techniques, maximal lifts, or lack of qualified adult supervision. To date, injury to the growth cartilage has not been reported in any prospective youth resistance training study that was characterized by appropriately prescribed training regimens and competent instructions. Moreover, there is no evidence to suggest that resistance training will negatively impact growth during childhood and adolescence.

As with most physical activities, resistance training does carry with it some degree of inherent risk of musculoskeletal injury, yet this risk is no greater than many other sports or recreational activities in which children regularly participate. However, due to individual differences in stress tolerance, professionals who work with children should sensibly progress the training program and allow for adequate recovery between training sessions. Based on the available scientific evidence as well as clinical observations, there are no justifiable safety reasons which preclude children from participating in supervised and well-designed resistance training programs.

Potential Benefits

Participation in a youth resistance training program provides children with an opportunity to improve their health, fitness, and quality of life. In addition to increasing muscular strength, the safe and proper prescription of resistance exercise has been shown to favorably influence bone mineral density, body composition, cardiovascular risk, and resistance to sports-related injuries [3]. These health-related benefits, along with performance-related benefits, such as improvements in motor performance skills (e.g., sprinting and jumping), will likely enhance the quality of life for children by enabling them to perform life's daily activities with more energy and vigor.

Traditional fears that resistance training would be harmful to the immature skeleton of young weight trainers have been replaced by current findings which suggest that childhood and adolescence may be the opportune time for the bone modeling and remodeling process to respond to the tensile and compressive forces associated with weight-bearing activities [1]. Concerns that resistance exercise would cause harm to the growth plates of youth lifters have been replaced by observations which indicate that the mechanical stress placed on developing growth plates from weight-bearing exercise or high-strain eliciting sports such as gymnastics are actually essential for bone formation and growth.

Regular participation in exercise programs that include resistance training can also improve the body composition of overweight youth and enhance the preparedness of young athletes for sports participation. Since overweight youth with low muscle fitness seem to have the poorest metabolic risk profile, the protective effect of muscular fitness on the cardiovascular risk profile of overweight youth is an important health benefit [3]. Moreover, the incidence of sports-related injuries in youth sports can be reduced by identifying contributory risk factors such as poor physical condition. A decrease in injury rates has been observed in adolescent athletes who have participated in a multi-component conditioning program which included resistance training and it seems

likely that children would experience similar benefit if age-appropriate training guidelines are followed. Preseason conditioning which includes resistance training has proven to be particularly beneficial for adolescent female athletes who appear to be more susceptible to knee injuries than young male athletes [5].

Measurements/Diagnostics

Resistance training can be a safe and effective method of conditioning for children provided that the program is carefully designed and qualified instruction is available. Although there is no minimum age for participating in a youth resistance training program, children should have the emotional maturity to accept and follow directions and should appreciate the benefits and concerns associated with this mode of exercise. If a child is ready for participation in some type of sport activity (generally age 7 or 8), then he or she may be ready to resistance train [4].

Youth resistance training programs need to be carefully prescribed and progressed. Over-prescription of resistance training may result in overtraining and injury, whereas under-prescription of resistance training will result in suboptimal adaptations. For that reason, the magnitude of individual effort along with the systematic structuring of the resistance training program needs to be carefully monitored. In addition, cautionary measures (e.g., qualified supervision, safe environment, health screening) need to be considered when children want to participate in a resistance training program [4].

A variety of resistance training programs have been developed and recommended for children. Different types of equipment and various combinations sets and repetitions have proven to be safe and effective. It has been recommended that children resistance train 2 or 3 days per week on nonconsecutive days and perform one to three sets of 6–15 repetitions on a variety of exercises that focus on the major muscle groups [3]. However, when beginning a resistance training program, performing one or two sets of 10–15 repetitions with a light to moderate weight will not only allow for positive changes in muscle function, but will also provide an opportunity for participants to gain confidence in their abilities before progressing to more advanced levels. Over time, continual gains can be made by gradually increasing the weight, the number of repetitions, or the number of sets. Table 1 highlights youth resistance training guidelines.

Finally, training-induced gains in muscle strength in children can be evaluated by repetition maximum (RM) testing procedures provided that youth participate in a habituation period prior to testing to learn proper exercise technique and qualified professionals closely supervise and administer each test. No injuries have been reported in prospective studies that utilized adequate warm-up periods, appropriate progression of loads, close and qualified supervision, and critically chosen maximal strength tests to evaluate resistance training-induced changes in children [5]. However, when properly administered RM tests are labor intensive and time consuming. Thus, in some instances (e.g., physical education class), the use of common field measures (e.g., handgrip, push-up, and abdominal curl up) may be more appropriate and time-efficient.

Resistance Training, Children. Table 1 Youth resistance training guidelines

Provide qualified instruction and close supervision
Ensure the exercise environment is safe and free of hazards
Begin each session with a 5–10 min dynamic warm-up
Focus on developing proper exercise technique and learning fundamental training principles
Perform 1–3 sets of 6–15 repetitions
Perform exercises for the upper body, lower body, and midsection
Include exercises that require balance and coordination
Cool down with less intense activities and stretching
Resistance train two to three times per week on nonconsecutive days
Keep the program fresh and challenging by systematically varying the training program

Cross-References

► Children, in Competitive Sports

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Resistance Training, Molecular Mechanisms

Andrew Philp, Keith Baar
Department of Neurobiology, Physiology and Behavior, University of California, Davis, CA, USA

Synonyms

Strength training

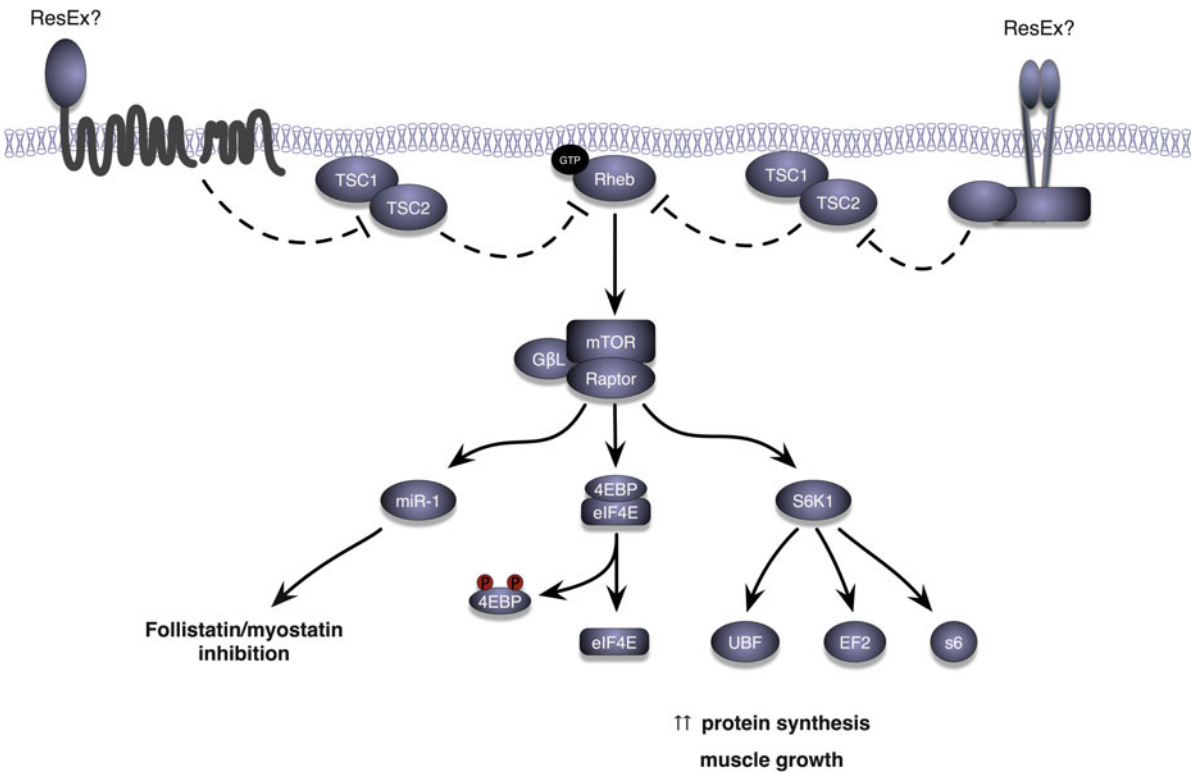
Definition

Resistance exercise is defined as exercise against a load that leads to an increase in muscle size and strength. The load can be external, a weight lifted, or internal, an antagonist muscle. Greater loads provide a stronger stimulus to increase muscle size and strength. However, the positive effects of the larger load have to be weighed against the greater possibility of injury. Molecular biology is defined as the study of life at the subcellular level. In other words, how the things within a cell (proteins, DNA, RNA, miRNA) respond to a change in homeostasis and how these changes lead to alterations in the phenotype of the cell. The molecular biology of resistance exercise is therefore the subcellular responses that lead from an increase in load across the cell to a bigger stronger muscle.

Basic Mechanisms

Since the times of the ancient Olympic games, people have understood that exercise against a progressively increasing load would increase muscle mass and strength. More recently, we have begun to learn how muscle transduces load into a signal to grow. Since muscle mass is largely dictated by how much protein is packed within the tissue, whether a muscle grows or shrinks is determined by the balance between ► protein synthesis and degradation (► protein balance). Even though both protein synthesis and degradation can be controlled, the regulation of protein synthesis is the primary determinant of muscle size and strength. Therefore, a great deal of focus has been placed on how resistance exercise can increase the rate of protein synthesis. These studies have identified a protein complex, called the mammalian target of rapamycin complex 1 (► mTORC1), as being central to this process. However, in mammals other molecular pathways also play an important role in the response to resistance exercise. How these pathways, including the growth inhibitor myostatin, the transcriptional regulator Notch, and the posttranscriptional regulating microRNAs (miRNA), control muscle size and strength is less clear. What is clear is that the interplay between these factors coordinates how much a muscle will grow in response to heavy loads.

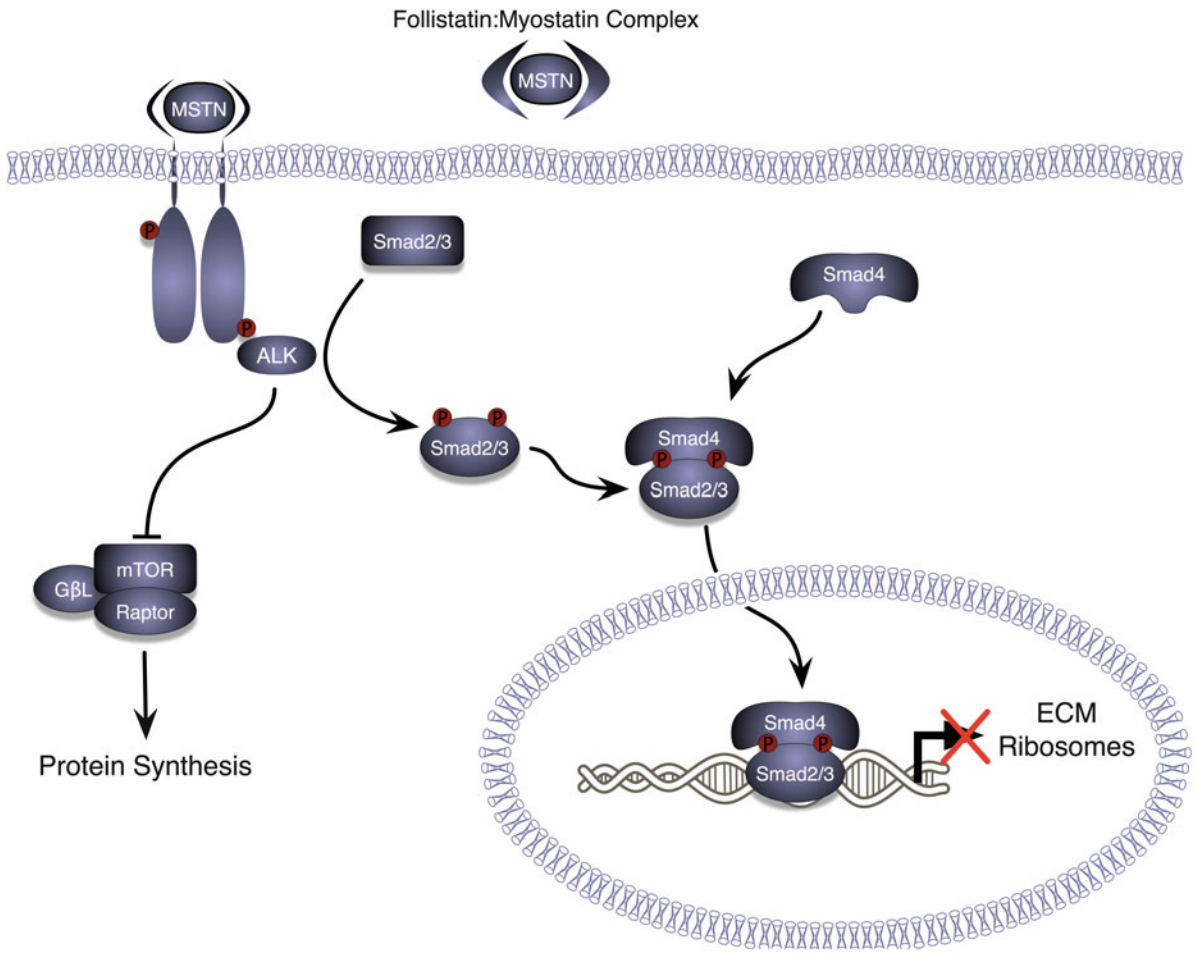
During resistance exercise, the high load on the muscle begins a chain reaction that leads to changes in muscle protein synthesis. The initial step in the process, namely, what senses the force on the muscle has yet to be identified. What we do know is that secondary to sensing the load, mTORC1 is activated. As the name implies, mTORC1 is a complex of three to four proteins that work together as a single unit to regulate protein synthesis and muscle growth [1]. Within complex 1 is mTOR, raptor (the rapamycin sensitive partner of mTOR), and Lst8 (lethal with SEC13 protein 8). mTOR is a serine/threonine protein kinase, a protein that places phosphate groups onto specific serines and threonines within other proteins (Fig. 1). The proteins that are phosphorylated by mTORC1 are specified by raptor. Raptor binds to proteins that contain a TOS (TOR signaling) motif, the five amino acid sequence F-(D/E)-(F/I/L/M)-(D/E)-(L/I), and this positions the target protein in such a way that it can be phosphorylated by mTOR. The best-characterized targets of mTORC1 are the ribosomal S6 protein kinase (S6K1) and the initiation factor 4E-binding protein (4EBP), but other targets, such as the mTORC1 inhibitor PRAS40 and the hypoxia inducible factor 1α, also play an important role in the actions of mTORC1. Immediately following resistance exercise there is up to a 60-fold increase in mTORC1 activity as determined by the phosphorylation of S6K1. The central role of mTORC1 activation in the development of muscle hypertrophy is best demonstrated by the fact that the phosphorylation of S6K1 30 min to 6 h after resistance exercise correlates with training induced muscle hypertrophy and the increase in strength in rats, mice, and people [2]. Furthermore, blocking mTORC1 with rapamycin can prevent both the increase in muscle protein synthesis after exercise as well as the increase in muscle size after training. mTORC1 is not only activated by resistance exercise, but is also regulated by ► growth factors like IGF-1, amino acids, like the branched chain amino acid leucine, and metabolic stress. Growth factors and amino acids increase mTORC1 activity whereas ► metabolic stress blocks the activation of mTORC1. It is therefore not surprising that growth factors and supplemental amino acids can be used to increase protein synthesis and the mass and strength gains induced by resistance exercise, whereas concurrent endurance exercise, that produces metabolic stress, attenuates the increase in muscle size and strength that accompanies resistance exercise. One of the most unique aspects of the activation of mTORC1 by resistance exercise is the fact that it remains active for at least 18 h [2]. This is the



Resistance Training, Molecular Mechanisms. Fig. 1 Schematic of mTORC1 activation following resistance exercise. Inactivation of the tuberous sclerosis complex (TSC1/2) by loading results in activation of Rheb (ras homologous enriched in brain) and mTORC1. Active mTORC1 increases miR-1 and phosphorylates the initiation factor 4E-binding protein (4EBP) and the ribosomal S6 protein kinase (S6K1) resulting in an increase in protein synthesis and muscle growth

longest reported period of activation for a kinase by any stimulus. The long duration of mTORC1 activation and the corresponding long period of increased protein synthesis is very important for the development of bigger, stronger muscles.

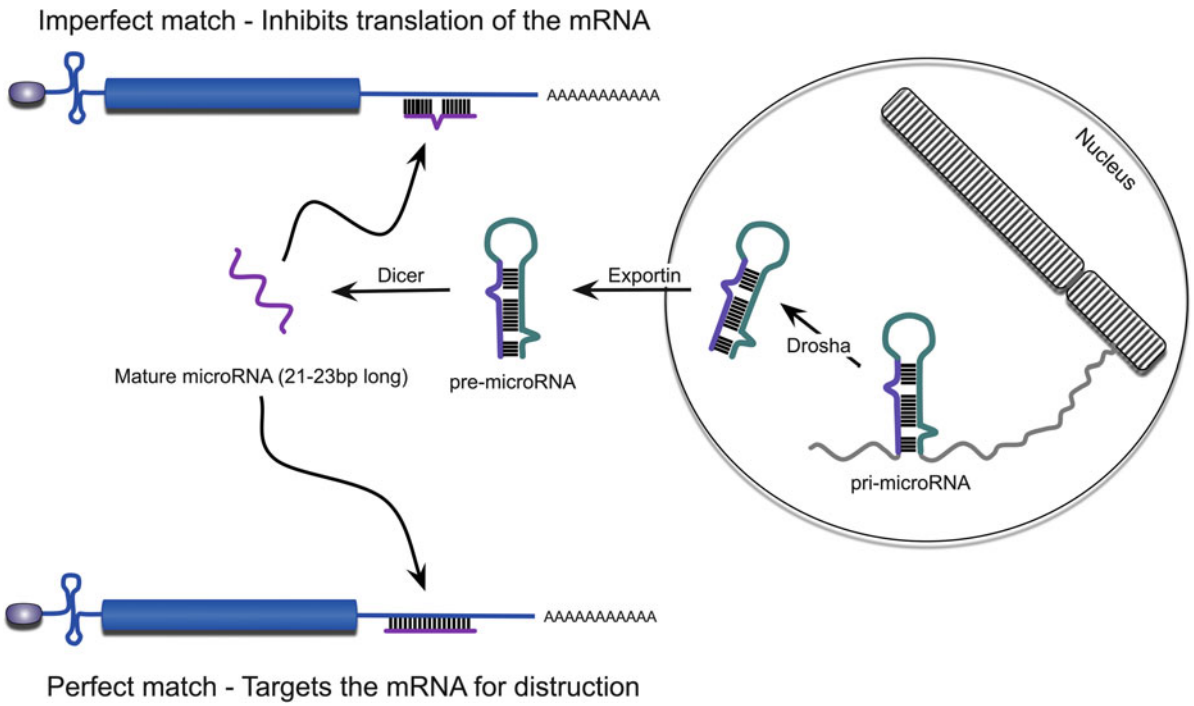
Even though mTORC1 plays an important role in regulating adult muscle mass, it is not the only factor that can influence muscle size and strength. The transforming growth factor (TGF) β family member myostatin is another well-known regulator of muscle size. Myostatin is not a hormone in the classic sense but rather a "► chalone," a chemical messenger that provides negative signals between cells. Myostatin is produced by and acts on muscle cells. When muscle cells grow to their mature size, enough myostatin circulates to prevent further muscle growth. When myostatin is absent, or is decreased experimentally, muscle mass increases. For instance, when myostatin or its receptor is mutated, or inhibitors of myostatin function like follistatin and c-ski are increased, the result is a huge increase in muscle mass. At this point, it is not clear how myostatin controls muscle size in the adult. Myostatin can act by binding to its receptor on the membrane (ActIIB) and inactivating a signaling cascade through Smad (small mothers against decapentaplegic) proteins (Fig. 2). Inactivating Smads alters transcription and leads to skeletal muscle hypertrophy [3]. Interestingly, the mTORC1 inhibitor rapamycin prevents ~40% of the increase in muscle mass induced by blocking myostatin activation, suggesting that the two pathways overlap significantly. Developmentally, myostatin can affect the proliferation of muscle precursor cells (MPC). MPC are cells that will fuse together to form muscle fibers. In the developing embryo, increasing the proliferation of MPC results in an increase in muscle fiber number. In the adult, increasing MPC or ► satellite cell proliferation may improve the ability to respond to muscle damage following resistance exercise resulting in improved growth. However, the muscle growth induced by blocking myostatin in adult animals occurs independent of satellite cell activation. Even though we know that



Resistance Training, Molecular Mechanisms. Fig. 2 Schematic of myostatin actions in muscle. Myostatin binds to the activin type IIB receptor and together with the type I receptor activate the alk (activin receptor-like kinase) proteins. ALK protein can phosphorylate the receptor Smads (2/3) and together with the coSmad (Smad4) move to the nucleus, bind Smad binding elements within DNA, and regulate transcription of genes involved in extracellular matrix (ECM) deposition and protein synthesis (ribosomes). Myostatin is also known to decrease mTORC1 activity and protein synthesis

myostatin exerts some of its influence on muscle size by regulating mTORC1, how myostatin mediates the other 60% of its actions on muscle size has yet to be determined.

In the last few years, microRNAs (miRNA) that are associated with muscle hypertrophy have been identified. miRNAs are molecules that can control the expression of large families of mRNA. miRNA are noncoding short chains of mRNA approximately 22 nt long. They bind to complementary sequences in the 3′UTR (untranslated region) of target transcripts repressing the translation and promoting the degradation of these mRNAs (Fig. 3). miRNA processing is required for normal development and when overexpressed, miRNAs have the potential to vastly alter the expression profile and phenotype of a cell. The most obvious relationship between miRNA and skeletal muscle hypertrophy is seen in the Texel sheep. In these sheep, there is a single point mutation in the myostatin gene (a guanine has been mutated to an adenine) that improves the binding of miR-1 and miR-206, two muscle-specific miRNAs. With more miR-1 and/or miR-206 binding to the myostatin mRNA, the translation of myostatin is inhibited and the large muscle phenotype develops. MicroRNAs may also play an important role in normal skeletal muscle hypertrophy. In response to overload hypertrophy, mice and people decrease the unprocessed pri-miR-1 and pri-miR-133 microRNAs even though the mature miRNA are unchanged. Even though the role of the unprocessed miRNA is not



Resistance Training, Molecular Mechanisms. Fig. 3 MicroRNA is made from DNA that forms a short hairpin after being transcribed. The pri-microRNA (precursor) is cleaved in the nucleus by the enzyme drosha and exported from the nucleus by exportin as a pre-microRNA. In the cytosol, dicer cleaves the pre-microRNA into its mature ~22 bp long microRNA sequence. The microRNA then binds to the 3′ untranslated region of the mRNA using complementary base pairing. A perfect pairing results in mRNA degradation, whereas an incomplete match results in the inhibition of translation

known, the data suggests that miRNAs could be involved in altering the transcription profile required for hypertrophy. MicroRNA may also serve to connect the activation of mTORC1 with the inhibition of myostatin. The activation of mTORC1 in muscle cells can increase the production of miR-1 [4]. One of the messages targeted by miR-1 is the histone deacetylase HDAC4. HDAC4 in turn can regulate the production of follistatin, the myostatin inhibitor. In this way, the activation of mTORC1 can lead through microRNA to the inhibition of myostatin, combining the two main pathways that control the size and strength of a muscle. It should also be noted that beyond the effects of miRNAs on the muscle fibers themselves, the positive effects of resistance exercise on the connective tissue of muscle may also be mediated by miRNA. MiR-29 is known to regulate the expression of collagens, and other proteins expressed within the extracellular matrix (ECM). Decreasing miR-29 stimulates the production of ECM exctracellular within the muscle and improves the force transmission and therefore the strength of the muscle.

Exercise Intervention

To maximize mTOR activation and the increase in muscle mass and strength, exercise should be performed against a high load. Since metabolic stress can decrease mTORC1 activation, each set should last ~60 s. This corresponds to the amount of high-energy phosphate stored in a normal muscle. Any longer and the muscle will turn on processes that shut down mTORC1, decreasing the response to the training. When performing controlled repetitions this means a maximum of 10 reps per set. If more than one set is used, enough time must be taken between sets to allow full recovery of phosphocreatine and ► ATP. This takes 2–3 times as long as the exercise itself (2–4 min).

Following resistance exercise, foods such as milk, that are high in branched chain amino acids like leucine, should be consumed while the blood flow to the trained muscle is still high. This will target the amino acids to the trained muscle and increase the activation of mTORC1. It is important to remember that keeping amino acid levels high for extended periods of time can actually result in a decrease in protein synthesis; therefore, it is unwise to

consume excessive amounts of protein or consume supplements in place of a good meal [5].

The last consideration is that mTORC1 activity should remain high for at least 18 h after training. Since the metabolic stress of endurance training can turn off mTORC1, for maximal increases in muscle size and strength the athletes should not perform endurance exercise until the next morning.

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Resolution of Inflammation

Resolution of inflammation is the process by which the positive loop of pro-inflammatory mediators is stopped to the benefice of anti-inflammatory compounds. Many mediators are involved in this process among which lipids play important roles. Macrophages are key cells involved in the dampening of the inflammatory response at time of resolution of inflammation. If not resolved, prolonged inflammation ceases to be a beneficial event and contributes to the pathogenesis of many disease states.

Respiratory Exchange Ratio

The ratio of carbon dioxide production to oxygen consumption ($\dot{V}CO_2/\dot{V}O_2$) measured across the mouth. In the steady state, when body CO_2 and O_2 stores are unchanging, this ratio serves as an indicator of gas exchange at the tissue level (i.e., respiratory quotient, RQ) and reflects the substrate utilization.

Respiratory Quotient

The ratio of the produced CO_2 to the consumed O_2.

Respiratory Sinus Arrhythmia (RSA)

Is the periodic fluctuation in heart rate at the respiratory frequency such that heart rate increases (R-R interval shortens) during inspiration and decreases (R-R interval prolongs) during expiration. This arrhythmia is considered to be normal and, in fact, is a hallmark of a healthy heart.

Cross-References

▶ Heart Rate Variability

Responses to Exercise

▶ Steroid Hormones

Resting Metabolic Rate (RMR)

The amount of oxygen consumed over a 24 h period in a resting supine position within a neutral environment, without feeding or movement.

Restless Legs Syndrome

A sleep disorder characterized by an unpleasant sensation (often described as a creeping, or tingling, sensation) in the legs combined with a compelling urge to move the legs, with these symptoms occurring primarily in the evening; sensations are at least temporarily relieved by movement; commonly abbreviated RLS.

Cross-References

▶ Sleep and Exercise

Retention

▶ Promotion of and Adherence to Physical Activity

Reticulocytes

Young erythrocytes which have already lost their nucleus and have passed the bone marrow–blood barrier. Approximately 1.5 days after their appearance in the blood, they have changed to mature red cells.

Retrograde Transport

Axons extend over long distances, and retrograde transport is the process whereby proteins are trafficked along the axon, towards the soma.

Return-to-Play Decision

A decision made by health care professionals associated with an sports team about the suitability of an athlete returning to full contact participation.

Reverse Cholesterol Transport (RCT)

Is the process describing the flux of cholesterol from the periphery (macrophage) by way of HDL to the liver with eventual disposal into the intestine for either enterohepatic recirculation or release in feces.

Reverse Periodization

One method of variation in which the goal of the training is to promote muscular endurance as the training objective.

Reverse Remodeling

Reversal of pathological cardiac hypertrophy or remodeling as a result of chronic physical activity and exercise training or conventional surgical and medical treatment that reduces the chronic stress and/or load exerted on the myocardium. The condition is also associated with improved pump function of the heart and delayed onset of heart dysfunction and failure.

Cross-References

► Cardiac Hypertrophy, Pathological

Rhabdomyolysis

A condition in which muscle cells break down, releasing cellular contents such as myoglobin and creatine kinase into circulation. Rhabdomyolysis can be caused by excessive exercise, use of certain drugs such as statins, or underlying disease. This condition is potentially fatal due to blockage of kidney function by elevated circulating myoglobin. Symptoms of rhabdomyolysis include dark urine, muscle soreness, and increased creatine kinase and myoglobin in blood.

Rhythm Disorder

► Cardiac Arrhythmias

Ribosome

A ribosome is an organelle located in the cytoplasm and is the site for translation.

Riding a Bike

► Cycling

Risk of Falling

Probability of occurrence of an unexpected change in body position to a lower level.

Cross-References

► Fall, Risk of

ROM

Range of motion.

R-R Interval Variability

► Heart Rate Variability

Runner's Diarrhea

► Diarrhea, Exercise Induced

Runner's Trots

► Diarrhea, Exercise Induced

Running

To move swiftly on foot so that both feet leave the ground during each stride.

RXR

The retinoid X receptor (RXR) is a ligand-activated transcription factor that forms a heterodimeric complex with the PPAR istotypes in order to regulate gene transcription.

Ryanodine Receptor

Ryanodine receptors (RyRs) appear in clusters and form a class of intracellular Ca^{2+} channels in various forms of excitable tissues, like muscles and neurons. In skeletal muscle, the ryanodine receptor is activated by dihydropyridine receptors of the t-tubules in response to sarcolemmal depolarization. In cardiac muscle, the ryanodine receptor is activated by a rise in intracellular calcium concentration. The ryanodine receptor is also activated by caffeine in the absence of sarcolemmal depolarization.