Essentials of
Exercise Physiology

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Contents

1

Skeletal Muscles and Exercise

MACRO AND MICRO STRUCTURE OF THE SKELETAL MUSCLE

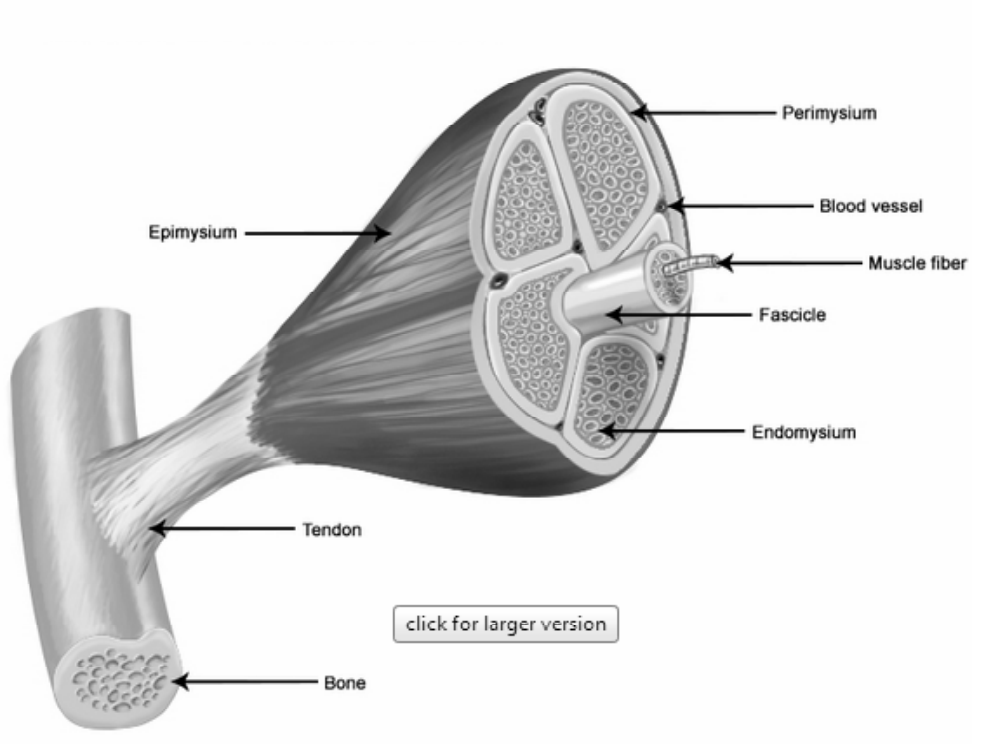
The muscular system is composed of specialized cells called muscle fibers. Their predominant function is contractibility. Muscles, attached to bones or internal organs and blood vessels, are responsible for movement. Nearly all movement in the body is the result of muscle contraction. Exceptions to this are the action of cilia, the flagellum on sperm cells, and amoeboid movement of some white blood cells. The integrated action of joints, bones, and skeletal muscles produces obvious movements such as walking and running. Skeletal muscles also produce more subtle movements that result in various facial expressions, eye movements, and respiration. In addition to movement, muscle contraction also fulfills some other important functions in the body, such as posture, joint stability, and heat production. Posture, such as sitting and standing, is maintained as a result of muscle contraction. The skeletal muscles are continually making fine adjustments that hold the body in stationary positions. The tendons of many muscles extend over joints and in this way contribute to joint stability. This is particularly evident in the knee and shoulder joints, where muscle tendons are a major factor in stabilizing the joint. Heat production, to maintain body temperature, is an important by-product of muscle metabolism. Nearly 85 percent of the heat produced in the body is the result of muscle contraction.

Structure of Skeletal Muscle

A whole skeletal muscle is considered an organ of the muscular system.

Each organ or muscle consists of skeletal muscle tissue, connective tissue, nerve tissue, and blood or vascular tissue.

Skeletal muscles vary considerably in size, shape, and arrangement of fibers. They range from extremely tiny strands such as the stapedium muscle of the middle ear to large masses such as the muscles of the thigh. Some skeletal muscles are broad in shape and some narrow. In some muscles the fibers are parallel to the long axis of the muscle; in some they converge to a narrow attachment; and in some they are oblique.



Each skeletal muscle fiber is a single cylindrical muscle cell. An individual skeletal muscle may be made up of hundreds, or even thousands, of muscle fibers bundled together and wrapped in a connective tissue covering. Each muscle is surrounded by a connective tissue sheath called the epimysium. Fascia, connective tissue outside the epimysium, surrounds and separates the muscles. Portions of the epimysium project inward to divide the muscle into compartments. Each compartment contains a bundle of muscle fibers. Each bundle of muscle fiber is called a fasciculus and is surrounded by a layer of connective tissue called the perimysium. Within the fasciculus, each individual muscle cell, called a muscle fiber, is surrounded by connective tissue called the endomysium.

Skeletal muscle cells (fibers), like other body cells, are soft and fragile. The connective tissue covering furnish support and protection for the delicate cells and allow them to withstand the forces of contraction. The coverings also provide pathways for the passage of blood vessels and nerves.

Commonly, the epimysium, perimysium, and endomysium extend beyond the fleshy part of the muscle, the belly or gaster, to form a thick ropelike tendon or a broad, flat sheet-like aponeurosis. The tendon and aponeurosis form indirect attachments from muscles to the periosteum of bones or to the connective tissue of other muscles. Typically a muscle spans a joint and is attached to bones by tendons at both ends. One of the bones remains relatively fixed or stable while the other end moves as a result of muscle contraction.

Skeletal muscles have an abundant supply of blood vessels and nerves. This is directly related to the primary function of skeletal muscle, contraction. Before a skeletal muscle fiber can contract, it has to receive an impulse from a nerve cell. Generally, an artery and at least one vein accompany each nerve that penetrates the epimysium of a skeletal muscle. Branches of the nerve and blood vessels follow the connective tissue components of the muscle of a nerve cell and with one or more minute blood vessels called capillaries.

Macro Structure

The functions of the muscles are to produce movement, maintain posture, stabilise joints and generate heat (Marieb, 2003). Muscle has five basic characteristics as expressed by Ward (2004):

- Excitability–the ability to respond to stimuli (nerve impulses or hormones)
- Conductivity–the ability to conduct nerve impulses along its length
- Contractility–the ability to contract (shorten and thicken) and thus produce force
- Extensibility–the ability to stretch or be stretched (within certain limits) without causing damage
- Elasticity–the ability to return to original shape following shortening or lengthening

Micro Structure

Each muscle is broken down into a cable like structures that are called ‘muscle fibers’ (Edman, 2003) with Marieb (2003) imparting each individual

muscle can consist of thousands of muscle fibres. The depiction of the muscle which is presented is that of layers which are progressively stripped away.

Each muscle fiber is composed of tightly packed sub units of 'myofibrils' which account for most of the volume of the fiber and are approximately 1 μm wide and run the entire length of the fiber (Hunter, 2000). The sarcolemma surrounds each muscle fibre and is the cell membrane which encases the sarcoplasm (Martini, 2006). The sarcolemma has a characteristic transmembrane potential due to the unequal distribution of positive and negative charges across the membrane, a sudden change in this transmembrane potential is the first step that leads to a contraction (Tortora and Grabowski, 2003). Encasing the myofibrils are the T tubules which act as the transductive highway for electrical neuromuscular situation which is termed the action potentials which triggers the muscle innovation (Martini, 2006).

CHEMICAL COMPOSITION

Chemical composition refers to the arrangement, type, and ratio of atoms in molecules of chemical substances. Chemical composition varies when chemicals are added or subtracted from a substance, when the ratio of substances changes, or when other chemical changes occur in chemicals. Chemical formulas show this information. The chemical composition of a substance determines the properties of the substance. This means that the way atoms are put together in something determines the color, density, strength, and other properties of the thing. The chemical composition of a substance determines its ratio of elements, the size of the compound, intramolecular forces, colour, texture etc. Chemists can use tests to learn the chemical composition of a substance, including a pH test, flammability test, heavy metal test etc. An example is Hydrogen Fluoride, or HF, which has 1 Hydrogen atom in ratio to every 1 Fluorine atom. This substance has strong intramolecular forces of attraction because it is a hydrogen bond.

SLIDING FILAMENT THEORY OF MUSCULAR CONSTRUCTION

The sliding filament theory explains the mechanism of muscle contraction based on muscle proteins that slide past each other to generate movement. It was independently introduced in 1954 by two research teams, one consisting of Andrew F. Huxley and Rolf Niedergerke from the University of Cambridge, and the other consisting of Hugh Huxley and Jean Hanson from the

Massachusetts Institute of Technology. It was originally conceived by Hugh Huxley in 1953. Andrew Huxley and Niedergerke introduced it as a "very attractive" hypothesis.

According to the sliding filament theory, the actin (thin) filaments of muscle fibers slide past the myosin (thick) filaments during muscle contraction, while the two groups of filaments remain at relatively constant length. Before the 1950s there were several competing theories on muscle contraction, including electrical attraction, protein folding, and protein modification. The novel theory directly introduced a new concept called cross-bridge theory (classically swinging cross-bridge, now mostly referred to as cross-bridge cycle) which explains the molecular mechanism of sliding filament. Cross-bridge theory states that actin and myosin form a protein complex (classically called actomyosin) by attachment of myosin head on the actin filament, thereby forming a sort of cross-bridge between the two filaments. These two complementary hypotheses turned out to be the correct description, and became a universally accepted explanation of the mechanism of muscle movement.

HISTORY

Early Works

The first muscle protein discovered was myosin by a German scientist Willy Kühne, who extracted and named it in 1864. In 1939 a Russian husband and wife team Vladimir Alexandrovich Engelhardt and Militsa Nikolaevna Lyubimova discovered that myosin had an enzymatic (called ATPase) property that can breakdown ATP to release energy. Albert Szent-Györgyi, a Hungarian physiologist, turned his focus on muscle physiology after winning the Nobel Prize in Physiology or Medicine in 1937 for his works on vitamin C and fumaric acid. He demonstrated in 1942 that ATP was the source of energy for muscle contraction. He actually observed that muscle fibres containing myosin B shortened in the presence of ATP, but not with myosin A, the experience which he later described as "perhaps the most thrilling moment of my life." With Brunó Ferenc Straub, he soon found that myosin B was associated with another protein, which they called actin, while myosin A was not. Straub purified actin in 1942, and Szent-Györgyi purified myosin A in 1943. It became apparent that myosin B was a combination of myosin A and actin, so that myosin A retained the original name, whereas they renamed myosin B as actomyosin. By the end of the 1940s Szent-Györgyi's team had postulated

with evidence that contraction of actomyosin was equivalent to muscle contraction as a whole. But the notion was generally opposed, even from the likes of Nobel laureates such as Otto Fritz Meyerhof and Archibald Hill, who adhered to the prevailing dogma that myosin was a structural protein and not a functional enzyme. However, in one of his last contributions to muscle research, Szent-Györgyi demonstrated that actomyosin driven by ATP was the basic principle of muscle contraction.

Origin of the Sliding Filament Theory

By the time Hugh Huxley earned his PhD from the University of Cambridge in 1952 on his research on the structure of muscle, Szent-Györgyi had turned his career into cancer research. Huxley went to Francis O. Schmitt's laboratory at the Massachusetts Institute of Technology with a post-doctoral fellowship in September 1952, where he was joined by another English post-doctoral fellow Jean Hanson in January 1953. Hanson had a PhD in muscle structure from King's College, London in 1951. Huxley had used X-ray diffraction to speculate that muscle proteins, particularly myosin, form structured filaments giving rise to sarcomere (a segment of muscle fibre). Their main aim was to use electron microscopy to study the details of those filaments as never done before. They soon discovered and confirmed the filament nature of muscle proteins. Myosin and actin form overlapping filaments, myosin filaments mainly constituting the A band (the dark region of a sarcomere), while actin filaments traverse both the A and I (light region) bands. Huxley was the first to suggest the sliding filament theory in 1953, stating:

- "… [I]f it is postulated that stretching of the muscle takes place, not by an extension of the filaments, but by a process in which the two sets of filaments slide past each other; extensibility will then be inhibited if the myosin and actin are linked together."

Later, in 1996, Huxley regretted that he should have included Hanson in the formulation of his theory because it was based on their collaborative work.

Andrew Huxley, whom Alan Hodgkin described as "wizard with scientific apparatus", had just discovered the mechanism of the nerve impulse (action potential) transmission (for which he and Hodgkin later won the Nobel Prize in Physiology or Medicine in 1963) in 1949 using his own design of voltage clamp, and was looking for an associate who could properly dissect out muscle fibres. Upon recommendation of a close friend Robert Stämpfli, a German physician Rolf Niedergerke joined him at the University of Cambridge in 1952.

By then he realised that the conventionally used phase contrast microscope was not suitable for fine structures of muscle fibres, and thus developed his own interference microscope. Between March 1953 and January 1954 they executed their research. Huxley recollected that at the time the only person who ever thought of sliding filaments before 1953 was Dorothy Hodgkin (later winner of the 1964 Nobel Prize in Chemistry). He spent the summer of 1953 at Marine Biological Laboratory at Woods Hole, Massachusetts, to use electron microscope there. There he met Hugh Huxley and Hanson with whom he shared data and information on their works. They parted with an agreement that they would keep in touch, and when their aim is achieved, they would publish together, if they ever "reached similar conclusions".

THE SLIDING FILAMENT THEORY

The sliding filament theory was born from two consecutive papers published on the 22 May 1954 issue of Nature under the common theme "Structural Changes in Muscle During Contraction". Though their conclusions were fundamentally similar, their underlying experimental data and propositions were different.

Huxley-Niedergerke hypothesis

The first paper, written by Andrew Huxley and Rolf Niedergerke, is titled "Interference microscopy of living muscle fibres". It was based on their study of frog muscle using interference microscope, which Andrew Huxley developed for the purpose. According to them:

1. The I bands are composed of actin filaments, and the A bands principally of myosin filaments; and
2. During contraction, the actin filaments move into the A bands between the myosin filaments.

Huxley-Hanson Hypothesis

The second paper, by Hugh Huxley and Jean Hanson, is titled "Changes in the cross-striations of muscle during contraction and stretch and their structural interpretation". It is more elaborate and was based on their study of rabbit muscle using phase contrast and electron microscopes. According to them:

1. The backbone of a muscle fibre is actin filaments which extend from Z line up to one end of H zone, where they are attached to an elastic component which they named S filament;

2. Myosin filaments extend from one end of the A band through the H zone up to the other end of the A band;
3. Myosin filaments remain in relatively constant length during muscle stretch or contraction;
4. If myosin filaments contract beyond the length of A band, their ends fold up to form contraction bands;
5. Myosin and actin filaments lie side-by-side in the A band and in the absence of ATP they do not form cross-linkages;
6. During stretching, only the I bands and H zone increase in length, while A bands remain the same;
7. During contraction, actin filaments move into the A bands and the H zone is filled up, the I bands shorten, the Z line comes in contact with the A bands;
8. The possible driving force of contraction is the actin-myosin linkages which depend on ATP hydrolysis by the myosin.

RECEPTION AND CONSEQUENCES

In spite of strong evidences, the sliding filament theory did not gain any support for several years to come. Szent-Györgyi himself refused to believe that myosin filaments were confined to the thick filament (A band). F.O. Schmitt, whose electron microscope provided the best data, also remained sceptical of the original images. There were also immediate arguments as to the organisation of the filaments, whether the two sets (myosin and actin) of filaments were merely overlapping or continuous. It was only with the new electron microscope that Hugh Huxley confirmed the overlapping nature of the filaments in 1957.

It was also from this publication that the existence of actin-myosin linkage (now called cross-bridge) was clearly shown. But he took another five years to provide evidence that the cross-bridge was a dynamic interaction between actin and myosin filaments. He obtained the actual molecular arrangement of the filaments using X-ray crystallography by teaming up with Kenneth Holmes, who was trained by Rosalind Franklin, in 1965. It was only after a conference in 1972 at Cold Spring Harbor Laboratory, where the theory and its evidences were deliberated, that it became generally accepted. At the conference, as Koscak Maruyama later recalled, Hanson had to answer the criticisms by shouting, “I know I cannot explain the mechanism yet, but the sliding is a

fact." The factual proofs came in the early 1980s when it could be demonstrated the actual sliding motion using novel sophisticated tools by different researchers.

Cross-bridge Mechanism

With substantial evidence, Hugh Huxley formally proposed the mechanism for sliding filament and is variously called swinging cross-bridge model, cross-bridge theory or cross-bridge model. (He himself preferred the name "swinging crossbridge model", because, as he recalled, "it [the discovery] was, after all, the 1960s".) He published his theory in the 20 June 1969 issue of Science under the title "The Mechanism of Muscular Contraction". According to his theory, filament sliding occurs by cyclic attachment and detachment of myosin on actin filaments. Contraction occurs when the myosin pulls the actin filament towards the centre of the A band, detaches from actin and creates a force (stroke) to bind to the next actin molecule. This idea was subsequently proven in detail, and is more appropriately known as the cross-bridge cycle.

TYPES OF MUSCLE FIBRE

In the body, there are three types of muscle: skeletal (striated), smooth, and cardiac.

Skeletal Muscle

Skeletal muscle, attached to bones, is responsible for skeletal movements. The peripheral portion of the central nervous system (CNS) controls the skeletal muscles. Thus, these muscles are under conscious, or voluntary, control. The basic unit is the muscle fiber with many nuclei. These muscle fibers are striated (having transverse streaks) and each acts independently of neighboring muscle fibers.

Smooth Muscle

Smooth muscle, found in the walls of the hollow internal organs such as blood vessels, the gastrointestinal tract, bladder, and uterus, is under control of the autonomic nervous system. Smooth muscle cannot be controlled consciously and thus acts involuntarily. The non-striated (smooth) muscle cell is spindle-shaped and has one central nucleus. Smooth muscle contracts slowly and rhythmically.

Cardiac Muscle

Cardiac muscle, found in the walls of the heart, is also under control of

the autonomic nervous system. The cardiac muscle cell has one central nucleus, like smooth muscle, but it also is striated, like skeletal muscle. The cardiac muscle cell is rectangular in shape. The contraction of cardiac muscle is involuntary, strong, and rhythmical. Smooth and cardiac muscle will be discussed in detail with respect to their appropriate systems. This unit mainly covers the skeletal muscular system.

MUSCLE TONE

In physiology, medicine, and anatomy, muscle tone (residual muscle tension or tonus) is the continuous and passive partial contraction of the muscles, or the muscle's resistance to passive stretch during resting state. It helps maintain posture and declines during REM sleep.

Purpose

If a sudden pull or stretch occurs, the body responds by automatically increasing the muscle's tension, a reflex which helps guard against danger as well as helping maintain balance. Such near-continuous innervation can be thought of as a "default" or "steady state" condition for muscles. Both the extensor and flexor muscles are involved in the maintenance of a constant tone while at rest. In skeletal muscles, this helps maintain a normal posture.

Resting muscle tone varies along a bell shaped curve. Low tone is experienced as "floppy, mushy, dead weight" and high tone is experienced as "light, tight, and strong". Muscles with high tone are not necessarily strong and muscles with low tone are not necessarily weak. In general, low tone does increase flexibility and decrease strength and high tone does decrease flexibility and increase strength, but with many exceptions. A person with low tone will most likely not be able to engage in "explosive" movement such as needed in a sprinter or high jumper. These athletes usually have high tone that is within normal limits. A person with high tone will usually not be flexible in activities such as dance and yoga. Joint laxity contributes greatly to flexibility, especially with flexibility in one or a few areas, instead of overall flexibility.

For example, a person can be high tone with normal to poor flexibility in most areas, but be able to put the palms of the hands on the floor with straight knees due to hypermobile sacroiliac joints. It is important to assess several areas before deciding if a person has high, low or normal muscle tone. A fairly

reliable assessment item is how the person feels when picked up. For example, small children with low tone can feel heavy while larger, high tone children feel light, which corresponds with the description of "dead weight".

Although cardiac muscle and smooth muscle are not directly connected to the skeleton, they also have tonus in the sense that although their contractions are not matched with those of antagonist muscles, the non-contractile state is characterized by (sometimes random) enervation.

Pathological Tonus

Physical disorders can result in abnormally low (hypotonia) or high (hypertonia) muscle tone. Another form of hypertonia is paratonia, which is associated with dementia. Hypotonia is seen in lower motor neuron disease like poliomyelitis. Hypotonia can present clinically as muscle flaccidity, where the limbs appear floppy, stretch reflex responses are decreased, and the limb's resistance to passive movement is also decreased. Hypertonia is seen in upper motor neuron diseases like lesions in pyramidal tract and extrapyramidal tract. Hypertonia can present clinically as either spasticity or rigidity. While spasticity is velocity-dependent resistance to passive stretch (*i.e.* passively moving an elbow quickly will elicit increased muscle tone, but passively moving elbow slowly may not elicit increased muscle tone), rigidity is velocity-independent resistance to passive stretch (*i.e.* there is uniform increased tone whether the elbow is passively moved quickly or slowly). Spasticity can be in the form of the clasp-knife response, in which there is increased resistance only at the beginning or at the end of the movement. Rigidity can be of the leadpipe type, in which there is resistance throughout to passive movement, or it may be of cogwheel type, in which the resistance to passive movement is in a jerky manner.

Tonus in Surgery

In ophthalmology, tonus may be a central consideration in eye surgery, as in the manipulation of extraocular muscles to repair strabismus. Tonicity aberrations are associated with many diseases of the eye (*e.g.* Adie syndrome).

Cramps

Normally, people are unaware of their muscle tone in their daily activities. The body maintains the balance between the tone of flexor and extensor muscle groups. Sometimes, in normal, healthy people, that tone is lost either in flexors

or extensor muscle groups in isolation, temporarily and intermittently resulting in “muscle cramps”. Treating these extensor or flexor group of muscles in isolation to relax can be difficult. Generally, muscle relaxants or quinine can help with cramps and is warranted when they become troublesome. But these medication cause their relaxing effect in both groups by moderating their tone. The cause of disproportionate intermittent contractions of either flexors or extensors or the cause of cramps is unknown. The stimulus for these “cramps” may originate in the cerebral cortex, the spinal cord, or the muscle itself. This could indicate developing pathology or other problems in the future.

CHEMISTRY OF MUSCULAR CONTRACTION

Muscle contraction is the activation of tension-generating sites within muscle fibers. In physiology, muscle contraction does not necessarily mean muscle shortening because muscle tension can be produced without changes in muscle length such as holding a heavy book or a dumbbell at the same position. The termination of muscle contraction is followed by muscle relaxation, which is a return of the muscle fibers to their low tension-generating state.

Muscle contractions can be described based on two variables: length and tension. A muscle contraction is described as isometric if the muscle tension changes but the muscle length remains the same. In contrast, a muscle contraction is isotonic if muscle length changes but the muscle tension remains the same. If the muscle length shortens, the contraction is concentric; if the muscle length lengthens, the contraction is eccentric. In natural movements that underlie locomotor activity, muscle contractions are multifaceted as they are able to produce changes in length and tension in a time-varying manner. Therefore, neither length nor tension is likely to remain the same in muscles that contract during locomotor activity.

In vertebrates, skeletal muscle contractions are neurogenic as they require synaptic input from motor neurons to produce muscle contractions. A single motor neuron is able to innervate multiple muscle fibers, thereby causing the fibers to contract at the same time. Once innervated, the protein filaments within each skeletal muscle fiber slide past each other to produce a contraction, which is explained by the sliding filament theory. The contraction produced can be described as a twitch, summation, or tetanus, depending on the frequency of action potentials. In skeletal muscles, muscle tension is at its greatest when the muscle is stretched to an intermediate length as described by the length-tension relationship.

Unlike skeletal muscle, the contractions of smooth and cardiac muscles are myogenic (meaning that they are initiated by the smooth or heart muscle cells themselves instead of being stimulated by an outside event such as nerve stimulation), although they can be modulated by stimuli from the autonomic nervous system. The mechanisms of contraction in these muscle tissues are similar to those in skeletal muscle tissues.

Types

Muscle contractions can be described based on two variables: force and length. Force itself can be differentiated as either tension or load. Muscle tension is the force exerted by the muscle on an object whereas a load is the force exerted by an object on the muscle. When muscle tension changes without any corresponding changes in muscle length, the muscle contraction is described as isometric. If the muscle length changes while muscle tension remains the same, then the muscle contraction is isotonic. In an isotonic contraction, the muscle length can either shorten to produce a concentric contraction or lengthen to produce an eccentric contraction. Furthermore, if the muscle length shortens, the contraction is concentric. But if the muscle length lengthens, then the contraction is eccentric. In natural movements that underlie locomotor activity, muscle contractions are multifaceted as they are able to produce changes in length and tension in a time-varying manner. Therefore, neither length nor tension is likely to remain constant when the muscle is active during locomotor activity.

Isometric Contraction

An isometric contraction of a muscle generates tension without changing length. An example can be found when the muscles of the hand and forearm grip an object; the joints of the hand do not move, but muscles generate sufficient force to prevent the object from being dropped.

Isotonic Contraction

In isotonic contraction, the tension in the muscle remains constant despite a change in muscle length. This occurs when a muscle's force of contraction matches the total load on the muscle.

Concentric Contraction

In concentric contraction, muscle tension is sufficient to overcome the

load, and the muscle shortens as it contracts. This occurs when the force generated by the muscle exceeds the load opposing its contraction.

During a concentric contraction, a muscle is stimulated to contract according to the sliding filament theory. This occurs throughout the length of the muscle, generating a force at the origin and insertion, causing the muscle to shorten and changing the angle of the joint. In relation to the elbow, a concentric contraction of the biceps would cause the arm to bend at the elbow as the hand moved from the leg to the shoulder (a biceps curl). A concentric contraction of the triceps would change the angle of the joint in the opposite direction, straightening the arm and moving the hand towards the leg.

Eccentric Contraction

In eccentric contraction, the tension generated is insufficient to overcome the external load on the muscle and the muscle fibers lengthen as they contract. Rather than working to pull a joint in the direction of the muscle contraction, the muscle acts to decelerate the joint at the end of a movement or otherwise control the repositioning of a load. This can occur involuntarily (*e.g.*, when attempting to move a weight too heavy for the muscle to lift) or voluntarily (*e.g.*, when the muscle is 'smoothing out' a movement). Over the short-term, strength training involving both eccentric and concentric contractions appear to increase muscular strength more than training with concentric contractions alone. However, exercise-induced muscle damage is also greater during lengthening contractions.

During an eccentric contraction of the biceps muscle, the elbow starts the movement while bent and then straightens as the hand moves away from the shoulder. During an eccentric contraction of the triceps muscle, the elbow starts the movement straight and then bends as the hand moves towards the shoulder. Desmin, titin, and other z-line proteins are involved in eccentric contractions, but their mechanism is poorly understood in comparison to crossbridge cycling in concentric contractions.

Though the muscle is doing a negative amount of mechanical work, (work is being done on the muscle), chemical energy (in fat, glucose or ATP) is nevertheless consumed, although less than would be consumed during a concentric contraction of the same force. For example, one expends more energy going up a flight of stairs than going down the same flight.

Muscles undergoing heavy eccentric loading suffer greater damage when

overloaded (such as during muscle building or strength training exercise) as compared to concentric loading. When eccentric contractions are used in weight training, they are normally called negatives. During a concentric contraction, muscle fibers slide across each other, pulling the Z-lines together.

During an eccentric contraction, the filaments slide past each other the opposite way, though the actual movement of the myosin heads during an eccentric contraction is not known. Exercise featuring a heavy eccentric load can actually support a greater weight (muscles are approximately 40% stronger during eccentric contractions than during concentric contractions) and also results in greater muscular damage and delayed onset muscle soreness one to two days after training. Exercise that incorporates both eccentric and concentric muscular contractions (*i.e.*, involving a strong contraction and a controlled lowering of the weight) can produce greater gains in strength than concentric contractions alone. While unaccustomed heavy eccentric contractions can easily lead to overtraining, moderate training may confer protection against injury.

Eccentric Contractions in Movement

Eccentric contractions normally occur as a braking force in opposition to a concentric contraction to protect joints from damage. During virtually any routine movement, eccentric contractions assist in keeping motions smooth, but can also slow rapid movements such as a punch or throw. Part of training for rapid movements such as pitching during baseball involves reducing eccentric braking allowing a greater power to be developed throughout the movement.

Eccentric contractions are being researched for their ability to speed rehabilitation of weak or injured tendons. Achilles tendinitis and patellar tendonitis (also known as jumper's knee or patellar tendonosis) have been shown to benefit from high-load eccentric contractions.

Vertebrate Animals

In vertebrate animals, there are three types of muscle tissues : skeletal, smooth, and cardiac. Skeletal muscle constitutes the majority of muscle mass in the body and is responsible for locomotor activity. Smooth muscle forms blood vessels, gastrointestinal tract, and other areas in the body that produce sustained contractions. Cardiac muscle make up the heart, which pumps blood. Skeletal and cardiac muscles are called striated muscle because of their striped

appearance under a microscope, which is due to the highly organized alternating pattern of A bands and I bands.

Skeletal Muscle

Excluding reflexes, all skeletal muscles contractions occur as a result of conscious effort originating in the brain. The brain sends electrochemical signals through the nervous system to the motor neuron that innervates several muscle fibers. In the case of some reflexes, the signal to contract can originate in the spinal cord through a feedback loop with the grey matter. Other actions such as locomotion, breathing, and chewing have a reflex aspect to them: the contractions can be initiated both consciously or unconsciously.

Neuromuscular Junction

A neuromuscular junction is a chemical synapse formed by the contact between a motor neuron and a muscle fiber. It is the site in which a motor neuron transmits a signal to a muscle fiber to initiate muscle contraction. The sequence of events that results in the depolarization of the muscle fiber at the neuromuscular junction begins when an action potential is initiated in the cell body of a motor neuron, which is then propagated by saltatory conduction along its axon toward the neuromuscular junction. Once it reaches the terminal bouton, the action potential causes a Ca^{2+}ion influx into the terminal by way of the voltage-gated calcium channels. The Ca^{2+}influx causes synaptic vesicles containing the neurotransmitter acetylcholine to fuse with the plasma membrane, releasing acetylcholine into the synaptic cleft between the motor neuron terminal and the neuromuscular junction of the skeletal muscle fiber. Acetylcholine diffuses across the synapse and binds to and activates nicotinic acetylcholine receptors on the neuromuscular junction. Activation of the nicotinic receptor opens its intrinsic sodium/potassium channel, causing sodium to rush in and potassium to trickle out. As a result, the sarcolemma reverses polarity and its voltage quickly jumps from the resting membrane potential of -90mV to as high as +75mV as sodium enters. The membrane potential then becomes hyperpolarized when potassium exits and is then adjusted back to the resting membrane potential. This rapid fluctuation is called the end-plate potential The voltage-gated ion channels of the sarcolemma next to the end plate open in response to the end plate potential. These voltage-gated channels are sodium and potassium specific and only allow one through. This wave of ion movements creates the action potential that spreads from the motor end

plate in all directions. If action potentials stop arriving, then acetylcholine ceases to be released from the terminal bouton. The remaining acetylcholine in the synaptic cleft is either degraded by active acetylcholine esterase or reabsorbed by the synaptic knob and none is left to replace the degraded acetylcholine.

Excitation-contraction Coupling

Excitation–contraction coupling is the process by which a muscular action potential in the muscle fiber causes the myofibrils to contract. In skeletal muscle, excitation–contraction coupling relies on a direct coupling between key proteins, the sarcoplasmic reticulum (SR) calcium release channel (identified as the ryanodine receptor, RyR) and voltage-gated L-type calcium channels (identified as dihydropyridine receptors, DHPRs). DHPRs are located on the sarcolemma (which includes the surface sarcolemma and the transverse tubules), while the RyRs reside across the SR membrane. The close apposition of a transverse tubule and two SR regions containing RyRs is described as a triad and is predominantly where excitation–contraction coupling takes place. Excitation–contraction coupling occurs when depolarization of skeletal muscle cell results in a muscle action potential, which spreads across the cell surface and into the muscle fiber's network of T-tubules, thereby depolarizing the inner portion of the muscle fiber.

Depolarization of the inner portions activates dihydropyridine receptors in the terminal cisternae, which are in close proximity to ryanodine receptors in the adjacent sarcoplasmic reticulum. The activated dihydropyridine receptors physically interact with ryanodine receptors to activate them via foot processes (involving conformational changes that allosterically activates the ryanodine receptors). As the ryanodine receptors open, $Ca^{2+}$is released from the sarcoplasmic reticulum into the local junctional space, which then diffuses into the bulk cytoplasm to cause a calcium spark. Note that the sarcoplasmic reticulum has a large calcium buffering capacity partially due to a calcium-binding protein called calsequestrin.

The near synchronous activation of thousands of calcium sparks by the action potential causes a cell-wide increase in calcium giving rise to the upstroke of the calcium transient. The Ca^{2+}released into the cytosol binds to Troponin C by the actin filaments, to allow crossbridge cycling, producing force and, in some situations, motion. The sarco/endoplasmic reticulum calcium-ATPase (SERCA) actively pumps Ca^{2+}back into the sarcoplasmic

reticulum. As Ca^{2+}declines back to resting levels, the force declines and relaxation occurs.

Sliding Filament Theory

The sliding filament theory describes a process used by muscles to contract. It is a cycle of repetitive events that cause a thin filament to slide over a thick filament and generate tension in the muscle. It was independently developed by Andrew Huxley and Rolf Niedergerke and by Hugh Huxley and Jean Hanson in 1954. Physiologically, this contraction is not uniform across the sarcomere; the central position of the thick filaments becomes unstable and can shift during contraction. However the actions of elastic proteins such as titin are hypothesised to maintain uniform tension across the sarcomere and pull the thick filament into a central position.

Crossbridge Cycling

Crossbridge cycling is a sequence of molecular events that underlies the sliding filament theory. A crossbridge is a myosin projection, consisting of two myosin heads, that extends from the thick filaments. Each myosin head has two binding sites: one for ATP and another for actin. The binding of ATP to a myosin head detaches myosin from actin, thereby allowing myosin to bind to another actin molecule. Once attached, the ATP is hydrolyzed by myosin, which uses the released energy to move into the "cocked position" whereby it binds weakly to a part of the actin binding site. The remainder of the actin binding site is blocked by tropomyosin. With the ATP hydrolyzed, the cocked myosin head now contains ADP + P_i. Two Ca^{2+}ions bind to troponin C on the actin filaments. The troponin-Ca^{2+}complex causes tropomyosin to slide over and unblock the remainder of the actin binding site. Unblocking the rest of the actin binding sites allows the two myosin heads to close and myosin to bind strongly to actin. The myosin head then releases the inorganic phosphate and initiates a power stroke, which generates a force of 2 pN. The power stroke moves the actin filament inwards, thereby shortening the sarcomere. Myosin then releases ADP but still remains tightly bound to actin. At the end of the power stroke, ADP is released from the myosin head, leaving myosin attached to actin in a rigor state until another ATP binds to myosin. A lack of ATP would result in the rigor state characteristic of rigor mortis. Once another ATP binds to myosin, the myosin head will again detach from actin and another crossbridges cycle occurs.

Crossbridge cycling is able to continue as long as there are sufficient amounts of ATP and Ca^{2+}in the cytoplasm. Termination of crossbridge cycling can occur when $Ca^{2+}$is actively pumped back into the sarcoplasmic reticulum. When $Ca^{2+}$is no longer present on the thin filament, the tropomyosin changes conformation back to its previous state so as to block the binding sites again. The myosin ceases binding to the thin filament, and the muscle relaxes. The Ca^{2+}ions leave the troponin molecule in order to maintain the Ca^{2+}ion concentration in the sarcoplasm. The active pumping of Ca^{2+}ions into the sarcoplasmic reticulum creates a deficiency in the fluid around the myofibrils. This causes the removal of Ca^{2+}ions from the troponin. Thus, the tropomyosin-troponin complex again covers the binding sites on the actin filaments and contraction ceases.

Gradation of Skeletal Muscle Contractions

The strength of skeletal muscle contractions can be broadly separated into twitch, summation, and tetanus. A twitch is a single contraction and relaxation cycle produced by an action potential within the muscle fiber itself. The time between a stimulus to the motor nerve and the subsequent contraction of the innervated muscle is called the latent period, which usually takes about 10 ms and is caused by the time taken for nerve action potential to propagate, the time for chemical transmission at the neuromuscular junction, then the subsequent steps in excitation-contraction coupling.

If another muscle action potential were to be produced before the complete relaxation of a muscle twitch, then the next twitch will simply sum onto the previous twitch, thereby producing a summation. Summation can be achieved in two ways: frequency summation and multiple fiber summation. In frequency summation, the force exerted by the skeletal muscle is controlled by varying the frequency at which action potentials are sent to muscle fibers. Action potentials do not arrive at muscles synchronously, and, during a contraction, some fraction of the fibers in the muscle will be firing at any given time. In a typical circumstance, when a human is exerting a muscle as hard as he/she is consciously able, roughly one-third of the fibers in that muscle will be firing at once, though this ratio can be affected by various physiological and psychological factors (including Golgi tendon organs and Renshaw cells). This ‘low’ level of contraction is a protective mechanism to prevent avulsion of the tendon—the force generated by a 95% contraction of all fibers is sufficient to damage the body. In multiple fiber summation, if the central nervous system

sends a weak signal to contract a muscle, the smaller motor units, being more excitable than the larger ones, are stimulated first. As the strength of the signal increases, more motor units are excited in addition to larger ones, with the largest motor units having as much as 50 times the contractile strength as the smaller ones. As more and larger motor units are activated, the force of muscle contraction becomes progressively stronger. A concept known as the size principle, allows for a gradation of muscle force during weak contraction to occur in small steps, which then become progressively larger when greater amounts of force are required.

Finally, if the frequency of muscle action potentials increases such that the muscle contraction reaches its peak force and plateaus at this level, then the contraction is a tetanus.

Length-tension Relationship

Length-tension relationship relates the strength of an isometric contraction to the length of the muscle at which the contraction occurs. Muscles operate with greatest active tension when close to an ideal length (often their resting length). When stretched or shortened beyond this (whether due to the action of the muscle itself or by an outside force), the maximum active tension generated decreases. This decrease is minimal for small deviations, but the tension drops off rapidly as the length deviates further from the ideal. Due to the presence of elastic proteins within a muscle cell (such as titin) and extracellular matrix, as the muscle is stretched beyond a given length, there is an entirely passive tension, which opposes lengthening. Combined together, there is a strong resistance to lengthening an active muscle far beyond the peak of active tension.

Force-velocity Relationships

Force–velocity relationship relates the speed at which a muscle changes its length (usually regulated by external forces, such as load or other muscles) to the amount of force that it generates. Force declines in a hyperbolic fashion relative to the isometric force as the shortening velocity increases, eventually reaching zero at some maximum velocity. The reverse holds true for when the muscle is stretched – force increases above isometric maximum, until finally reaching an absolute maximum. This has strong implications for the rate at which muscles can perform mechanical work (power). Since power is equal to force times velocity, the muscle generates no power at either isometric

force (due to zero velocity) or maximal velocity (due to zero force). Instead, the optimal shortening velocity for power generation is approximately one-third of maximum shortening velocity.

These two fundamental properties of muscle have numerous biomechanical consequences, including limiting running speed, strength, and jumping distance and height.

Smooth Muscle

Smooth muscles can be divided into two subgroups: single-unit (unitary) and multi-unit. Single-unit smooth muscle cells can be found in the gut and blood vessels. Because these cells are linked together by gap junctions, they are able to contract as a syncytium. Single-unit smooth muscle cells contract myogenically, which can be modulated by the autonomic nervous system.

Unlike single-unit smooth muscle cells, multi-unit smooth muscle cells are found in the muscle of the eye and in the base of hair follicles. Multi-unit smooth muscle cells contract by being separately stimulated by nerves of the autonomic nervous system. As such, they allow for fine control and gradual responses, much like motor unit recruitment in skeletal muscle.

Mechanisms of Smooth Muscle Contraction

The contractile activity of smooth muscle cells is influenced by multiple inputs such as spontaneous electrical activity, neural and hormonal inputs, local changes in chemical composition, and stretch. This is in contrast to the contractile activity of skeletal muscle cells, which relies on a single neural input. Some types of smooth muscle cells are able to generate their own action potentials spontaneously, which usually occur following a pacemaker potential or a slow wave potential. These action potentials are generated by the influx of extracellular Ca^{2+}, and not Na+. Like skeletal muscles, cytosolic Ca2+ions are also required for crossbridge cycling in smooth muscle cells.

The two sources for cytosolic Ca^{2+}in smooth muscle cells are the extracellular Ca2+entering through calcium channels and the Ca^{2+}ions that are released from the sarcoplasmic reticulum. The elevation of cytosolic Ca^{2+}results in more Ca^{2+} binding to calmodulin, which then binds and activates myosin light-chain kinase. The calcium-calmodulin-myosin light-chain kinase complex phosphorylates myosin on the 20 kilodalton (kDa) myosin light chains on amino acid residue-serine 19, initiating contraction and activating the myosin ATPase. Unlike skeletal muscle cells, smooth muscle cells lack

troponin, even though they contain the thin filament protein tropomyosin and other notable proteins – caldesmon and calponin. Thus, smooth muscle contractions are initiated by the Ca^{2+} activated phosphorylation of myosin rather than Ca^{2+}binding to the troponin complex that regulates myosin binding sites on actin like in skeletal and cardiac muscles.

Termination of crossbridge cycling (and leaving the muscle in latch-state) occurs when myosin light chain phosphatase removes the phosphate groups from the myosin heads. Phosphorylation of the 20 kDa myosin light chains correlates well with the shortening velocity of smooth muscle. During this period, there is a rapid burst of energy utilization as measured by oxygen consumption. Within a few minutes of initiation, the calcium level markedly decreases, the 20 kDa myosin light chains' phosphorylation decreases, and energy utilization decreases; however, force in tonic smooth muscle is maintained. During contraction of muscle, rapidly cycling crossbridges form between activated actin and phosphorylated myosin, generating force. It is hypothesized that the maintenance of force results from dephosphorylated "latch-bridges" that slowly cycle and maintain force. A number of kinases such as rho kinase, ZIP kinase, and protein kinase C are believed to participate in the sustained phase of contraction, and Ca^{2+} flux may be significant.

Neuromodulation

Although smooth muscle contractions are myogenic, the rate and strength of their contractions can be modulated by the autonomic nervous system. Postganglionic nerve fibers of parasympathetic nervous system release the neurotransmitter acetylcholine, which binds to muscarinic acetylcholine receptors (mAChRs) on smooth muscle cells. These receptors are metabotropic, or G-protein coupled receptors that initiate a second messenger cascade. Conversely, postganglionic nerve fibers of the sympathetic nervous system release the neurotransmitters epinephrine and norepinephrine, which bind to adrenergic receptors that are also metabotropic. The exact effects on the smooth muscle depend on the specific characteristics of the receptor activated—both parasympathetic input and sympathetic input can be either excitatory (contractile) or inhibitory (relaxing).

Cardiac Muscle

There are two types of cardiac muscle cells: autorhythmic and contractile. Autorhythmic muscle cells do not contract, but instead set the pace of

contraction for other cardiac muscle cells, which can be modulated by the autonomic nervous system. In contrast, contractile muscle cells constitute the majority of the heart muscle and are able to contract.

Excitation-contraction Coupling

Unlike skeletal muscle, excitation–contraction coupling in cardiac muscle is thought to depend primarily on a mechanism called calcium-induced calcium release. Though the proteins involved are similar, the DHPR and RyR (type 2) are not physically coupled. Instead, RyRs are activated by a calcium trigger, which is brought about by the activation of DHPRs. Further, cardiac muscle tend to exhibit diad (or dyad) structures, rather than triads.

Excitation-contraction coupling in cardiac muscle cells occurs when an action potential is initiated by pacemaker cells in the Sinoatrial node or Atrioventricular node and conducted to all cells in the heart via gap junctions. The action potential travels along the surface membrane into T-tubules (the latter are not seen in all cardiac cell types) and the depolarisation causes extracellular $Ca^{2+}$to enter the cell via L-type calcium channels and possibly sodium-calcium exchanger during the early part of the plateau phase. This Ca^{2+} influx causes a small local increase in intracellular Ca^{2+}. The increase in $Ca^{2+}$is detected by ryanodine receptors in the membrane of the sarcoplasmic reticulum which releases Ca^{2+}in a positive feedback physiological response.

This positive feedback is known as calcium-induced calcium release and gives rise to calcium sparks (Ca2+sparks). The spatial and temporal summation of ~30,000 Ca^{2+} sparks gives a cell-wide increase in cytoplasmic calcium concentration. The cytoplasmic calcium binds to Troponin C, moving the tropomyosin complex off the actin binding site allowing the myosin head to bind to the actin filament. From this point on, the contractile mechanism is essentially the same as for skeletal muscle (above). Briefly, using ATP hydrolysis, the myosin head pulls the actin filament toward the centre of the sarcomere. Intracellular calcium is taken up by the sarco/endoplasmic reticulum ATPase pump back into the sarcoplasmic reticulum ready for the next cycle to begin.

Calcium is also ejected from the cell mainly by the sodium-calcium exchanger and, to a lesser extent, a plasma membrane calcium ATPase and/or taken up by the mitochondria. An enzyme, phospholamban, serves as a brake for the ATPase. At low heart rates, phospholamban is active and slows down the activity of the ATPase so that Ca^{2+} does not have to leave the cell entirely.

At high heart rates, phospholamban is phosphorylated and deactivated thus removing most Ca^{2+} from the cell back into the sarcoplasmic reticulum. This allows the heart muscles to relax to allow for ventricular filling. Intracellular calcium concentration drops and troponin complex returns over the active site of the actin filament, ending contraction.

Invertebrate Animals

Circular and Longitudinal Muscles

In annelids such as earthworms and leeches, circular and longitudinal muscles cells form the body wall of these animals and are responsible for their movement. In an earthworm that is moving through a soil, for example, contractions of circular and longitudinal muscles occur reciprocally while the coelomic fluid serves as a hydroskeleton by maintaining turgidity of the earthworm. When the circular muscles in the anterior segments contract, the anterior portion of animal's body begins to constrict radially, which pushes the incompressible coelomic fluid forward and increasing the length of the animal. As a result, the front end of the animal moves forward. As the front end of the earthworm becomes anchored and the circular muscles in the anterior segments become relaxed, a wave of longitudinal muscle contractions passes backwards, which pulls the rest of animal's trailing body forward. These alternating waves of circular and longitudinal contractions is called peristalsis, which underlies the creeping movement of earthworms.

Obliquely Striated Muscles

Invertebrates such as annelids, mollusks, and nematodes, possess obliquely striated muscles, which contain bands of thick and thin filaments that are arranged helically rather than transversely, like in vertebrate skeletal or cardiac muscles. In bivalves, the obliquely striated muscles can maintain tension over long periods without using too much energy. Bivalves use these muscles to keep their shells closed.

Asynchronous Muscles

Advanced insects such as wasps, flies, bees, and beetles possess asynchronous muscles that constitute the flight muscles in these animals. These flight muscles are often called fibrillar muscles because they contain myofibrils that are thick and conspicuous. A remarkable feature of these muscles is that

they do not require stimulation for each muscle contraction. Hence, they are called asynchronous muscles because the number of contractions in these muscles do not correspond (or synchronize) with the number of action potentials. For example, a wing muscle of a tethered fly may receive action potentials at a frequency of 3 Hz but it is able to beat at a frequency of 120 Hz. The high frequency beating is made possible because the muscles are connected to a resonant system, which is driven to a natural frequency of vibration.

HEAT PRODUCTION IN THE MUSCLE

The branches of science that will help you understand the body parts and functions are anatomy and physiology. Anatomy deals with the study of the human body (the component parts, structure and position) and physiology the study of how the body functions.

Body Systems

The body comprises of a number of systems including the: Cardiovascular system, Digestive system, Endocrine system, Muscular system, Neurological system, Respiratory system and the Skeletal system.

The Muscular System

Muscle tissue has four main properties: Excitability (ability to respond to stimuli), Contractibility (ability to contract), Extensibility (ability of a muscle to be stretched without tearing) and Elasticity (ability to return to its normal shape).

Through contraction, the muscular system performs three important functions:

- Motion—walking, running etc.
- Heat production—maintain normal body temperature.
- Maintenance of posture—standing, sitting etc.

Motion

To understand how the muscles combine with the skeleton in providing motion we must look at the basic mechanics of movement. The main framework of the body is covered by muscle, whose function is to permit movement. We know that to move or lift a load against another force, it is easier to use levers, and it is this principle which the musculoskeletal system adopts and which we must examine.

The component parts that are used in a lever are as follows:

- Lever—nearly always the bone
- Fulcrum—pivot point of the lever, which is usually the joint
- Muscle Force—force that draws the opposite ends of the muscles together
- Resistive Force—force generated by a factor external to the body (*e.g.* gravity, friction etc.) that acts against muscle force
- Torque—the degree to which a force tends to rotate an object about a specified fulcrum

There are different types of levers dependent upon the position of fulcrum, effort and resistive force.

- ***First Class lever:*** Muscle force and resistive force is on different sides of the fulcrum *e.g.* the head resting on the vertebral column. As the head is raised, the facial portion of the skull is the resistance, the fulcrum is between the atlas and occipital bone, and the effort is the contraction of the muscles of the back.
- ***Second Class lever:*** Muscle force and resistive force act on the same side of the fulcrum, with the muscle force acting through the level longer than that through which the resistive force acts - *e.g.* raising the body up onto the toes. The body is the resistance, the ball of the foot is the fulcrum, and the effort is the contraction of the calf muscle.
- ***Third Class lever:*** Muscle force and resistive force act on the same side of the fulcrum, with the muscle force acting through the lever shorter than that through which the resistive force acts - *e.g.* adduction of the thigh. The weight of the thigh is the resistance, the hip joint is the fulcrum, and the contraction of the adductor muscle is the effort.

Most of the limbs of the human body are articulated by third class levers.

Agonist, Antagonist, Fixator and Synergist Muscles

Muscles can only exert a pulling force so work in pairs. When we move a limb one muscle, the agonist muscle also known as the prime mover, causes the movement and an antagonist muscle works in opposition to the agonist muscle.

Example: Biceps curl - the biceps is the agonist muscle causing the movement and the triceps are the antagonist muscle working in opposition to the biceps.

The function of a fixator muscle is to stabilize the origin of the agonist muscle so that it can move efficiently.

Other muscles, known as synergist muscles, stabilize muscle movements to keep them even, and control the movement so that it falls within a range of motion which is safe and desired.

Heat Production

Muscle contractions produce heat and as much as 70% of body heat is produced by energy produced in muscle tissue. Blood is an essential element in temperature control during exercise, taking heat from the body core and working muscles and redirecting it to the skin when the body is overheating.

When the internal heat of the body reaches too low a level thermoreceptors in the skin relay a message to the hypothalamus in the brain. In response to this signal, the skeletal muscles contract and relax in an involuntary manner (shivering) increasing muscle activity to generate heat. In turn, muscles are also responsive to exterior heat - cold air increases muscle tone, and hot conditions have a relaxing effect on muscles.

Maintenance of Posture

As well as enabling movement, muscles also maintain posture and body position. Sensory receptors in the muscles monitor the tension and length of the muscles and provide the nervous system with crucial information about the position of the body parts, therefore enabling posture to be maintained.

Muscles are never completely at rest, nor do they actually have to shorten in length when they contract. The tension or tone produced as a result of these contractions between various opposing groups of muscle helps us remain in a static position, even when we are asleep.

Muscle Origin and Insertion

Each end of a muscle is attached to a bone and these connections are known as the origin and insertion. The muscle’s origin is attached to the immovable bone and the muscle’s insertion is attached to the movable bone.

Effect of Exercise on the Muscular System

The effects of regular exercise on the muscular system:

- Strengthens muscles and the connective tissues.

- Improves muscle control and balance.
- An increase in muscle size and efficiency.
- The amount of myoglobin within skeletal muscle increases.
- Muscles are capable of storing a larger amount of glycogen.
- Muscle became more efficient at disposing of waste products through the bloodstream.
- Increase in muscle recruitment.

EFFECTS OF EXERCISE AND TRAINING ON THE MUSCULAR SYSTEM

The effects of exercise on muscles is important for courses such as GCSE Physical Education (PE) and for careers in health *e.g.* nursing, caring, fitness training, massage, reflexology etc. The effects of exercise or any physical activity on muscles depend on:

- Type of physical activity *e.g.* walking, playing tennis, playing bowls.
- Intensity of the activity *e.g.* gentle slow walk or 200m sprint.
- Duration of the activity *e.g.* 30 mins or 4 hours.

The effects of exercise on muscles include both short term and long term changes due to physical exercise:

- Short term effects of exercise persist during the activity itself and perhaps for a short time afterwards.
- Long term effects of exercise are on-going and can apply for much longer lengths of time including between physical activities.

Short Term Effects of Exercise on Muscles

Blood Flow:

- The volume of blood flow to muscle tissues increases during exercise.
- It can increase by up to 25 times (that is 2400% !) during especially demanding exercise.

Respiration and Oxygen Debt:

- During exercise muscles repeatedly contract and relax, using and requiring ENERGY to do so.
- The energy comes from a chemical called adenosine triphosphate (sometimes called just ATP) that is broken down during exercise into another chemical called Adenosine diphosphate (ADP),
  ATP $\rightarrow$Adenosine diphosphate (ADP) + ENERGY + inorganic Phosphate.

- When there is plenty of oxygen available in the muscle tissues the ENERGY for muscle action is produced aerobically but in cases of prolonged or vigorous activity there may be insufficient oxygen available in the tissues so the ENERGY is produced anaerobically.
- In the case of anaerobic energy production, ATP is generated by converting glycogen to lactic acid. Lactic acid is a toxic substance that can only be removed from the body by the supply of further oxygen to the affected tissues - hence anaerobic activity leads to oxygen debt.
- Exercise can generate an oxygen debt of 10-12 dm (up to 18-20 dm in trained athletes).
- The need for oxygen to repay the "oxygen debt" built up in exercised muscle tissues explains the increased requirement for air/oxygen indicated by panting after extreme exercise - or even just more demanding exercise than one is used to, *e.g.* running a few strides for a bus if unfit.

Fatigue :

- Muscle fatigue is short-term decline in the ability of a muscle to generate force.
- Another way to describe muscle fatigue is as the short-term inability to continue to repeat muscular contractions with the same force (*i.e.* when the same or greater effort seems to result in output of lower mechanical force).

Exhaustion :

- When exercise continues through muscle fatigue after time it can lead to muscle exhaustion.

Muscle damage :

- Muscles can be damaged by injuries sustained during or as a result of exercise.
- A common example is strained muscles or muscle tears due to over-stretching without warming-up the muscles before using them intensely.
- Muscle damage is both a possible short-term effect of exercise and a possible long-term effect of exercise because, depending on the damage caused, it may take a long or short time to heal. It is included here as a "short term effect of exercise" because damage can even occur after just a short amount of physical activity, *e.g.* to someone who has not exercised for a long time then suddenly uses muscles intensely, perhaps without having first warmed-up properly.

Cramp :

- Muscle cramp is powerful, on-going, uncontrolled muscle contraction due to over-exercise of muscles receiving insufficient blood circulation. It can be painful.

Glycogen and potassium depletion :

- Glycogen and potassium are both important solutes required by the tissues in the body.
- Depletion of these from muscle tissues due to excessive exercise are associated with both fatigue and exhaustion.

Depending on the level and requirements of the course and the number of marks available (if a homework question, test, or exam) it may be sufficient to just list the short term effects of exercise on muscles, or it may be necessary to explain each point with examples where appropriate.

Long Term Effects of Exercise on Muscles

Muscle size :

- Although muscle size (and other physical characteristics such as height) is largely determined by a person's genes, muscle size can be affected to a certain extent by :
  - Drugs *e.g.* anabolic steroids.
  - Lifestyle choices *e.g.* exercise for work or leisure.
- Not all forms of sports or exercise have a significant effect on muscle size because some sports rely more on concentration, co-ordination and control than on physical power and strength. However, in general, exercising specific muscles regularly can increase their size by up to approx. 60%. This increase in muscle size is mainly due to increased diameter of individual muscle fibres.

Blood supply (to and through muscles) :

- As a result of frequent exercise over a sustained period of time both the quantity of blood vessels (incl. *e.g.* arterioles and venules) and the extent of the capillary beds increases.
- The benefits of these effects on blood supply to muscle tissues include:
  - Improving delivery of substrates to the tissues by the blood
  - Improving the blood system's efficiency in removing toxic products from the tissues

Muscle Co-ordination :

- Frequent exercise and especially use of specific muscles for the same or similar skilled tasks *e.g.* dribbling a ball in a game of football leads to improved co-ordination.
- For example, antagonistic pairs of muscles work together even more effectively; when the prime mover contracts more rapidly the antagonist (muscle) must also relax as quickly.

- Improved muscle co-ordination is not just about muscle cells and tissues but also the nerves that innervate those muscles. The somatic nervous system controls skeletal muscle *e.g.* the muscles that move the arms and legs together with external sensory organs such as the skin.

Muscle Biochemistry:

- Many beneficial biochemical changes take place in muscle tissues as a result of regular long term exercise. These include :
  - Increase in the size and quantity of mitochondria in the cells.
  - Increase in activity of enzymes in the tricarboxylic acid cycle (which is also known as the TCA cycle, the Krebs cycle and as the citric acid cycle), a series of enzyme-catalyzed chemical reactions that form a key part of aerobic respiration in cells.
  - Increase in fatty acid oxidation (fatty acid oxidation in mitochondria provides energy to cells when glucose levels are low).

Note: The above explanations of some long term effects of exercise on muscles exceed the requirements of introductory level courses (*e.g.* GCSE PE) in order to include terms used in A-Level courses (*e.g.* A Level Human Biology).

Short-term *vs.* Long-term Effects of Exercise on the Muscles

What is a 'Short-term Effect'?

One single period of sufficient physical activity can have short term effects on muscles, including during the activity itself and perhaps for a short time afterwards.

What is a 'Long-term Effect', or a 'Longer-term Effect'?

Frequent regular physical activity has longer-term effects than one-off periods of similar activity. This means that the effects of the exercise on the muscles continue to affect the body long after the exercise itself has stopped. For example, after a while someone who plays active sports such as tennis or hockey for at least an hour on Tuesdays, Thursdays and Saturdays would also experience the effects of this exercise on his or her muscles during the other days of the week as well.

2

Cardiovascular System and Exercise

HEART VALVES AND DIRECTION OF THE BLOOD FLOW

Heart Valves

Pumps need a set of valves to keep the fluid flowing in one direction and the heart is no exception. The heart has two types of valves that keep the blood flowing in the correct direction. The valves between the atria and ventricles are called atrioventricular valves (also called cuspid valves), while those at the bases of the large vessels leaving the ventricles are called semilunar valves. The right atrioventricular valve is the tricuspid valve. The left atrioventricular valve is the bicuspid, or mitral, valve. The valve between the right ventricle and pulmonary trunk is the pulmonary semilunar valve. The valve between the left ventricle and the aorta is the aortic semilunar valve.

When the ventricles contract, atrioventricular valves close to prevent blood from flowing back into the atria. When the ventricles relax, semilunar valves close to prevent blood from flowing back into the ventricles.

Direction of the Blood Flow

The human circulatory system is really a two-part system whose purpose is to bring oxygen-bearing blood to all the tissues of the body. When the heart contracts it pushes the blood out into two major loops or cycles. In the systemic loop, the blood circulates into the body's systems, bringing oxygen to all its organs, structures and tissues and collecting carbon dioxide waste. In the

pulmonary loop, the blood circulates to and from the lungs, to release the carbon dioxide and pick up new oxygen. The systemic cycle is controlled by the left side of the heart, the pulmonary cycle by the right side of the heart. Let's look at what happens during each cycle:

The systemic loop begins when the oxygen-rich blood coming from the lungs enters the upper left chamber of the heart, the left atrium. As the chamber fills, it presses open the mitral valve and the blood flows down into the left ventricle. When the ventricles contract during a heartbeat, the blood on the left side is forced into the aorta. This largest artery of the body is an inch wide. The blood leaving the aorta brings oxygen to all the body's cells through the network of ever smaller arteries and capillaries. The used blood from the body returns to the heart through the network of veins. All of the blood from the body is eventually collected into the two largest veins: the superior vena cava, which receives blood from the upper body, and the inferior vena cava, which receives blood from the lower body region. Both venae cavae empty the blood into the right atrium of the heart.

From here the blood begins its journey through the pulmonary cycle. From the right atrium the blood descends into the right ventricle through the tricuspid valve. When the ventricle contracts, the blood is pushed into the pulmonary artery that branches into two main parts: one going to the left lung, one to the right lung. The fresh, oxygen-rich blood returns to the left atrium of the heart through the pulmonary veins.

Although the circulatory system is made up of two cycles, both happen at the same time. The contraction of the heart muscle starts in the two atria, which push the blood into the ventricles. Then the walls of the ventricles squeeze together and force the blood out into the arteries: the aorta to the body and the pulmonary artery to the lungs. Afterwards, the heart muscle relaxes, allowing blood to flow in from the veins and fill the atria again. In healthy people the normal (resting) heart rate is about 72 beats per minute, but it can go much higher during strenuous exercise. Scientists have estimated that it takes about 30 seconds for a given portion of the blood to complete the entire cycle: from lungs to heart to body, back to the heart and out to the lungs.

How Does Blood Travel Through the Heart?

As the heart beats, it pumps blood through a system of blood vessels, called the circulatory system. The vessels are elastic, muscular tubes that carry blood to every part of the body.

Blood is essential. In addition to carrying fresh oxygen from the lungs and nutrients to your body's tissues, it also takes the body's waste products, including carbon dioxide, away from the tissues. This is necessary to sustain life and promote the health of all the body's tissues.

There are three main types of blood vessels:

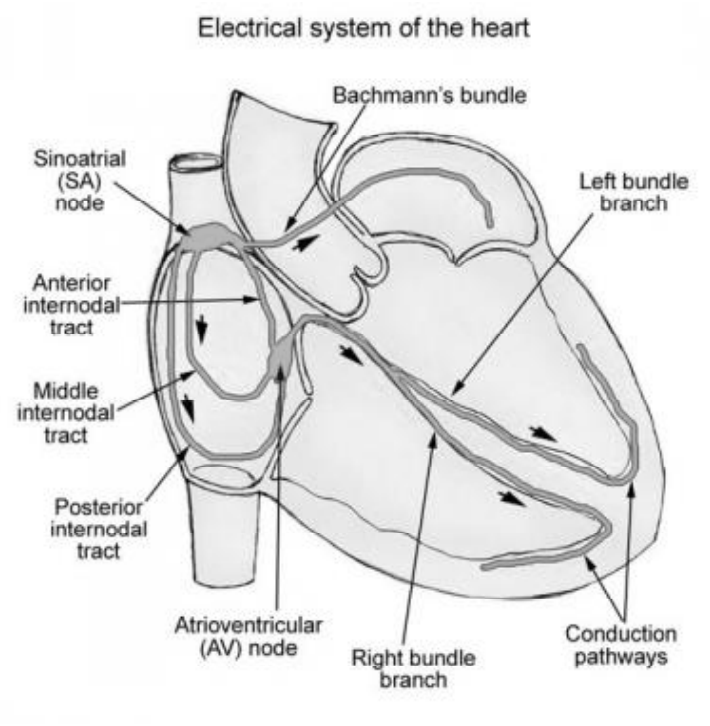
- ***Arteries:*** Arteries carry oxygen-rich blood away from the heart to all of the body's tissues. They branch several times, becoming smaller and smaller as they carry blood farther from the heart and into organs.
- ***Capillaries:*** These are small, thin blood vessels that connect the arteries and the veins. Their thin walls allow oxygen, nutrients, carbon dioxide, and other waste products to pass to and from cells.
- ***Veins:*** These are blood vessels that take blood back to the heart; this blood contains less oxygen and is rich in waste products that are to be excreted or removed from the body. Veins become larger as they get closer to the heart. The superior vena cava is the large vein that brings blood from the head and arms to the heart, and the inferior vena cava brings blood from the abdomen and legs into the heart.

This vast system of blood vessels — arteries, veins, and capillaries — is over 60,000 miles long. That's long enough to go around the world more than twice! Blood flows continuously through your body's blood vessels. Your heart is the pump that makes it all possible.

CONDUCTION SYSTEM OF THE HEART

The conducting system of the heart consists of cardiac muscle cells and conducting fibers (not nervous tissue) that are specialized for initiating impulses and conducting them rapidly through the heart. They initiate the normal cardiac cycle and coordinate the contractions of cardiac chambers. Both atria contract together, as do the ventricles, but atrial contraction occurs first.

The conducting system provides the heart its automatic rhythmic beat. For the heart to pump efficiently and the systemic and pulmonary circulations to operate in synchrony, the events in the cardiac cycle must be coordinated.



BLOOD SUPPLY TO THE HEART

This is a tutorial on the vascular supply to the heart. I'm first going to talk a bit about the arterial supply and then I'll talk about the venous drainage of the heart. Like the rest of the body, the heart needs oxygenated blood to function. Blood that's received from the lungs into the left side of the heart is pumped out of the aorta and the aorta has some branches which supply the heart.

Coronary Arteries

At the base of the aorta just after the aortic valves, you've got two branches which come off the right and left coronary arteries. Here you can see the right branch coming from the base of the aorta and the left branch which is slightly hidden under the pulmonary trunk. You've got left coronary artery coming off the base of the aorta. The right aortic sinus gives rise to the right coronary artery and the left aortic sinus gives rise to the left coronary artery. You've got these two main branches coming from the base of the aorta, the right and left coronary arteries. They've got various branches which I'm now going to talk about.

Sulci

Also on the heart, you've got grooves. You've got grooves between the atrium and the ventricles and you've got grooves between the ventricles. Between the atrium and the ventricles, you've got a groove called the coronary sulcus. In anatomy, in reference to any groove, you'll hear the word 'sulcus'. In the brain, the grooves are called 'sulci' (plural) or 'sulcus' (singular) and on the heart, the same thing apply. You've got grooves which are called sulci. The coronary sulcus runs between the atrium and the ventricles and the coronary arteries run in this coronary sulcus. Between the ventricles, you've got an interventricular groove. An interventricular sulcus. This groove separates the right and left ventricle and some major vessels run down this groove.

Right Coronary Artery

Just following the right coronary artery around its course, it winds around along the coronary sulcus to the back of the heart and it gives off two main branches. You can see this branch on the right margin of the heart coming off the right coronary artery. This is called the right marginal branch. That's the first branch. And as we follow the right coronary artery right to the back, you can see this groove running between the atrium and the ventricles separating the atrium from the ventricle, it runs right around the heart. And then you can see this branch here. This is the posterior interventricular sulcus. The one I showed you on the front is the anterior interventricular sulcus.

The artery that branches from the right coronary artery and runs down the posterior interventricular groove is the posterior interventricular artery, which is also known as the posterior descending artery. You've got two branches of the right coronary artery, you've got the right marginal artery and you've got the posterior interventricular artery or the posterior descending artery. This is the right coronary artery you can see here in the coronary sulcus.

Left Coronary Artery

The left coronary artery arises from the left aortic sinus at the base of the aorta. Looking directly at the heart, you can't actually see this branch. It's hidden underneath the pulmonary trunk.

Again, this artery has a few branches. The first branch which you can see running down the anterior interventricular sulcus is the anterior interventricular artery, otherwise known as the left anterior descending artery. That's the first

branch of the left coronary artery. This thing here is the right atrial appendage. I'll just remove that so we can have a good look at the arteries.

This is the left coronary artery giving off the anterior interventricular artery as its first branch. And then it winds around all the way to the back just like the right coronary artery. This branch which winds all the way around is known as the circumflex artery. This gives off a branch here.

Like we've got this artery coming from the right coronary artery lying on the right margin of the heart called the right marginal branch or artery, we've got the artery on the left margin. It's the left marginal branch. This comes off the circumflex artery.

The circumflex artery winds all the way to the back to the base of the heart and extends down.

The circumflex artery extends very far down. There is anatomical variation between people. Sometimes, the posterior interventricular artery which usually arises from the right coronary artery, it can arise at the circumflex artery of the left coronary artery. This is known as coronary dominance. Someone whose posterior interventricular artery arises from the circumflex artery, they'll be left dominant, whereas if the posterior interventricular artery rises from the right coronary artery, then they'll be called right dominant.

In the majority of people, the posterior interventricular artery arises in the right side. But in some patients, the posterior interventricular artery arises from the circumflex artery, in which case, they're left dominant.

In the case of this model, you can see both arteries run in equal lengths. This would be a case of co-dominance. There's an equal supply from the right and the left coronary arteries to the posterior surface of the heart.

Recap

Just to quickly go over that again, you've got two arteries which branch off from the base of the aorta arising from the aortic sinuses. You've got the right aortic sinus giving rise to the right coronary artery and the left aortic sinus giving rise to the left coronary artery. The right coronary artery winds around along the coronary sulcus giving off two branches – the right marginal branch and the posterior interventricular artery, which runs down the posterior interventricular sulcus.

The right coronary artery supplies the right atrium and the right ventricle. It supplies both the sinoatrial node and the atrioventricular node in most people. But remember, there is a certain degree of anatomical variation. The left

coronary artery gives off a few branches. You've got this first branch which runs down the anterior interventricular sulcus and is known as the anterior interventricular artery also known as the anterior descending artery, the left anterior descending artery. And then you've got this branch, the circumflex branch, which winds around all the way to the posterior surface of the heart. The circumflex artery gives rise to this artery, the left marginal branch, which sits on the left margin of the heart, hence the name.

And in some people, the circumflex artery actually gives rise to the posterior interventricular artery in which case, the person is known as left dominant. A person's coronary artery dominance is determined by which artery supplies the posterior interventricular artery. If it's the left coronary artery as a branch of the circumflex, then they're left dominant. If it's the right coronary artery, then they're right dominant. That's the arterial supply to the heart. Next, I'm going to be talking about the venous drainage of the heart.

Venous Drainage

Okay! So the venous drainage of the heart is by several cardiac veins which drain into the coronary sinus, which lies on the posterior aspect of the heart on the inferior surface (this diaphragmatic surface). You've got this coronary sinus which lies between the left atrium and the left ventricle. It lies in the coronary sulcus between the left atrium and ventricle. The coronary sinus drains blood back into the right side of the heart. Just like all the other deoxygenated blood, it returns blood to the right atrium.

This is the coronary sinus here. It receives four tributaries. You've got the great cardiac vein, which runs the anterior interventricular sulcus and winds around to join the coronary sulcus at the back. That's the great cardiac vein. It runs down the anterior interventricular surface, winds around and drains into the coronary sinus.

You've got this vein which runs down the posterior interventricular sulcus and this is called the middle cardiac vein. This joins into the coronary sinus.

This one on the margin of the heart is the posterior cardiac vein. It meets the great cardiac vein to join into the coronary sinus. We just rotate to get around, you can see it lies on the left margin of the heart and it drains into the coronary sinus. This is the posterior cardiac vein.

And then on the right side of the heart, you've got this small cardiac vein. This thin, little vein here running in the coronary sulcus is called the small cardiac vein. That runs between the right atrium and the right ventricle.

And you've got this little branch which comes off the small cardiac vein. This is the right marginal vein. This drains into the small cardiac vein, which drains into the coronary sinus, which drains blood into the right atrium.

You've got the coronary sinus, which has four tributaries. You've got the great cardiac vein running in the anterior interventricular sulcus. You've got the posterior cardiac vein, which runs on the left margin of the heart, which joins the great cardiac vein and joins into the coronary sinus. And then you've got the middle cardiac vein, which runs right down the middle of the back of the heart, the diaphragmatic surface of the heart in the posterior interventricular sulcus. And you've got the small cardiac vein, which drains into the coronary sinus. Four tributaries which drain to the coronary sinus. And then you've got these other two veins, which you need to know, the right marginal vein, which drains into the small cardiac vein and you've got these veins here which are anterior veins. These drain the anterior portion of the right ventricle.

CARDIAC CYCLE

The cardiac cycle refers to the sequence of mechanical and electrical events that repeats with every heartbeat. It includes the phase of relaxation diastole and the phase of contraction systole. Because the human heart is a four chambered organ, there are atrial systole, atrial diastole, ventricular systole and ventricular diastole. The frequency of the cardiac cycle is described by the heart rate, which is typically expressed as beats per minute. Each cycle of the heart, from the point of view of the ventricles and the status of their valves, involves a minimum of four major stages: Inflow phase, Isovolumetric contraction, outflow phase and Isovolumetric relaxation.

The first and the fourth stages, together constitute the "ventricular diastole" stage, involve the movement of blood from the atria into the ventricles. Stages 2 and 3 involve the "ventricular systole" *i.e.* the movement of blood from the ventricles to the pulmonary artery (in the case of the right ventricle) and the aorta (in the case of the left ventricle).

"Ventricular diastole," begins when the ventricles starts to relax. At this point, some blood of the previous cycle's systole is still flowing out of the ventricles through the semilunar valves, due to the inertia of the moving blood column, which overcomes the higher pressure in the aorta/pulmonary trunk with respect to the pressure in the ventricles. This short lasting phase, called "protodiastole" ends with the closure of the semilunar valves, producing the second heart sound (S_2). Now that both the AV valves and the semilunar valves

are closed, the ventricles are now closed chambers. Hence, this phase is known as isovolumetric (also called isovolumic, isometric) relaxation phase. Then the atrioventricular (AV) valves (the mitral valve and the tricuspid valve) open, allowing blood to fill the ventricles. This ventricular inflow phase can be sub-divided into the 'first rapid filling phase' as blood rushes in from the atria as a result of ventricular dilation; a phase of slow ventricular filling called 'Diastasis', and the 'last rapid filling phase' due to atrial contraction (systole).

As the ventricular systole begins, pressure within the ventricle rises and the AV valves close producing the 'first heart sound' (S_1). The semilunar valves remain closed. The contracting ventricles become closed chambers again and this phase is termed as "isovolumic contraction". As the name implies, there is no change in volume, but intra-ventricular pressure rises. The outflow phase, "ventricular ejection," is when the intra-ventricular pressure has achieved a higher pressure than the blood in the aorta (or the pulmonary trunk), the corresponding semilunar valves open. Ejection phase begins.

Throughout the cardiac cycle, blood pressure increases and decreases. The cardiac cycle is coordinated by a series of electrical impulses that are produced by specialised pacemaker cells found within the sinoatrial node and the atrioventricular node. The cardiac muscle is composed of myocytes which initiate their own contraction without the help of external nerves (with the exception of modifying the heart rate due to metabolic demand). The duration of the cardiac cycle is the reciprocal of heart rate. Assuming a heart rate of 75 beats per minute, each cycle takes 0.8 seconds.

Physiology

The heart is a four-chambered organ consisting of right and left halves. The upper two chambers, the left and right atria, are entry-points into the heart, while the lower two chambers, the left and right ventricles, are responsible for contractions that send the blood through the circulation. The circulation is split into the pulmonary and systemic circulation. The role of the right ventricle is to pump deoxygenated blood to the lungs through the pulmonary trunk and pulmonary arteries. The role of the left ventricle is to pump newly oxygenated blood to the body through the aorta.

Heart Conducting System

Cardiac muscle has automaticity, which means that it is self-excitable. The muscle contractions are generated by the muscle cell itself or are passed

down by another set of specialized cardiomyocytes (cardiac muscle cells), called the 'junctional fibers'. This is in contrast with skeletal muscle, which requires nervous stimuli (either conscious or reflex) for excitation. The heart's rhythmic contractions occur spontaneously, although the rate of contraction can be changed by nervous or hormonal influences. For example, stimulating the sympathetic nerve accelerates heart rate while stimulating the vagus nerve decelerates the heart rate.

The rhythmic sequence of contractions (sinus rhythm), is coordinated by the sinoatrial (SA) and atrioventricular (AV) nodes. The sinoatrial node, often known as the cardiac pacemaker, is located in the upper wall of the right atrium and is responsible for the wave of electrical stimulation that initiates atrial contraction by creating an action potential. Once the wave reaches the AV node, situated in the lower right atrium, it is delayed there before being conducted through the bundles of His and back up the Purkinje fibers, leading to a contraction of the ventricles. The delay at the AV node allows enough time for all of the blood in the atria to fill their respective ventricles. In the event of severe pathology, the AV node can also act as a pacemaker; this is usually not the case because its rate of spontaneous firing is considerably lower than that of the SA node and hence it is overridden.

Stages

The following is a summary of the cardiac cycle:

- ***Atrial Systole:*** Coincides with the 'last rapid filling phase' of ventricular diastole (ventricular filling)

	AV valves*	***Semilunar***	***Status of ventricles and valves atria***
1. Atrial Systole(inflow phase)	open	closed	• Atrial contraction
2. Isovolumetric Contraction	closed	closed	• Ventricles begin to contract.
3. Ventricular Ejection	closed	open	• LVP > aorta P, RVP > PAP
4. Isovolumetric Relaxation	closed	closed	• semilunar valves (AV,PV)
5. Ventricular Filling	open	closed	• Ventricles relaxed

Atrial Systole

Atrial systole is the contraction of the atrial syncytium of cardiac muscle

cells of the left and right atria, following electrical stimulation. This conduction takes place via the gap junctions of the connecting intercalated discs. Normally, both atria contract at the same time. The term systole is synonymous with contraction (movement or shortening) of a muscle. Electrical systole is the electrical activity that stimulates the cardiac muscle of the heart chambers to make them contract. This is soon followed by mechanical systole, which is the mechanical contraction of the heart.

As the atria contract, the blood pressure in each atrium increases, forcing additional blood into the ventricles. The additional flow of blood is called atrial kick.

80% of the blood flows passively down to the ventricles, so the atria do not have to contract a great amount.

Atrial kick is absent if there is loss of normal electrical conduction in the heart, such as during atrial fibrillation, atrial flutter, and complete heart block. Atrial kick is also different in character depending on the condition of the heart, such as stiff heart, which is found in patients with diastolic dysfunction.

Atrial systole, also known as auricular systole due to the contraction of the two auricles of the heart, takes approximately 0.1 seconds.

Detection

Electrical systole of the atria begins with the onset of the P wave on the ECG. The wave of depolarization that stimulates both atria to contract at the same time is due to the sinoatrial node which is located on the upper wall of the right atrium. The sinoatrial node can be detected by catheterization.

Ventricular Systole

Ventricular systole is the contraction of the ventricular syncytium of cardiac muscle cells of the left and right ventricles, following electrical stimulation. This conduction takes place via the gap junctions of the connecting intercalated discs.

At the later part of the ejection phase, although the ventricular pressure falls below the aortic pressure, the aortic valve remains open because of the inertial energy of the ejected blood.

The graph of aortic pressure throughout the cardiac cycle displays a small dip (the “incisure” or “dicrotic notch”) which coincides with the aortic valve closure. The dip in the graph is immediately followed by a brief rise (the “dicrotic wave”) then gradual decline. Just as the ventricles enter into diastole,

the brief reversal of flow from the aorta back toward the left ventricle causes the aortic valves to shut. This results in the slight increase in aortic pressure caused by the elastic recoil of the semilunar valves and aorta.

The total volume of blood remaining in the ventricle just at the end of the ventricular contraction is called end-systolic volume (ESV).

Assuming a pulse of 72 beats per minutes, ventricular systole takes 0.3 seconds to complete.

Detection

Heart Sounds

The closing of the mitral and tricuspid valves (known together as the atrioventricular valves) at the beginning of ventricular systole cause the first part (the lubb) of the "lubb-dubb" sound made by the heart as it beats. Formally, this sound is known as the first heart sound, or S_1. This first heart sound is created by the closure of the mitral and tricuspid valves and is actually a two component sound, M1, T1.

The second part (the dubb) of the "lubb-dubb" (the second heart sound, or S_2), is caused by the closure of the aortic and pulmonary valves at the end of ventricular systole. As the left ventricle empties, its pressure falls below the pressure in the aorta, and the aortic valve closes. Similarly, as the pressure in the right ventricle falls below the pressure in the pulmonary artery, the pulmonary valve closes. The second heart sound is also two components, A2 and P2. The aortic valve closes earlier than the pulmonary valve and they are audibly separated from each other in the second heart sound. This "splitting" of S_2 is only audible during inhalation. However, some cardiac conduction abnormalities such as left bundle branch block (LBBB) allow the P2 sound to be heard before the A2 sound during expiration. With LBBB, inhalation brings A2 and P2 closer together where they cannot be audibly distinguished.

Electrocardiogram

In an electrocardiogram, electrical systole of the ventricles begins at the beginning of the QRS complex.

Diastole

Cardiac diastole is the period of time when the heart relaxes after contraction in preparation for refilling with circulating blood. Ventricular

diastole is when the ventricles are relaxing, while atrial diastole is when the atria are relaxing. Together they are known as complete cardiac diastole.

During ventricular diastole, the pressure in the (left and right) ventricles drops from the peak that it reaches in systole. When the pressure in the left ventricle drops to below the pressure in the left atrium, the mitral valve opens, and the left ventricle fills with blood that was accumulating in the left atrium. The isovolumic relaxation time (IVRT) is the interval from the aortic component of the second heart sound, that is, closure of the aortic valve, to onset of filling by opening of the mitral valve. Likewise, when the pressure in the right ventricle drops below that in the right atrium, the tricuspid valve opens, and the right ventricle fills with blood that was accumulating in the right atrium. During diastole the pressure within the left ventricle is lower than that in aorta, allowing blood to circulate in the heart itself via the coronary arteries.

STROKE VOLUME

In cardiovascular physiology, stroke volume (SV) is the volume of blood pumped from the left ventricle per beat. Stroke volume is calculated using measurements of ventricle volumes from an echocardiogram and subtracting the volume of the blood in the ventricle at the end of a beat (called end-systolic volume) from the volume of blood just prior to the beat (called end-diastolic volume). The term stroke volume can apply to each of the two ventricles of the heart, although it usually refers to the left ventricle. The stroke volumes for each ventricle are generally equal, both being approximately 70 mL in a healthy 70-kg man.

Stroke volume is an important determinant of cardiac output, which is the product of stroke volume and heart rate, and is also used to calculate ejection fraction, which is stroke volume divided by end-diastolic volume. Because stroke volume increase in certain conditions and disease states, stroke volume itself correlates with cardiac function.

Calculation

Its value is obtained by subtracting end-systolic volume (ESV) from end-diastolic volume (EDV) for a given ventricle.

$$SV = EDV - ESV$$

In a healthy 70-kg man, ESV is approximately 50 mL and EDV is approximately 120mL, giving a difference of 70 mL for the stroke volume.

"Stroke work" refers to the work, or pressure of the blood ("P") multiplied by the stroke volume.

Determinants

Men, on average, have higher stroke volumes than women due to the larger size of their hearts. However, stroke volume depends on several factors such as heart size, contractility, duration of contraction, preload (end-diastolic volume), and afterload.

Exercise

Prolonged aerobic exercise training may also increase stroke volume, which frequently results in a lower (resting) heart rate. Reduced heart rate prolongs ventricular diastole (filling), increasing end-diastolic volume, and ultimately allowing more blood to be ejected.

Preload

Stroke volume is intrinsically controlled by preload (the degree to which the ventricles are stretched prior to contracting). An increase in the volume or speed of venous return will increase preload and, through the Frank–Starling law of the heart, will increase stroke volume. Decreased venous return has the opposite effect, causing a reduction in stroke volume.

Afterload

Elevated afterload (commonly measured as the aortic pressure during systole) reduces stroke volume. Though not usually affecting stroke volume in healthy individuals, increased afterload will hinder the ventricles in ejecting blood, causing reduced stroke volume. Increased afterload may be found in aortic stenosis and arterial hypertension.

Stroke Volume Index

Similar to cardiac index, is a method of relating the stroke volume (SV) to the size of the person Body surface area (BSA).

$$SVI = \frac{SV}{BSA} = \frac{(CO / HR)}{BSA} = \frac{CO}{HR \times BSA}$$

CARDIAC OUTPUT

Cardiac output (CO, also denoted by the symbols Q and Q_c), is a term used in cardiac physiology that describes the volume of blood being pumped by the heart, in particular by the left or right ventricle, per unit time.

Cardiac output is the product of the heart rate (HR), which is the number of heart beats per minute, and the stroke volume (SV), which is the volume of blood pumped from the ventricle per beat; thus, CO = HR × SV. Cardiac output values can be represented using many physical units, such as dm^3/min, but is usually denoted as L/min. In a subject weighing 70 kg, the cardiac output at rest would be around 5 L/min; assuming a heart rate of 70 beats/min, the stroke volume would be approximately 70 mL.

Because cardiac output is related to the quantity of blood delivered to various parts of the body, it can be used as an important indicator of how efficiently the heart can meet the body's demands for perfusion.

For instance, exercise requires a higher level of CO to support increased muscle activity. In heart failure, CO may be insufficient to even support simple activities of daily living and cannot increase sufficiently to match the higher metabolic demands stemming from even moderate exercise.

Cardiac output is a global blood flow parameter of interest in hæmodynamics, the study of the flow of blood.

There are many methods of measuring CO, both invasively and non-invasively, each with its own advantages and drawbacks. No standard or reference measurement against which all of these methods can be compared exists.

Definition

The function of the heart is to drive blood through the circulatory system in a cycle that delivers oxygen, nutrients and chemicals to the body's cells and removes cellular waste. Because it pumps out whatever blood comes back into it from the venous system, the quantity of blood returning to the heart effectively determines the quantity of blood the heart pumps out – its cardiac output, Q. Cardiac output is classically defined alongside stroke volume (SV) and the heart rate (HR) as:

$$CO_{[L/\mathrm{min}]} = SV_{[L/beat]} \times HR_{[beat/\mathrm{min}]}$$

In standardizing what CO values are considered to be within normal range independent of the size of the subject's body, the accepted convention is to further index equation (1) using Body surface area (BSA), giving rise to the Cardiac index (CI). This is detailed in equation (2) below.

Measurement

There are a number of clinical methods to measure cardiac output, ranging

from direct intracardiac catheterisation to non-invasive measurement of the arterial pulse. Each method has advantages and drawbacks. Relative comparison is limited by the absence of a widely accepted "gold standard" measurement. Cardiac output can also be affected significantly by the phase of respiration – intra-thoracic pressure changes influence diastolic filling and therefore cardiac output. This is especially important during mechanical ventilation, in which cardiac output can vary by up to 50% across a single respiratory cycle. Cardiac output should therefore be measured at evenly spaced points over a single cycle or averaged over several cycles.

Invasive methods are well accepted, but there is increasing evidence that these methods are neither accurate nor effective in guiding therapy. Consequently, the focus on development of non-invasive methods is growing.

Doppler Ultrasound

This method uses ultrasound and the Doppler effect to measure cardiac output. The blood velocity through the heart causes a Doppler shift in the frequency of the returning ultrasound waves. This shift can then be used to calculate flow velocity and volume, and effectively cardiac output, using the following equations:

- $Q = SV \times HR$
- $SV = VTI \times CSA$
- $CSA = \pi r^2$

where:

- CSA is the valve orifice cross sectional area,
- r is the valve radius,
- VTI is the velocity time integral of the trace of the Doppler flow profile.

Being non-invasive, accurate and inexpensive, Doppler ultrasound is a routine part of clinical ultrasound; it has high levels of reliability and reproducibility, and has been in clinical use since the 1960s.

Echocardiography

Echocardiography is a non-invasive method of quantifying cardiac output using ultrasound. Two-dimensional (2D) ultrasound and Doppler measurements are used together to calculate cardiac output. 2D measurement of the diameter (d) of the aortic annulus allows calculation of the flow cross-

sectional area (CSA), which is then multiplied by the VTI of the Doppler flow profile across the aortic valve to determine the flow volume per beat (stroke volume, SV). The result is then multiplied by the heart rate (HR) to obtain cardiac output. Although used in clinical medicine, it has a wide test-retest variability. It is said to require extensive training and skill, but the exact steps needed to achieve clinically adequate precision have never been disclosed. 2D measurement of the aortic valve diameter is one source of noise; others are beat-to-beat variation in stroke volume and subtle differences in probe position. An alternative that is not necessarily more reproducible is the measurement of the pulmonary valve to calculate right-sided CO. Although it is in wide general use, the technique is time consuming and is limited by the reproducibility of its component elements. In the manner used in clinical practice, precision of SV and CO is of the order of ±20%.

Transcutaneous

The Ultrasonic Cardiac Output Monitor (USCOM) uses continuous wave Doppler to measure the Doppler flow profile VTI. It uses anthropometry to calculate aortic and pulmonary valve diameters and CSAs, allowing right-sided and left-sided Q measurements. In comparison to the echocardiographic method, USCOM significantly improves reproducibility and increases sensitivity of the detection of changes in flow. Real-time, automatic tracing of the Doppler flow profile allows beat-to-beat right-sided and left-sided Q measurements, simplifying operation and reducing the time of acquisition compared to conventional echocardiography. USCOM has been validated from 0.12 l/min to 18.7 l/min in new-born babies, children and adults. The method can be applied with equal accuracy to patients of all ages for the development of physiologically rational haemodynamic protocols. USCOM is the only method of cardiac output measurement to have achieved equivalent accuracy to the implantable flow probe. This accuracy has ensured high levels of clinical use in conditions including sepsis, heart failure and hypertension.

Transoesophageal

Transoesophageal Doppler includes two main technologies; transoesophageal echocardiogram —which is primarily used for diagnostic purposes, and oesophageal Doppler monitoring—which is primarily used for the clinical monitoring of cardiac output. The latter uses continuous wave Doppler to measure blood velocity in the descending thoracic aorta. An

ultrasound probe is inserted either orally or nasally into the oesophagus to mid-thoracic level, at which point the oesophagus lies alongside the descending thoracic aorta. Because the transducer is close to the blood flow, the signal is clear. The probe may require re-focussing to ensure an optimal signal. This method has good validation, is widely used for fluid management during surgery with evidence for improved patient outcome, and has been recommended by the UK's National Institute for Health and Clinical Excellence (NICE). Oesophageal Doppler monitoring measures the velocity of blood and not true Q, therefore relies on a nomogram based on patient age, height and weight to convert the measured velocity into stroke volume and cardiac output. This method generally requires patient sedation and is accepted for use in both adults and children.

Pulse Pressure Methods

Pulse pressure (PP) methods measure the pressure in an artery over time to derive a waveform and use this information to calculate cardiac performance. However, any measure from the artery includes changes in pressure associated with changes in arterial function, for example compliance and impedance. Physiological or therapeutic changes in vessel diameter are assumed to reflect changes in Q. PP methods measure the combined performance of the heart and the blood vessels, thus limiting their application for measurement of Q. This can be partially compensated for by intermittent calibration of the waveform to another Q measurement method then monitoring the PP waveform. Ideally, the PP waveform should be calibrated on a beat-to-beat basis. There are invasive and non-invasive methods of measuring PP.

Finapres Methodology

In 1967, the Czech physiologist Jan Peñαz invented and patented the volume clamp method of measuring continuous blood pressure. The principle of the volume clamp method is to dynamically provide equal pressures, on either side of an artery wall. By clamping the artery to a certain volume, inside pressure—intra-arterial pressure—balances outside pressure—finger cuff pressure. Peñαz decided the finger was the optimal site to apply this volume clamp method. The use of finger cuffs excludes the device from application in patients without vasoconstriction, such as in sepsis or in patients on vasopressors.

In 1978, scientists at BMI-TNO, the research unit of Netherlands

Organisation for Applied Scientific Research at the University of Amsterdam, invented and patented a series of additional key elements that make the volume clamp work in clinical practice. These methods include the use of modulated infrared light in the optical system inside the sensor, the lightweight, easy-to-wrap finger cuff with velcro fixation, a new pneumatic proportional control valve principle, and a set point strategy for the determining and tracking the correct volume at which to clamp the finger arteries—the Physiocal system. An acronym for physiological calibration of the finger arteries, this Physiocal tracker was found to be accurate, robust and reliable.

The Finapres methodology was developed to use this information to calculate arterial pressure from finger cuff pressure data. A generalised algorithm to correct for the pressure level difference between the finger and brachial sites in patients was developed. This correction worked under all of the circumstances it was tested in—even when it was not designed for it—because it applied general physiological principles. This innovative brachial pressure waveform reconstruction method was first implemented in the Finometer, the successor of Finapres that BMI-TNO introduced to the market in 2000.

The availability of a continuous, high-fidelity, calibrated blood pressure waveform opened up the perspective of beat-to-beat computation of integrated haemodynamics, based on two notions: pressure and flow are inter-related at each site in the arterial system by their so-called characteristic impedance. At the proximal aortic site, the 3-element Windkessel model of this impedance can be modelled with sufficient accuracy in an individual patient with known age, gender, height and weight. According to comparisons of non-invasive peripheral vascular monitors, modest clinical utility is restricted to patients with normal and invariant circulation.

Invasive

Invasive PP monitoring involves inserting a manometer pressure sensor into an artery—usually the radial or femoral artery—and continuously measuring the PP waveform. This is generally done by connecting the catheter to a signal processing device with a display. The PP waveform can then be analysed to provide measurements of cardiovascular performance. Changes in vascular function, the position of the catheter tip or damping of the pressure waveform signal will affect the accuracy of the readings. Invasive PP measurements can be calibrated or uncalibrated.

Calibrated PP – PiCCO, LiDCO

PiCCO (PULSION Medical Systems AG, Munich, Germany) and PulseCO (LiDCO Ltd, London, England) generate continuous Q by analysing the arterial PP waveform. In both cases, an independent technique is required to provide calibration of continuous Q analysis because arterial PP analysis cannot account for unmeasured variables such as the changing compliance of the vascular bed. Recalibration is recommended after changes in patient position, therapy or condition.

In PiCCO, transpulmonary thermodilution, which uses the Stewart-Hamilton principle but measures temperatures changes from central venous line to a central arterial line, *i.e.*, the femoral or axillary arterial line, is used as the calibrating technique. The Q value derived from cold-saline thermodilution is used to calibrate the arterial PP contour, which can then provide continuous Q monitoring.

The PiCCO algorithm is dependent on blood pressure waveform morphology (mathematical analysis of the PP waveform), and it calculates continuous Q as described by Wesseling and colleagues. Transpulmonary thermodilution spans right heart, pulmonary circulation and left heart, allowing further mathematical analysis of the thermodilution curve and giving measurements of cardiac filling volumes (GEDV), intrathoracic blood volume and extravascular lung water. Transpulmonary thermodilution allows for less invasive Q calibration but is less accurate than PA thermodilution and requires a central venous and arterial line with the accompanied infection risks.

In LiDCO, the independent calibration technique is lithium chloride dilution using the Stewart-Hamilton principle. Lithium chloride dilution uses a peripheral vein and a peripheral arterial line.

Like PiCCO, frequent calibration is recommended when there is a change in Q. Calibration events are limited in frequency because they involve the injection of lithium chloride and can be subject to errors in the presence of certain muscle relaxants. The PulseCO algorithm used by LiDCO is based on pulse power derivation and is not dependent on waveform morphology.

Statistical Analysis of Arterial Pressure — FloTrac/Vigileo

FloTrac/Vigileo (Edwards Lifesciences LLC, U.S.A.) is an uncalibrated, haemodynamic monitor based on pulse contour analysis. It estimates cardiac output (Q) using a standard arterial catheter with a manometer located in the femoral or radial artery. The device consists of a high-fidelity pressure

transducer, which, when used with a supporting monitor (Vigileo or EV1000 monitor), derives left-sided cardiac output (Q) from a sample of arterial pulsations. The device uses an algorithm based on the Frank–Starling law of the heart, which states pulse pressure (PP) is proportional to stroke volume (SV). The algorithm calculates the product of the standard deviation of the arterial pressure (AP) wave over a sampled period of 20 seconds and a vascular tone factor (Khi, or ÷) to generate stroke volume. The equation in simplified form is:

$$SV = std(AP).\chi$$

or

$$BP.k(cons\tan t)$$

Khi is designed to reflect arterial resistance; compliance is a multivariate polynomial equation that continuously quantifies arterial compliance and vascular resistance. Khi does this by analyzing the morphological changes of arterial pressure waveforms on a bit-by-bit basis, based on the principle that changes in compliance or resistance affect the shape of the arterial pressure waveform. By analyzing the shape of said waveforms, the effect of vascular tone is assessed, allowing the calculation of SV. Q is then derived using equation. Only perfused beats that generate an arterial waveform are counted for in HR.

This system estimates Q using an existing arterial catheter with variable accuracy. These arterial monitors do not require intracardiac catheterisation from a pulmonary artery catheter. They require an arterial line and are therefore invasive. As with other arterial waveform systems, the short set-up and data acquisition times are benefits of this technology. Disadvantages include its inability to provide data regarding right-sided heart pressures or mixed venous oxygen saturation. The measurement of Stroke Volume Variation (SVV), which predicts volume responsiveness is intrinsic to all arterial waveform technologies. It is used for managing fluid optimisation in high-risk surgical or critically ill patients. A physiologic optimization program based on haemodynamic principles that incorporates the data pairs SV and SVV has been published.

Arterial monitoring systems are unable to predict changes in vascular tone; they estimate changes in vascular compliance. The measurement of pressure in the artery to calculate the flow in the heart is physiologically irrational and of questionable accuracy, and of unproven benefit. Arterial pressure monitoring is limited in patients off-ventilation, in atrial fibrillation, in patients on

vasopressors, and in those with a dynamic autonomic system such as those with sepsis.

Uncalibrated, Pre-estimated Demographic Data-free—PRAM

Pressure Recording Analytical Method (PRAM), estimates Q from the analysis of the pressure wave profile obtained from an arterial catheter—radial or femoral access. This PP waveform can then be used to determine Q. As the waveform is sampled at 1000 Hz, the detected pressure curve can be measured to calculate the actual beat-to-beat stroke volume. Unlike FloTrac, neither constant values of impedance from external calibration, nor form pre-estimated in vivo or in vitro data, are needed.

PRAM has been validated against the considered gold standard methods in stable condition and in various haemodynamic states. It can be used to monitor pediatric and mechanically supported patients.

Generally monitored haemodynamic values, fluid responsiveness parameters and an exclusive reference are provided by PRAM: Cardiac Cycle Efficiency (CCE). It is expressed by a pure number ranging from 1 (best) to -1 (worst) and it indicates the overall heart-specialised for application in pediatric ICU patients and has been demonstrated to be relatively safe although invasive and reproducible.

Electrical Cardiometry

Electrical Cardiometry is a non-invasive method similar to Impedance cardiography; both methods measure thoracic electrical bioimpedance (TEB). The underlying model differs between the two methods; Electrical cardiometry attributes the steep increase of TEB beat-to-beat to the change in orientation of red blood cells. Four standard ECG electrodes are required for measurement of cardiac output. Electrical Cardiometry is a method trademarked by Cardiotronic, Inc., and shows promising results in a wide range of patients. It is currently approved in the US for use in adults, children and babies. Electrical cardiometry monitors have shown promise in postoperative cardiac surgical patients, in both haemodynamicially stable and unstable cases.

Magnetic Resonance Imaging

Velocity-encoded phase contrast Magnetic Resonance Imaging (MRI) is the most accurate technique for measuring flow in large vessels in mammals. MRI flow measurements have been shown to be highly accurate compared to

measurements made with a beaker and timer, and less variable than the Fick principle and thermodilution.

Velocity-encoded MRI is based on the detection of changes in the phase of proton precession. These changes are proportional to the velocity of the protons' movement through a magnetic field with a known gradient. When using velocity-encoded MRI, the result is two sets of images, one for each time point in the cardiac cycle. One is an anatomical image and the other is an image in which the signal intensity in each pixel is directly proportional to the through-plane velocity. The average velocity in a vessel, *i.e.*, the aorta or the pulmonary artery, is quantified by measuring the average signal intensity of the pixels in the cross-section of the vessel then multiplying by a known constant. The flow is calculated by multiplying the mean velocity by the cross-sectional area of the vessel. This flow data can be used in a flow-versus-time graph. The area under the flow-versus-time curve for one cardiac cycle is the stroke volume. The length of the cardiac cycle is known and determines heart rate; Q can be calculated using equation (1). MRI is typically used to quantify the flow over one cardiac cycle as the average of several heart beats. It is also possible to quantify the stroke volume in real-time on a beat-for-beat basis.

While MRI is an important research tool for accurately measuring Q, it is currently not clinically used for haemodynamic monitoring in emergency or intensive care settings. As of 2015, cardiac output measurement by MRI is routinely used in clinical cardiac MRI examinations.

Influences

Cardiac output is primarily controlled by the oxygen requirement of tissues in the body. In contrast to other pump systems, the heart is a demand pump that does not regulate its own output. When the body has a high metabolic oxygen demand, the metabolically controlled flow through the tissues is increased, leading to a greater flow of blood back to the heart, leading to higher cardiac output. The capacitance, also known as compliance, of the arterio-vascular channels that carry the blood also controls cardiac output. As the body's blood vessels actively expand and contract, the resistance to blood flow increases and decreases respectively. Thin-walled veins have about eighteen times the capacitance of thick-walled arteries because they are able to carry more blood by virtue of being more distensible.

From this formula, it is clear the factors affecting stroke volume and heart rate also affect cardiac output.

Equation reveals HR and SV to be the primary determinants of cardiac output Q. The primary factors that influence HR are autonomic innervation plus endocrine control. Environmental factors, such as electrolytes, metabolic products, and temperature are not shown. The determinants of SV during the cardiac cycle are the contractility of the heart muscle, the degree of preload of myocardial distention prior to shortening and the afterload during ejection. Other factors such as electrolytes may be classified as either positive or negative inotropic agents.

Clinical Significance

When Q increases in a healthy but untrained individual, most of the increase can be attributed to an increase in heart rate (HR). Change of posture, increased sympathetic nervous system activity, and decreased parasympathetic nervous system activity can also increase cardiac output. HR can vary by a factor of approximately 3—between 60 and 180 beats per minute—while stroke volume (SV) can vary between 70 and 120 ml (2.5 and 4.2 imp fl oz; 2.4 and 4.1 US fl oz), a factor of only 1.7.

Diseases of the cardiovascular system are often associated with changes in Q, particularly the pandemic diseases hypertension and heart failure. Increased Q can be associated with cardiovascular disease that can occur during infection and sepsis. Decreased Q can be associated with cardiomyopathy and heart failure. Sometimes, in the presence of ventricular disease associated with dilatation, EDV may vary. An increase in EDV could counterbalance LV dilatation and impaired contraction. From equation (3), the resulting cardiac output Q may remain constant. The ability to accurately measure Q is important in clinical medicine because it provides for improved diagnosis of abnormalities and can be used to guide appropriate management.

HEART RATE

Heart rate is the speed of the heartbeat measured by the number of contractions of the heart per minute (bpm). The heart rate can vary according to the body's physical needs, including the need to absorb oxygen and excrete carbon dioxide. It is usually equal or close to the pulse measured at any peripheral point. Activities that can provoke change include physical exercise, sleep, anxiety, stress, illness, and ingestion of drugs.

Many texts cite the normal resting adult human heart rate as ranging from 60–100 bpm. Tachycardia is a fast heart rate, defined as above 100 bpm at

rest. Bradycardia is a slow heart rate, defined as below 60 bpm at rest. Several studies, as well as expert consensus indicates that the normal resting adult heart rate is probably closer to a range between 50 and 90 bpm. During sleep a slow heartbeat with rates around 40–50 bpm is common and is considered normal. When the heart is not beating in a regular pattern, this is referred to as an arrhythmia. Abnormalities of heart rate sometimes indicate disease.

Physiology

While heart rhythm is regulated entirely by the sinoatrial node under normal conditions, heart rate is regulated by sympathetic and parasympathetic input to the sinoatrial node. The accelerans nerve provides sympathetic input to the heart by releasing norepinephrine onto the cells of the sinoatrial node (SA node), and the vagus nerve provides parasympathetic input to the heart by releasing acetylcholine onto sinoatrial node cells. Therefore, stimulation of the accelerans nerve increases heart rate, while stimulation of the vagus nerve decreases it.

Due to individuals having a constant blood volume, one of the physiological ways to deliver more oxygen to an organ is to increase heart rate to permit blood to pass by the organ more often. Normal resting heart rates range from 60–100 bpm. Bradycardia is defined as a resting heart rate below 60 bpm. However, heart rates from 50 to 60 bpm are common among healthy people and do not necessarily require special attention. Tachycardia is defined as a resting heart rate above 100 bpm, though persistent rest rates between 80–100 bpm, mainly if they are present during sleep, may be signs of hyperthyroidism or anemia.

- Central nervous system stimulants such as substituted amphetamines increase heart rate.
- Central nervous system depressants or sedatives decrease the heart rate (apart from some particularly strange ones with equally strange effects, such as ketamine which can cause - amongst many other things - stimulant-like effects such as tachycardia).

There are many ways in which the heart rate speeds up or slows down. Most involve stimulant-like endorphins and hormones being released in the brain, many of which are those that are ‘forced’/ ‘enticed’ out by the ingestion and processing of drugs.

This section discusses target heart rates for healthy persons and are inappropriately high for most persons with coronary artery disease.

Influences from the Central Nervous System

Cardiovascular Centres

The heart rate is rhythmically generated by the sinoatrial node. It is also influenced by central factors through sympathetic and parasympathetic nerves. Nervous influence over the heartrate is centralized within the two paired cardiovascular centers of the medulla oblongata. The cardioaccelerator regions stimulate activity via sympathetic stimulation of the cardioaccelerator nerves, and the cardioinhibitory centers decrease heart activity via parasympathetic stimulation as one component of the vagus nerve. During rest, both centers provide slight stimulation to the heart, contributing to autonomic tone. This is a similar concept to tone in skeletal muscles. Normally, vagal stimulation predominates as, left unregulated, the SA node would initiate a sinus rhythm of approximately 100 bpm. Both sympathetic and parasympathetic stimuli flow through the paired cardiac plexus near the base of the heart.

The cardioaccelerator center also sends additional fibers, forming the cardiac nerves via sympathetic ganglia (the cervical ganglia plus superior thoracic ganglia T1–T4) to both the SA and AV nodes, plus additional fibers to the atria and ventricles. The ventricles are more richly innervated by sympathetic fibers than parasympathetic fibers. Sympathetic stimulation causes the release of the neurotransmitter norepinephrine (also known as noradrenaline) at the neuromuscular junction of the cardiac nerves. This shortens the repolarization period, thus speeding the rate of depolarization and contraction, which results in an increased heartrate. It opens chemical or ligand-gated sodium and calcium ion channels, allowing an influx of positively charged ions.

Norepinephrine binds to the beta–1 receptor. High blood pressure medications are used to block these receptors and so reduce the heart rate.

Parasympathetic stimulation originates from the cardioinhibitory region with impulses traveling via the vagus nerve (cranial nerve X). The vagus nerve sends branches to both the SA and AV nodes, and to portions of both the atria and ventricles. Parasympathetic stimulation releases the neurotransmitter acetylcholine (ACh) at the neuromuscular junction. ACh slows HR by opening chemical- or ligand-gated potassium ion channels to slow the rate of spontaneous depolarization, which extends repolarization and increases the time before the next spontaneous depolarization occurs. Without any nervous stimulation, the SA node would establish a sinus rhythm of approximately

100 bpm. Since resting rates are considerably less than this, it becomes evident that parasympathetic stimulation normally slows HR.

This is similar to an individual driving a car with one foot on the brake pedal. To speed up, one need merely remove one's foot from the brake and let the engine increase speed. In the case of the heart, decreasing parasympathetic stimulation decreases the release of ACh, which allows HR to increase up to approximately 100 bpm. Any increases beyond this rate would require sympathetic stimulation.

Input to the Cardiovascular Centres

The cardiovascular centers receive input from a series of visceral receptors with impulses traveling through visceral sensory fibers within the vagus and sympathetic nerves via the cardiac plexus. Among these receptors are various proprioreceptors, baroreceptors, and chemoreceptors, plus stimuli from the limbic system which normally enable the precise regulation of heart function, via cardiac reflexes. Increased physical activity results in increased rates of firing by various proprioreceptors located in muscles, joint capsules, and tendons. The cardiovascular centers monitor these increased rates of firing, suppressing parasympathetic stimulation or increasing sympathetic stimulation as needed in order to increase blood flow.

Similarly, baroreceptors are stretch receptors located in the aortic sinus, carotid bodies, the venae cavae, and other locations, including pulmonary vessels and the right side of the heart itself. Rates of firing from the baroreceptors represent blood pressure, level of physical activity, and the relative distribution of blood. The cardiac centers monitor baroreceptor firing to maintain cardiac homeostasis, a mechanism called the baroreceptor reflex. With increased pressure and stretch, the rate of baroreceptor firing increases, and the cardiac centers decrease sympathetic stimulation and increase parasympathetic stimulation. As pressure and stretch decrease, the rate of baroreceptor firing decreases, and the cardiac centers increase sympathetic stimulation and decrease parasympathetic stimulation.

There is a similar reflex, called the atrial reflex or Bainbridge reflex, associated with varying rates of blood flow to the atria. Increased venous return stretches the walls of the atria where specialized baroreceptors are located. However, as the atrial baroreceptors increase their rate of firing and as they stretch due to the increased blood pressure, the cardiac center responds by increasing sympathetic stimulation and inhibiting parasympathetic stimulation to increase HR. The opposite is also true.

Increased metabolic byproducts associated with increased activity, such as carbon dioxide, hydrogen ions, and lactic acid, plus falling oxygen levels, are detected by a suite of chemoreceptors innervated by the glossopharyngeal and vagus nerves. These chemoreceptors provide feedback to the cardiovascular centers about the need for increased or decreased blood flow, based on the relative levels of these substances.

The limbic system can also significantly impact HR related to emotional state. During periods of stress, it is not unusual to identify higher than normal HRs, often accompanied by a surge in the stress hormone cortisol. Individuals experiencing extreme anxiety may manifest panic attacks with symptoms that resemble those of heart attacks. These events are typically transient and treatable. Meditation techniques have been developed to ease anxiety and have been shown to lower HR effectively. Doing simple deep and slow breathing exercises with one's eyes closed can also significantly reduce this anxiety and HR.

Factors Influencing Heart Rate

Table: Major Factors Increasing Heart Rate and Force of Contraction

Factor	*Effect*
Cardioaccelerator nerves	Release of norepinephrine
Proprioreceptors	Increased rates of firing during exercise
Chemoreceptors	Decreased levels of O_2; increased levels of H^+, CO_2, and lactic acid
Baroreceptors	Decreased rates of firing, indicating falling blood volume/pressure
Limbic system	Anticipation of physical exercise or strong emotions
Catecholamines	Increased epinephrine and norepinephrine
Thyroid hormones	Increased T3 and T4
Calcium	Increased Ca^{2+}
Potassium	Decreased K^+
Sodium	Decreased Na^+
Body temperature	Increased body temperature
Nicotine and caffeine	Stimulants, increasing heart rate

Table 2: Factors Decreasing Heart Rate and Force of Contraction

Factor	*Effect*
Cardioinhibitor nerves (vagus)	Release of acetylcholine

Proprioreceptors	Decreased rates of firing following exercise
Chemoreceptors	Increased levels of O_2; decreased levels of H^+ and CO_2
Baroreceptors	Increased rates of firing, indicating higher blood volume/pressure
Limbic system	Anticipation of relaxation
Catecholamines	Decreased epinephrine and norepinephrine
Thyroid hormones	Decreased T3 and T4
Calcium	Decreased Ca^{2+}
Potassium	Increased K^+
Sodium	Decreased Na^+
Body temperature	Decrease in body temperature

Using a combination of autorhythmicity and innervation, the cardiovascular center is able to provide relatively precise control over the heart rate, but other factors can impact on this. These include hormones, notably epinephrine, norepinephrine, and thyroid hormones; levels of various ions including calcium, potassium, and sodium; body temperature; hypoxia; and pH balance.

Epinephrine and Norepinephrine

The catecholamines, epinephrine and norepinephrine, secreted by the adrenal medulla form one component of the extended fight-or-flight mechanism. The other component is sympathetic stimulation.

Epinephrine and norepinephrine have similar effects: binding to the beta-1 adrenergic receptors, and opening sodium and calcium ion chemical- or ligand-gated channels. The rate of depolarization is increased by this additional influx of positively charged ions, so the threshold is reached more quickly and the period of repolarization is shortened. However, massive releases of these hormones coupled with sympathetic stimulation may actually lead to arrhythmias. There is no parasympathetic stimulation to the adrenal medulla.

Thyroid Hormones

In general, increased levels of the thyroid hormones (thyroxine(T4) and triiodothyronine (T3)), increase the heart rate; excessive levels can trigger tachycardia. The impact of thyroid hormones is typically of a much longer duration than that of the catecholamines.

The physiologically active form of triiodothyronine, has been shown to directly enter cardiomyocytes and alter activity at the level of the genome. It also impacts the beta adrenergic response similar to epinephrine and norepinephrine.

Calcium

Calcium ion levels greatly impact on heartrate and contractility; increased levels cause an increase in both. High levels of calcium ions result in (hypercalcemia) and excessive levels can induce cardiac arrest. Drugs known as calcium channel blockers slow HR by binding to these channels and blocking or slowing the inward movement of calcium ions.

Caffeine and Nicotine

Caffeine and nicotine are both stimulants of the nervous system and of the cardiac centers causing an increased heart rate. Caffeine works by increasing the rates of depolarization at the SA node, whereas nicotine stimulates the activity of the sympathetic neurons that deliver impulses to the heart. Both stimulants are legal and unregulated, and are known to be very addictive.

Factors Decreasing Heart Rate

The heart rate can be slowed by altered sodium and potassium levels, hypoxia, acidosis, alkalosis, and hypothermia. The relationship between electrolytes and HR is complex, but maintaining electrolyte balance is critical to the normal wave of depolarization. Of the two ions, potassium has the greater clinical significance. Initially, both hyponatremia (low sodium levels) and hypernatremia (high sodium levels) may lead to tachycardia. Severely high hypernatremia may lead to fibrillation, which may cause CO to cease. Severe hyponatremia leads to both bradycardia and other arrhythmias.

Hypokalemia (low potassium levels) also leads to arrhythmias, whereas hyperkalemia (high potassium levels) causes the heart to become weak and flaccid, and ultimately to fail.

Heart muscle relies exclusively on aerobic metabolism for energy. Hypoxia (an insufficient supply of oxygen) leads to decreasing HRs, since metabolic reactions fueling heart contraction are restricted.

Acidosis is a condition in which excess hydrogen ions are present, and the patient’s blood expresses a low pH value. Alkalosis is a condition in which

there are too few hydrogen ions, and the patient's blood has an elevated pH. Normal blood pH falls in the range of 7.35–7.45, so a number lower than this range represents acidosis and a higher number represents alkalosis. Enzymes, being the regulators or catalysts of virtually all biochemical reactions - are sensitive to pH and will change shape slightly with values outside their normal range. These variations in pH and accompanying slight physical changes to the active site on the enzyme decrease the rate of formation of the enzyme-substrate complex, subsequently decreasing the rate of many enzymatic reactions, which can have complex effects on HR. Severe changes in pH will lead to denaturation of the enzyme.

The last variable is body temperature. Elevated body temperature is called hyperthermia, and suppressed body temperature is called hypothermia. Slight hyperthermia results in increasing HR and strength of contraction. Hypothermia slows the rate and strength of heart contractions.

This distinct slowing of the heart is one component of the larger diving reflex that diverts blood to essential organs while submerged. If sufficiently chilled, the heart will stop beating, a technique that may be employed during open heart surgery. In this case, the patient's blood is normally diverted to an artificial heart-lung machine to maintain the body's blood supply and gas exchange until the surgery is complete, and sinus rhythm can be restored. Excessive hyperthermia and hypothermia will both result in death, as enzymes drive the body systems to cease normal function, beginning with the central nervous system.

In Different Circumstances

Heart rate is not a stable value and it increases or decreases in response to the body's need in a way to maintain an equilibrium (basal metabolic rate) between requirement and delivery of oxygen and nutrients. The normal SA node firing rate is affected by autonomic nervous system activity: sympathetic stimulation increases and parasympathetic stimulation decreases the firing rate. A number of different metrics are used to describe heart rate.

Resting Heart Rate

The basal or resting heart rate (HR_{rest}) is defined as the heart rate when a person is awake, in a neutrally temperate environment, and has not been subject to any recent exertion or stimulation, such as stress or surprise. Most texts cite the typical resting heart rate in adults as 60–100 beats per minute (bpm). A

large body of evidence indicates that the normal range is actually 50-90 beats per minute. For example, all-cause mortality is increased by 1.22 (hazard ratio) when heart rate exceeds 90 beats per minute. The mortality rate of patients with myocardial infarction increased from 15% to 41% if their admission heart rate was greater than 90 beats per minute. ECG of 46,129 individuals with low risk for cardiovascular disease revealed that 96% had resting heart rates ranging from 48-98 beats per minute. Finally, expert consensus reveals that 98% of cardiologists believe that the "60 to 100" range is too high, with a vast majority of them agreeing that 50 to 90 beats per minute is more appropriate. The normal resting heart rate is based on the at-rest firing rate of the heart's sinoatrial node, where the faster pacemaker cells driving the self-generated rhythmic firing and responsible for the heart's autorhythmicity are located. For endurance athletes at the elite level, it is not unusual to have a resting heart rate between 33 and 50 bpm.

Maximum Heart Rate

The maximum heart rate (HR_{max}) is the highest heart rate an individual can achieve without severe problems through exercise stress, and generally decreases with age. Since HR_{max} varies by individual, the most accurate way of measuring any single person's HR_{max} is via a cardiac stress test. In this test, a person is subjected to controlled physiologic stress (generally by treadmill) while being monitored by an ECG. The intensity of exercise is periodically increased until certain changes in heart function are detected on the ECG monitor, at which point the subject is directed to stop. Typical duration of the test ranges ten to twenty minutes.

Adults who are beginning a new exercise regimen are often advised to perform this test only in the presence of medical staff due to risks associated with high heart rates. For general purposes, a formula is often employed to estimate a person's maximum heart rate. However, these predictive formulas have been criticized as inaccurate because they generalized population-averages and usually focus on a person's age. It is well-established that there is a "poor relationship between maximal heart rate and age" and large standard deviations relative to predicted heart rates. A number of formulas are used to estimate HR_{max}.

Effects of Stress

Both surprise and stress induce physiological response: elevate heart rate substantially. In a study conducted on 8 female and male student actors ages

18 to 25, their reaction to an unforeseen occurrence (the cause of stress) during a performance was observed in terms of heart rate. In the data collected, there was a noticeable trend between the location of actors (onstage and offstage) and their elevation in heart rate in response to stress; the actors present offstage reacted to the stressor immediately, demonstrated by their immediate elevation in heart the minute the unexpected event occurred, but the actors present onstage at the time of the stressor reacted in the following 5 minute period (demonstrated by their increasingly elevated heart rate). This trend regarding stress and heart rate is supported by previous studies; negative emotion/ stimulus has a prolonged effect on heart rate in individuals who are directly impacted. In regard to the characters present onstage, a reduced startle response has been associated with a passive defense, and the diminished initial heart rate response has been predicted to have a greater tendency to dissociation. Further, note that heart rate is an accurate measure of stress and the startle response which can be easily observed to determine the effects of certain stressors.

Nes, et al.

Based on measurements of 3320 healthy men and women aged between 19 and 89, and including the potential modifying effect of gender, body composition, and physical activity, Nes et al found:

- $HR_{max} = 211 - (0.64 \times age)$

This relationship was found to hold substantially regardless of gender, physical activity status, maximal oxygen uptake, smoking, or body mass index. However, a standard error of the estimate of 10.8 beats/min must be accounted for when applying the formula to clinical settings, and the researchers concluded that actual measurement via a maximal test may be preferable whenever possible.

Tanaka, Monahan, and Seals

From Tanaka, Monahan, and Seals (2001):

- $HR_{max} = 208 - (0.7 \times age)$

Their meta-analysis (of 351 prior studies involving 492 groups and 18,712 subjects) and laboratory study (of 514 healthy subjects) concluded that, using this equation, HR_{max} was very strongly correlated to age ($r = -0.90$). The regression equation that was obtained in the laboratory-based study ($209 - 0.7 \times age$), was virtually identical to that of the meta-study. The results showed

HR_{max} to be independent of gender and independent of wide variations in habitual physical activity levels. This study found a standard deviation of ~10 beats per minute for individuals of any age, meaning the HR_{max} formula given has an accuracy of ±20 beats per minute.

In 2007, researchers at the Oakland University analyzed maximum heart rates of 132 individuals recorded yearly over 25 years, and produced a linear equation very similar to the Tanaka formula, $HR_{max} = 206.9 - (0.67 \times age)$, and a nonlinear equation, $HR_{max} = 191.5 - (0.007 \times age^2)$. The linear equation had a confidence interval of ±5–8 bpm and the nonlinear equation had a tighter range of ±2–5 bpm. Also a third nonlinear equation was produced: $HR_{max} = 163 + (1.16 \times age) - (0.018 \times age^2)$.

Haskell & Fox

Notwithstanding the research of Tanaka, Monahan, and Seals, the most widely cited formula for HR_{max} (which contains no reference to any standard deviation) is still:

- $HR_{max} = 220 - age$

Although attributed to various sources, it is widely thought to have been devised in 1970 by Dr. William Haskell and Dr. Samuel Fox. Inquiry into the history of this formula reveals that it was not developed from original research, but resulted from observation based on data from approximately 11 references consisting of published research or unpublished scientific compilations. It gained widespread use through being used by Polar Electro in its heart rate monitors, which Dr. Haskell has "laughed about", as the formula "was never supposed to be an absolute guide to rule people's training."

While it is the most common (and easy to remember and calculate), this particular formula is not considered by reputable health and fitness professionals to be a good predictor of HR_{max}. Despite the widespread publication of this formula, research spanning two decades reveals its large inherent error, S_{xy} = 7–11 bpm. Consequently, the estimation calculated by $HR_{max} = 220 - age$ has neither the accuracy nor the scientific merit for use in exercise physiology and related fields.

Robergs & Landwehr

A 2002 study of 43 different formulas for HR_{max} published in the Journal of Exercise Psychology concluded that:

1. no "acceptable" formula currently existed (they used the term

"acceptable" to mean acceptable for both prediction of VO_2, and prescription of exercise training HR ranges).

2. The least objectionable formula was:

$HR_{max} = 205.8 - (0.685 \times age)$

This had a standard deviation that, although large (6.4 bpm), was considered acceptable for prescribing exercise training HR ranges.

Gulati (for Women)

Research conducted at Northwestern University by Martha Gulati, *et al.*, in 2010 suggested a maximum heart rate formula for women:

$HR_{max} = 206 - (0.88 \times age)$

Gellish

A 2008 study from Lund, Sweden gives reference values (obtained during bicycle ergometry) for men:

$HR_{max} = 203.7 / (1 + \exp(0.033 \times (age - 104.3)))$

and for women:

$HR_{max} = 190.2 / (1 + \exp(0.0453 \times (age - 107.5)))$

Other formulae

- $HR_{max} = 206.3 - (0.711 \times age)$:
  - (Often attributed to "Londeree and Moeschberger from the University of Missouri")
- $HR_{max} = 217 - (0.85 \times age)$:
  - (Often attributed to "Miller *et al.* from Indiana University")

Limitations

Maximum heart rates vary significantly between individuals. Even within a single elite sports team, such as Olympic rowers in their 20s, maximum heart rates have been reported as varying from 160 to 220. Such a variation would equate to a 60 or 90 year age gap in the linear equations above, and would seem to indicate the extreme variation about these average figures.

For example, an endurance runner's rates will typically be lower due to the increased size of the heart required to support the exercise, while a sprinter's rates will be higher due to the improved response time and short duration. While each may have predicted heart rates of 180 (= 220 - age), these two people could have actual HR_{max} 20 beats apart (*e.g.*, 170-190).

Further, note that individuals of the same age, the same training, in the same sport, on the same team, can have actual HR_{max} 60 bpm apart (160–220): the range is extremely broad, and some say "The heart rate is probably the least important variable in comparing athletes."

Heart Rate Reserve

Heart rate reserve ($HR_{reserve}$) is the difference between a person's measured or predicted maximum heart rate and resting heart rate. Some methods of measurement of exercise intensity measure percentage of heart rate reserve. Additionally, as a person increases their cardiovascular fitness, their HR_{rest} will drop, and the heart rate reserve will increase. Percentage of $HR_{reserve}$ is equivalent to percentage of VO_2 reserve.

$HR_{reserve} = HR_{max}$ " HR_{rest}

This is often used to gauge exercise intensity (first used in 1957 by Karvonen). Karvonen's study findings have been questioned, due to the following:

- The study did not use VO_2 data to develop the equation.
- Only six subjects were used, and the correlation between the percentages of $HR_{reserve}$ and VO_2 max was not statistically significant.

Target Heart Rate

For healthy people, the Target Heart Rate or Training Heart Rate (THR) is a desired range of heart rate reached during aerobic exercise which enables one's heart and lungs to receive the most benefit from a workout. This theoretical range varies based mostly on age; however, a person's physical condition, sex, and previous training also are used in the calculation. Below are two ways to calculate one's THR. In each of these methods, there is an element called "intensity" which is expressed as a percentage. The THR can be calculated as a range of 65–85% intensity. However, it is crucial to derive an accurate HR_{max} to ensure these calculations are meaningful. Example for someone with a HR_{max} of 180 (age 40, estimating HR_{max} As 220 " age):

- ***65% Intensity:*** (220 " (age = 40)) × 0.65 ! 117 bpm
- ***85% Intensity:*** (220 " (age = 40)) × 0.85 ! 153 bpm

Karvonen Method

The Karvonen method factors in resting heart rate (HR_{rest}) to calculate target heart rate (THR), using a range of 50–85% intensity:

- THR = ((HR_{max} “ HR_{rest}) × % intensity) + HR_{rest}

Equivalently,

- THR = ($HR_{reserve}$ × % intensity) + HR_{rest}

Example for someone with a HR_{max} of 180 and a HR_{rest} of 70 (and therefore a $HR_{reserve}$ of 110):

- 50% Intensity: ((180 “ 70) × 0.50) + 70 = 125 bpm
- 85% Intensity: ((180 “ 70) × 0.85) + 70 = 163 bpm

Zoladz Method

An alternative to the Karvonen method is the Zoladz method, which derives exercise zones by subtracting values from HR_{max}:

- THR = HR_{max} “ Adjuster ± 5 bpm
- Zone 1 Adjuster = 50 bpm
- Zone 2 Adjuster = 40 bpm
- Zone 3 Adjuster = 30 bpm
- Zone 4 Adjuster = 20 bpm
- Zone 5 Adjuster = 10 bpm

Example for someone with a HR_{max} of 180:

- Zone 1(easy exercise): 180 “ 50 ± 5 ! 125 “ 135 bpm
- Zone 4(tough exercise): 180 “ 20 ± 5 ! 155 “ 165 bpm

Heart Rate Recovery

Heart rate recovery ($HR_{recovery}$) is the reduction in heart rate at peak exercise and the rate as measured after a cool-down period of fixed duration. A greater reduction in heart rate after exercise during the reference period is associated with a higher level of cardiac fitness.

Heart rates that do not drop by more than 12 bpm one minute after stopping exercise are associated with an increased risk of death. Investigators of the Lipid Research Clinics Prevalence Study, which included 5,000 subjects, found that patients with an abnormal $HR_{recovery}$ (defined as a decrease of 42 beats per minutes or less at two minutes post-exercise) had a mortality rate 2.5 times greater than patients with a normal recovery. Another study by Nishime *et al.*, and featuring 9,454 patients followed for a median period of 5.2 years found a four-fold increase in mortality in subjects with an abnormal $HR_{recovery}$ (d”12 bpm reduction one minute after the cessation of exercise). Shetler *et al.* studied 2,193 patients for thirteen years and found that a $HR_{recovery}$ of d”22 bpm after

two minutes “best identified high-risk patients”. They also found that while $HR_{recovery}$ had significant prognostic value it had no diagnostic value.

Development

The human heart beats more than 3.5 billion times in an average lifetime. The heartbeat of a human embryo begins at approximately 21 days after conception, or five weeks after the last normal menstrual period (LMP), which is the date normally used to date pregnancy in the medical community.

The electrical depolarizations that trigger cardiac myocytes to contract arise spontaneously within the myocyte itself. The heartbeat is initiated in the pacemaker regions and spreads to the rest of the heart through a conduction pathway. Pacemaker cells develop in the primitive atrium and the sinus venosus to form the sinoatrial node and the atrioventricular node respectively. Conductive cells develop the bundle of His and carry the depolarization into the lower heart.

The human heart begins beating at a rate near the mother’s, about 75-80 beats per minute (BPM). The embryonic heart rate then accelerates linearly for the first month of beating, peaking at 165-185 BPM during the early 7th week, (early 9th week after the LMP). This acceleration is approximately 3.3 BPM per day, or about 10 BPM every three days, an increase of 100 BPM in the first month.

After peaking at about 9.2 weeks after the LMP, it decelerates to about 150 BPM (+/-25 BPM) during the 15th week after the LMP. After the 15th week the deceleration slows reaching an average rate of about 145 (+/-25 BPM) BPM at term. The regression formula which describes this acceleration before the embryo reaches 25 mm in crown-rump length or 9.2 LMP weeks is:

Age in days = HER(0.3) + 6

There is no difference in male and female heart rates before birth.

Clinical Significance

Measurement

Manual Measurement

Heart rate is measured by finding the pulse of the heart. This pulse rate can be found at any point on the body where the artery’s pulsation is transmitted

to the surface by pressuring it with the index and middle fingers; often it is compressed against an underlying structure like bone. (A good area is on the neck, under the corner of the jaw.) The thumb should not be used for measuring another person's heart rate, as its strong pulse may interfere with the correct perception of the target pulse.

The radial artery is the easiest to use to check the heart rate. However, in emergency situations the most reliable arteries to measure heart rate are carotid arteries. This is important mainly in patients with atrial fibrillation, in whom heart beats are irregular and stroke volume is largely different from one beat to another.

In those beats following a shorter diastolic interval left ventricle doesn't fill properly, stroke volume is lower and pulse wave is not strong enough to be detected by palpation on a distal artery like the radial artery. It can be detected, however, by doppler. Possible points for measuring the heart rate are:

1. The ventral aspect of the wrist on the side of the thumb (radial artery).
2. The ulnar artery.
3. The neck (carotid artery).
4. The inside of the elbow, or under the biceps muscle (brachial artery).
5. The groin (femoral artery).
6. Behind the medial malleolus on the feet (posterior tibial artery).
7. Middle of dorsum of the foot (dorsalis pedis).
8. Behind the knee (popliteal artery).
9. Over the abdomen (abdominal aorta).
10. The chest (apex of the heart), which can be felt with one's hand or fingers. It is also possible to auscultate the heart using a stethoscope.
11. The temple (superficial temporal artery).
12. The lateral edge of the mandible (facial artery).
13. The side of the head near the ear (posterior auricular artery).

Electronic Measurement

A more precise method of determining heart rate involves the use of an electrocardiograph, or ECG (also abbreviated EKG). An ECG generates a pattern based on electrical activity of the heart, which closely follows heart function. Continuous ECG monitoring is routinely done in many clinical settings, especially in critical care medicine. On the ECG, instantaneous heart rate is calculated using the R wave-to-R wave (RR) interval and multiplying/dividing in order to derive heart rate in heartbeats/min. Multiple methods exist:

- HR = 1,500/(RR interval in millimeters)
- HR = 60/(RR interval in seconds)
- HR = 300/number of "large" squares between successive R waves.
- HR = 1,500 number of large blocks

Heart rate monitors allow measurements to be taken continuously and can be used during exercise when manual measurement would be difficult or impossible (such as when the hands are being used). Various commercial heart rate monitors are also available. Some monitors, used during sport, consist of a chest strap with electrodes. The signal is transmitted to a wrist receiver for display. Alternative methods of measurement include pulse oximetry and seismocardiography.

Tachycardia

Tachycardia is a resting heart rate more than 100 beats per minute. This number can vary as smaller people and children have faster heart rates than average adults. Physiological conditions where tachycardia occurs:

1. Exercise
2. Pregnancy
3. Emotional conditions such as anxiety or stress

Pathological conditions where tachycardia occurs:

1. Sepsis
2. Fever
3. Anemia
4. Hypoxia
5. Hyperthyroidism
6. Hypersecretion of catecholamines
7. Cardiomyopathy
8. Valvular heart diseases
9. Acute Radiation Syndrome

Bradycardia

Bradycardia was defined as a heart rate less than 60 beats per minute when textbooks asserted that the normal range for heart rates was 60–100 BPM. The normal range has since been revised in textbooks to 50–90 BPM for a human at total rest. Setting a lower threshold for bradycardia prevents misclassification of fit individuals as having a pathologic heart rate. The normal heart rate number can vary as children and adolescents tend to have faster heart rates than average adults. Bradycardia may be associated with medical conditions such as hypothyroidism.

Trained athletes tend to have slow resting heart rates, and resting bradycardia in athletes should not be considered abnormal if the individual

has no symptoms associated with it. For example, Miguel Indurain, a Spanish cyclist and five time Tour de France winner, had a resting heart rate of 28 beats per minute, one of the lowest ever recorded in a healthy human. Daniel Green achieved the world record for the slowest heartbeat in a healthy human with a heart rate of just 26 bpm in 2014.

Arrhythmia

Arrhythmias are abnormalities of the heart rate and rhythm (sometimes felt as palpitations). They can be divided into two broad categories: fast and slow heart rates. Some cause few or minimal symptoms. Others produce more serious symptoms of lightheadedness, dizziness and fainting.

Correlation with Cardiovascular Mortality Risk

A number of investigations indicate that faster resting heart rate has emerged as a new risk factor for mortality in homeothermic mammals, particularly cardiovascular mortality in human beings. Faster heart rate may accompany increased production of inflammation molecules and increased production of reactive oxygen species in cardiovascular system, in addition to increased mechanical stress to the heart. There is a correlation between increased resting rate and cardiovascular risk. This is not seen to be “using an allotment of heart beats” but rather an increased risk to the system from the increased rate.

An Australian-led international study of patients with cardiovascular disease has shown that heart beat rate is a key indicator for the risk of heart attack. The study, published in The Lancet (September 2008) studied 11,000 people, across 33 countries, who were being treated for heart problems. Those patients whose heart rate was above 70 beats per minute had significantly higher incidence of heart attacks, hospital admissions and the need for surgery. Higher heart rate is thought to be correlated with an increase in heart attack and about a 46 percent increase in hospitalizations for non-fatal or fatal heart attack.

Other studies have shown that a high resting heart rate is associated with an increase in cardiovascular and all-cause mortality in the general population and in patients with chronic disease. A faster resting heart rate is associated with shorter life expectancy and is considered a strong risk factor for heart disease and heart failure, independent of level of physical fitness. Specifically, a resting heart rate above 65 beats per minute has been shown to have a strong

independent effect on premature mortality; every 10 beats per minute increase in resting heart rate has been shown to be associated with a 10–20% increase in risk of death. In one study, men with no evidence of heart disease and a resting heart rate of more than 90 beats per minute had a five times higher risk of sudden cardiac death. Similarly, another study found that men with resting heart rates of over 90 beats per minute had an almost two-fold increase in risk for cardiovascular disease mortality; in women it was associated with a three-fold increase.

Given these data, heart rate should be considered in the assessment of cardiovascular risk, even in apparently healthy individuals. Heart rate has many advantages as a clinical parameter: It is inexpensive and quick to measure and is easily understandable. Although the accepted limits of heart rate are between 60 and 100 beats per minute, this was based for convenience on the scale of the squares on electrocardiogram paper; a better definition of normal sinus heart rate may be between 50 and 90 beats per minute.

Standard textbooks of physiology and medicine mention that heart rate (HR) is readily calculated from the ECG as follows:

- HR = 1,500/RR interval in millimeters, HR = 60/RR interval in seconds, or HR = 300/number of large squares between successive R waves. In each case, the authors are actually referring to instantaneous HR, which is the number of times the heart would beat if successive RR intervals were constant. However, because the above formula is almost always mentioned, students determine HR this way without looking at the ECG any further.

Lifestyle and pharmacological regimens may be beneficial to those with high resting heart rates. Exercise is one possible measure to take when an individual's heart rate is higher than 80 beats per minute. Diet has also been found to be beneficial in lowering resting heart rate: In studies of resting heart rate and risk of death and cardiac complications on patients with type 2 diabetes, legumes were found to lower resting heart rate. This is thought to occur because in addition to the direct beneficial effects of legumes, they also displace animal proteins in the diet, which are higher in saturated fat and cholesterol. A very slow heart rate (bradycardia) may be associated with heart block. It may also arise from autonomous nervous system impairment.

FACTORS AFFECTING HEART RATE

As trainers, we know that the heart is an amazing piece of machinery. One muscle working constantly to allow our bodies to function! Impressive.

The heart is a complex organ that operates uniquely within each of our clients. When we use heart rate training, it is important for us to understand the various factors that influence heart rate – both from a safety and programming perspective.

In this post, we'll briefly cover several of these factors. While this is not an exhaustive list, we hope you can utilize this knowledge when programming for your clients and when answering their questions (which they will inevitably ask) about their heart rate. The MYZONE heart rate training wearable is a great tool for both you and your client to use in monitoring their heart rate over time and looking for variations to normal patterns.

Fitness Level

Remember that cardiac output (the volume of blood pumped by the heart each minute) is the product of stroke volume (the volume of blood pumped per beat) and heart rate (the amount of times the heart beats per minute)? Individuals of a higher aerobic fitness level tend to rely more on stroke volume to increase cardiac output. As such, they tend to have a lower heart rate compared to untrained individuals at any work rate. Explain to your clients that as their cardiorespiratory system becomes more conditioned, their resting heart rate and submaximal heart rate at any work rate will most likely decrease. This means their heart has to do less work and is more efficient! It also means that as your clients become more fit, they may have to work harder and increase their workload to get their heart rate up into the yellow and red zones.

Biological Variability

Even among healthy, well-conditioned individuals, heart rate naturally varies day-to-day during rest, submaximal exercise, and maximal exercise. In one study, exercisers performed exercise on a cycle ergometer at 10 different intensities. The test-retest reliability yielded a strong – but imperfect – correlation. This means our heart rate on Monday might be different from our heart rate on Tuesday, even if we're doing the exact same workout. If your clients are concerned that their heart rate is slightly different between workouts, you can confirm that some variation between workouts is expected and normal.

Acute Fatigue and Cardiovascular Drift

Have you ever seen your heart rate slowly increase during a longer workout

– especially in a warm environment – even if you didn't change the exercise intensity? This may have been due to the phenomenon of cardiovascular drift, which is characterized by a small, progressive increase in core temperature, reduction in stroke volume, and increase in heart rate after more than about 10-15 minutes of exercise. Research suggests that cardiovascular drift may be associated with dehydration, so make sure that your clients are staying hydrated during their workouts. If you notice that your client's heart rate is increasing during prolonged exercise, check in with them about their rate of perceived exertion (RPE) and monitor for other signs or symptoms that suggest they should discontinue exercise (*i.e.* lightheadedness).

Emotional State

Yep, having a stressful day can influence heart rate. Previous research indicates that feelings of nervousness or anxiety can elicit a heart rate response similar to that of moderate-intensity exercise! If your client has had a stressful day at work, have them perform some breathing exercises before they jump into their workout, or have them spend some extra time warming up in the blue or green zones.

Music

Music is an environmental factor that may increase or decrease heart rate, depending on the music itself! While calming music might result in a slower heart rate, upbeat music that gets us pumped up can have the opposite effect. When selecting music to play during workouts with your clients or in group fitness classes, match the music to the heart rate zone you are trying to elicit (more mellow for blue and green and more upbeat for yellow and red).

Chronic Fatigue/Overtraining

Changes in our heart rate may be a signal that our bodies are in a state of chronic fatigue or overtraining. Some signs include an elevated resting heart rate, difficulty elevating our heart rate into higher-intensity zones, a slower recovery heart rate, and lower peak heart rate. If your clients exhibit these signs, it might be time for a low-intensity recovery workout or rest.

Sex

Women tend to have a smaller cardiovascular system than men, resulting in lower stroke volume. This means they must rely more heavily on heart rate

to get blood pumping to their muscles, and they tend to have a higher heart rate than their male counterparts.

Environment

Is it getting hot in here? Heart rate tends to increase during exercise as the ambient temperature goes up. We also have higher heart rates during exercise as we move to higher altitudes.

Site of Muscular Activity

Research has found that arm exercise, such as kranking on an upper body ergometer, increases heart rate more than leg exercise at any submaximal power output. Test this out with your clients. Have them perform 5 to 10 minutes of cardio on an upper body piece of equipment and a lower body piece of equipment at a consistent work rate (for example, use watts displayed on computerized equipment) and see which one produces a higher heart rate.

Body Position

Heart rate can be expected to decrease when moving from standing to sitting to lying down. Understanding how heart rate varies can be very valuable for programming and teaching our clients.

If you notice any variations in your clients' heart rates as they train with their MYZONE heart rate training wearable, use the aforementioned factors as reference. And, as always, refer your clients to their physician if the variations in their heart rate cause concern for either you or them.

CARDIAC HYPERTROPHY

Cardiac hypertrophy is a thickening of the heart muscle (myocardium) which results in a decrease in size of the chamber of the heart, including the left and right ventricles. A common cause of cardiac hypertrophy is high blood pressure (hypertension) and heart valve stenosis.

EFFECT OF EXERCISE AND TRAINING ON THE CARDIOVASCULAR SYSTEM

The cardiovascular system serves five important functions during exercise:

1. Delivers oxygen to working muscles
2. Oxygenates blood by returning it to the lungs
3. Transports heat (a by-product of activity) from the core to the skin

4. Delivers nutrients and fuel to active tissues
5. Transports hormones

Exercise places an increased demand on the cardiovascular system. Oxygen demand by the muscles increases sharply. Metabolic processes speed up and more waste is created. More nutrients are used and body temperature rises. To perform as efficiently as possible the cardiovascular system must regulate these changes and meet the bodys increasing demands. Below we will examine the acute or immediate response to exercise and also the long-term adaptations that take place in the cardiovascular system with repeated exercise. The most important aspects of the cardiovascular system to examine include:

- Heart rate
- Stroke volume
- Cardiac output
- Blood flow
- Blood pressure
- Blood

IMMEDIATE RESPONSE OF THE CARDIOVASCULAR SYSTEM TO EXERCISE

Heart Rate

Resting heart rate averages 60 to 80 beats/min in healthy adults. In sedentary, middle aged individuals it may be as high as 100 beats/min. In elite endurance athletes heart rates as low as 28 to 40 beats/min have been recorded.

Before exercise even begins heart rate increases in anticipation. This is known as the anticipatory response. It is mediated through the releases of a neurotransmitters called epinephrine and norepinephrine also known as adrenaline and noradrenaline.

After the initial anticipatory response, heart rate increases in direct proportion to exercise intensity until a maximum heart rate is reached. Maximum heart rate is estimated with the formula 220-age. But this is only an estimation, and not particularly accurate. The only direct method for determining maximum heart rate is to exercise at increasing intensities until a plateau in heart rate is found despite the increasing work rate.

Although heart rate increases rapidly with the onset of activity, providing

exercise intensity remains constant, heart rate will level off. This is known as steady-state heart rate where the demands of the active tissues can be adequately met by the cardiovascular system. However, there is an exception to this.

During prolonged steady-state exercise, particularly in a hot climate, a steady-state heart rate will gradually increase. This phenomenon is known as cardiac drift and is thought to occur due to increasing body temperature.

Stroke Volume

Stroke volume is the amount of blood ejected per beat from left ventricle and measured in ml/beat.

Stroke volume increases proportionally with exercise intensity. In untrained individuals stroke volume at rest it averages 50-70ml/beat increasing up to 110-130ml/beat beat during intense, physical activity. In elite athletes resting stroke volume averages 90-110ml/beat increasing to as much as 150-220ml/beat.

Stroke volume may increase only up to 40-60% of maximal capacity after which it plateaus. Beyond this relative exercise intensity, stroke volume remains unchanged right up until the point of exhaustion. But this is not conclusive and other studies suggest stroke volume continues to rise until the pint of exhaustion.

Interestingly, swimmers see a smaller increase in stroke volume compared to runners or cyclists for example. It is believed that the supine position prevents blood from pooling in the lower extremities enhancing venous return.

Why does stroke volume increase with the onset of exercise? One explanation is that the left ventricle fills more completely, stretching it further, with the elastic recoil producing a more forceful contraction. This is known as the Frank-Starling mechanism. Other contributing factors include increased contractility of the ventricles and reduced peripheral resistance due to greater vasodilation of the blood vessels.

Cardiac Output

Cardiac output is the amount of blood pumped by the heart in 1 minute measured in L/min. It is a product of stroke volume and heart rate (SV x HR). If either heart rate or stroke volume increase, or both, cardiac output increases also.

Cardiac output increases proportionally with exercise intensity - which is

predictable from understanding the response of heart rate and stroke volume to activity. At rest the cardiac output is about 5L/min. During intense exercise this can increase to 20-40L/min.

Blood Flow

The vascular system can redistribute blood to those tissues with the greatest immediate demand and away from areas that have less demand for oxygen.

At rest 15-20% of circulating blood supplies skeletal muscle. During vigorous exercise this increases to 80-85% of cardiac output. Blood is shunted away from major organs such as the kidneys, liver, stomach and intestines. It is then redirected to the skin to promote heat loss.

Athletes are often advised not to eat several hours before training or competition. This is advice worth adhering to, as food in the stomach will lead to competition for blood flow between the digestive system and muscles. It has been shown that gastrointestinal blood flow during exercise shortly after a meal is greater compared to exercising on an empty stomach.

Blood Pressure

At rest, a typical systolic blood pressure in a healthy individual ranges from 110-140mmHg and 60-90mmHg for diastolic blood pressure.

During exercise systolic pressure, the pressure during contraction of the heart (known as systole) can increase to over 200mmHg and levels as high as 250mmHg have been reported in highly trained, healthy athletes.

Diastolic pressure on the other hand remains relatively unchanged regardless of exercise intensity. In fact an increase of more than 15 mm Hg as exercise intensity increases can indicate coronary heart disease and is used as marker for cessing an exercise tolerance test.

Both systolic and diastolic blood pressure can rise to high, albeit brief, levels during resistance exercise. Values of 480/350mmHg have been reported to coincide with a Valsalva manoeuvre - *i.e.* trying to exhale against a closed mouth, nose and glottis.

Blood

During resting conditions the oxygen content of blood varies from about 20ml of oxygen per 100ml of arterial blood to 14ml of oxygen per 100ml of venous blood. The difference in oxygen content of arterial and venous blood is known as a-vO2 difference. As exercise intensity increase the a-vO2

difference increase also and at maximal exertion the difference between arterial and venous blood oxygen concentration can be three times that at a resting level.

Blood plasma volume decreases with the onset of exercise. The increase in blood pressure and changes in intramuscular osmotic pressures force water from the vascular compartment to the interstitial space. During prolonged exercise, plasma volume can decrease by 10-20% and by 15-20% in 1-minute bouts of exhaustive exercise. Resistance training with 40% and 70% one repetition maximum can cause a 7.7% and 13.9% reduction in blood plasma respectively. A reduction in plasma increase the concentration of hemoglobin or hematocrit. Although no extra red blood cells have been produced, the greater concentration of hemoglobin per unit of blood significantly increases the bloods oxygen carrying capacity. This is one of the main adaptations during immediate acclimatization to altitude. Blood pH can change from a slightly alkaline 7.4 at rest to as low as 6.5 during all-out sprinting activity. This is primarily due to an increased reliance on anaerobic energy systems and the accumulation of hydrogen ions.

ADAPTATIONS IN THE CARDIOVASCULAR SYSTEM

Following training the cardiovascular system and its components go through various adaptations. Here are the most important:

Heart Size

The hearts mass and volume increase and cardiac muscle undergoes hypertrophy.

It is the left ventricle that adapts to the greatest extent. As well as the chamber size increasing as a result of endurance training, more recent studies show that the myocardial wall thickness also increases.

Heart Rate

Resting heart rate can decrease significantly following training in a previously sedentary individual. During a 10-week exercise program, an individual with an initial resting heart rate of 80beats/min can reasonably expect to see a reduction of about 10beats/min in their resting heart rate. As mentioned earlier, highly conditioned athletes such as Lance Armstrong can have resting heart rates in the low 30s.

During submaximal exercise, heart rate is lower at any given intensity

compared to pre-training. This difference is more marked at higher relative exercise intensities. For example, at low work rates there may only be a marginal difference in heart rate pre and post training. As intensity reaches maximal levels, the difference can be as much as 30beats/min following training.

Maximum heart rate tends to remain unchanged by training and seems to be genetically limited. However, there are some reports that maximum heart rate is reduced in elite athletes compared to untrained individuals of the same age.

Following an exercise bout, heart rate remains elevated before slowly recovering to a resting level. After a period of training, the time it takes for heart rate to recover to its resting value is shortened. This can be a useful tool for tracking the effects of a training program. However, it is not so useful to compare to other people as various individual factors other than cardiorespiratory fitness play a role in how quickly heart rate returns to a resting level.

Stroke Volume

Stroke volume increases at rest, during submaximal exercise and maximal exercise following training. Stroke volume at rest averages 50-70 ml/beat in untrained individuals, 70-90ml/beat in trained individuals and 90-110ml/beat in world-class endurance athletes. This all-round increase in stroke volume in attributable to greater end-diastolic filling. This greater filling of the left ventricle is due to a) an increase in blood plasma and so blood volume and b) reduced heart rate which increases the diastolic filling time. According to the Frank-Starling mechanism, this increased filling on the left ventricle increases its elastic recoil thus producing a more forceful contraction. So not only is the heart filled with more blood to eject, it expels a greater percentage of the end-diastolic volume compared to before training.

Cardiac Output

If heart rate decreases at rest and during submaximal exercise and stroke volume increases, what is the net effect on cardiac output? In actual fact, cardiac output remains relatively unchanged or decreases only slightly following endurance training. During maximal exercise on the other hand, cardiac output increases significantly. This is a result of an increase in maximal stoke volume as maximal heart rate remains unchanged with training. In

untrained individuals, maximal cardiac output may be 14-20L/min compared to 25-35L/min in trained subjects. In large, elite athletes, maximal cardiac output can be as high as 40L.min.

Blood Flow

Skeletal muscle receives a greater blood supply following training. This is due to :

- Increased number of capillaries
- Greater opening of existing capillaries
- More effective blood redistribution
- Increased blood volume

Blood Pressure

Blood pressure can decrease (both systolic and diastolic pressure) at rest and during submaximal exercise by as much as 10mmHg in people with hypertension. However, at a maximal exercise intensity systolic blood pressure is decreased compared to pre-training. It is interesting to note that although resistance exercises can raise systolic and diastolic blood pressure significantly during the activity, it too can lead to a long-term reduction in blood pressure.

Blood Volume

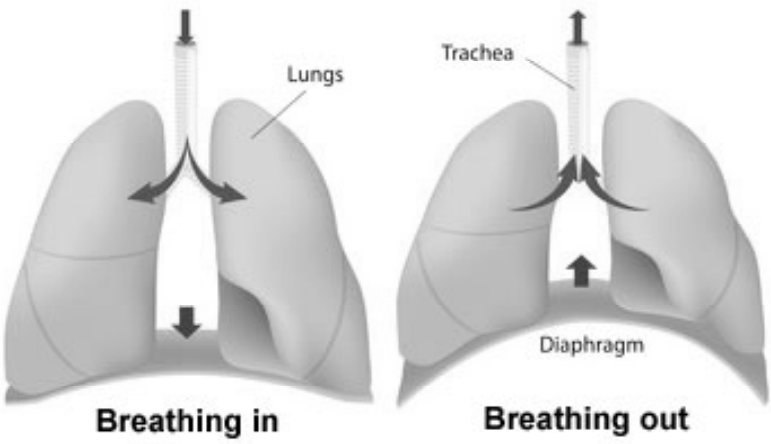
Endurance training increase blood volume. While plasma volume accounts for the majority of the increase, a greater production of red blood cells can also a contributory factor. Recall that hematocrit is the concentration of hemoglobin per unit of blood. An increase in red blood cells should increase hematocrit but this is not the case. Because blood plasma increases to a greater extent than red blood cells, hematocrit actually reduces following training.

3

Respiratory System and Exercise

MECHANICS OF BREATHING

The action of breathing in and out is due to changes of pressure within the thorax, in comparison with the outside. This action is also known as external respiration. When we inhale the intercostal muscles (between the ribs) and diaphragm contract to expand the chest cavity. The diaphragm flattens and moves downwards and the intercostal muscles move the rib cage upwards and out. This increase in size decreases the internal air pressure and so air from the outside (at a now higher pressure that inside the thorax) rushes into the lungs to equalise the pressures.



When we exhale the diaphragm and intercostal muscles relax and return to their resting positions. This reduces the size of the thoracic cavity, thereby increasing the pressure and forcing air out of the lungs.

Breathing Rate

The rate at which we inhale and exhale is controlled by the respiratory center, within the Medulla Oblongata in the brain. Inspiration occurs due to increased firing of inspiratory nerves and so the increased recruitment of motor units within the intercostals and diaphragm. Exhalation occurs due to a sudden stop in impulses along the inspiratory nerves. Our lungs are prevented from excess inspiration due to stretch receptors within the bronchi and bronchioles which send impulses to the Medulla Oblongata when stimulated.

Breathing rate is all controlled by chemoreceptors within the main arteries which monitor the levels of Oxygen and Carbon Dioxide within the blood. If oxygen saturation falls, ventilation accelerates to increase the volume of Oxygen inspired.

If levels of Carbon Dioxide increase a substance known as carbonic acid is released into the blood which causes Hydrogen ions (H+) to be formed. An increased concentration of H+ in the blood stimulates increased ventilation rates. This also occurs when lactic acid is released into the blood following high intensity exercise.

RESPIRATORY MUSCLES

The muscles of respiration are those muscles that contribute to inhalation and exhalation, by aiding in the expansion and contraction of the thoracic cavity. The diaphragm and, to a lesser extent, the intercostal muscles drive respiration during quiet breathing. Additional 'accessory muscles of respiration' are typically only used under conditions of high metabolic demand (*e.g.* exercise) or respiratory dysfunction (*e.g.* an asthma attack).

Diaphragm

The diaphragm is the major muscle responsible for breathing. It is a thin, dome-shaped muscle that separates the abdominal cavity from the thoracic cavity. During inhalation, the diaphragm contracts, so that its centre moves caudally (downward) and its edges move rostrally (upward). This compresses the abdominal cavity, raises the ribs upward and outward and thus expands the thoracic cavity. This expansion draws air into the lungs. When the diaphragm relaxes, elastic recoil of the thoracic wall causes the thoracic cavity to contract, forcing air out of the lungs.

The diaphragm is also involved in non-respiratory functions, helping to expel vomit, faeces, and urine from the body by increasing intra-abdominal pressure, and preventing acid reflux by exerting pressure on the esophagus as it passes through the esophageal hiatus.

Intercostal Muscles

Along with the diaphragm, the intercostal muscles are one of the most important groups of respiratory muscles. These muscles are attached between the ribs and are important in manipulating the width of the rib cage. There are three layers of intercostal muscles. The external intercostal muscles are most significant in respiration. These have fibers that are angled obliquely downward and forward from rib to rib. The contraction of these fibers raises each rib toward the rib above, with the overall effect of raising the rib cage, assisting in inhalation.

Accessory Muscles of Respiration

"Accessory muscles" refers to muscles that assist, but do not play a primary role, in breathing. There is some controversy concerning which muscles may be considered accessory muscles of inhalation. However, the sternocleidomastoid and the scalene muscles (anterior, middle and posterior scalene) are typically considered accessory muscles of breathing. Both assist in elevating the rib cage. The involvement of these muscles seems to depend on the degree of respiratory effort. During quiet breathing, the scalenes are consistently phasically active, while the sternocleidomastoids are quiet. With an increase in the respiratory volume, sternocleidomastoids also become active. Both muscles are simultaneously activated when one breathes in at the maximal flow rate.

Apart from the above neck muscles, the following muscles have also been observed contributing to respiration: serratus anterior, pectoralis major and pectoralis minor, trapezius, latissimus dorsi, erector spinae, iliocostalis lumborum, quadratus lumborum, serratus posterior superior, serratus posterior inferior, levatores costarum, transversus thoracis, subclavius (Kendall *et al.*, 2005). Use of the accessory muscles while at rest is often interpreted as a sign of respiratory distress.

Muscles of Exhalation

During quiet breathing, there is little or no muscle contraction involved

in exhalation; this process is simply driven by the elastic recoil of the thoracic wall. When forceful exhalation is required, or when the elasticity of the lungs is reduced (as in emphysema), active exhalation can be achieved by contraction of the abdominal wall muscles (rectus abdominis, transverse abdominis, external oblique muscle and internal oblique muscle). These press the abdominal organs cranially (upward) into the diaphragm, reducing the volume of the thoracic cavity. The internal intercostal muscles have fibres that are angled obliquely downward and backward from rib to rib. These muscles can therefore assist in lowering the rib cage, adding force to exhalation.

MINUTE VENTILATION

Respiratory minute volume (or minute ventilation or minute volume) is the volume of gas inhaled (inhaled minute volume) or exhaled (exhaled minute volume) from a person's lungs per minute. It is an important parameter in respiratory medicine due to its relationship with blood carbon dioxide levels. It can be measured with devices such as a Wright respirometer or can be calculated from other known respiratory parameters. Although minute volume can be viewed as a unit of volume, it is usually treated in practice as a flow rate (given that it represents a volume change over time).

Several symbols can be used to represent minute volume. They include $\dot{V}$ V ÿ {\displaystyle {\dot {V}} ($\dot{V}$ or V-dot) or Q (which are general symbols for flow rate), MV, and V_E.

Determination of Minute Volume

Minute volume can either be measured directly or calculated from other known parameters.

Measurement of Minute Volume

Minute volume is the amount of gas inhaled or exhaled from a person's lungs in one minute. It can be measured by a Wright respirometer or other device capable of cumulatively measuring gas flow, such as mechanical ventilators.

Calculation of Minute Volume

If both tidal volume (V_T) and respiratory rate (f or RR) are known, minute volume can be calculated by multiplying the two values. One must also take

care to consider the effect of dead space on alveolar ventilation, as seen below in "Relationship to other physiological rates".

$$\dot{V} = V_T \times f$$

Physiological Significance of Minute Volume

Blood carbon dioxide ($PaCO_2$) levels generally vary inversely with minute volume. For example, a person with increased minute volume (*e.g.* due to hyperventilation) should demonstrate a lower blood carbon dioxide level. The healthy human body will alter minute volume in an attempt to maintain physiologic homeostasis. A normal minute volume while resting is about 5–8 liters per minute in humans. Minute volume generally decreases when at rest, and increases with exercise. For example, during light activities minute volume may be around 12 litres. Riding a bicycle increases minute ventilation by a factor of 2 to 4 depending on the level of exercise involved. Minute ventilation during moderate exercise may be between 40 and 60 litres per minute.

Hyperventilation is the term for having a minute ventilation higher than physiologically appropriate. Hypoventilation describes a minute volume less than physiologically appropriate.

VENTILATION AT REST AND DURING EXERCISE

During exercise, the increase in ventilation which occurs to meet the increasing oxygen demands (called "hyperpnea") is not fully explained by the control of the peripheral or central chemoreceptors alone. There are non-chemical controls of ventilation that are required to provide input to the respiratory centre to increase ventilation, especially during the initiation of exercise when ventilation needs to increase quickly.

These "non-chemical controls" of ventilation include:

- The motor cortex (cortical control): feed-forward mechanism to increase ventilation at the onset of exercise
- Active muscles and joint receptors: active muscles and joints provide feedback to the respiratory center to increase ventilation (muscle metaboreflex) in order to meet the higher oxygen demands and to remove carbon dioxide
- Core body temperature: higher body temperature stimulates increased ventilation
- Stretch receptors in the lungs tissue and bronchioles: when these receptors are stretched, they send a signal to the medulla to stop

inhalation and start exhalation. This ensures that the lungs will never exceed their maximal physical capacity.

Minute Ventilation

At Rest

The normal respiratory cycle of a healthy individual at rest is constant and predictable. The rate and depth of breathing is considered “automatic” with no conscious input required from the individual. This results in a predictable number of breaths per minute with a similar amount of time between breaths.Minute Ventilation is determined by the following equation :

Minute Ventilation (VE) = VT x f B

VE = 6L/min at rest

Where V_T is the tidal volume per breath and f_B is the frequency of breaths per minute. Generally a healthy individual should have a minute volume of 6 L/min at rest. This number, of course, depends on size, age, and health status on an individual.

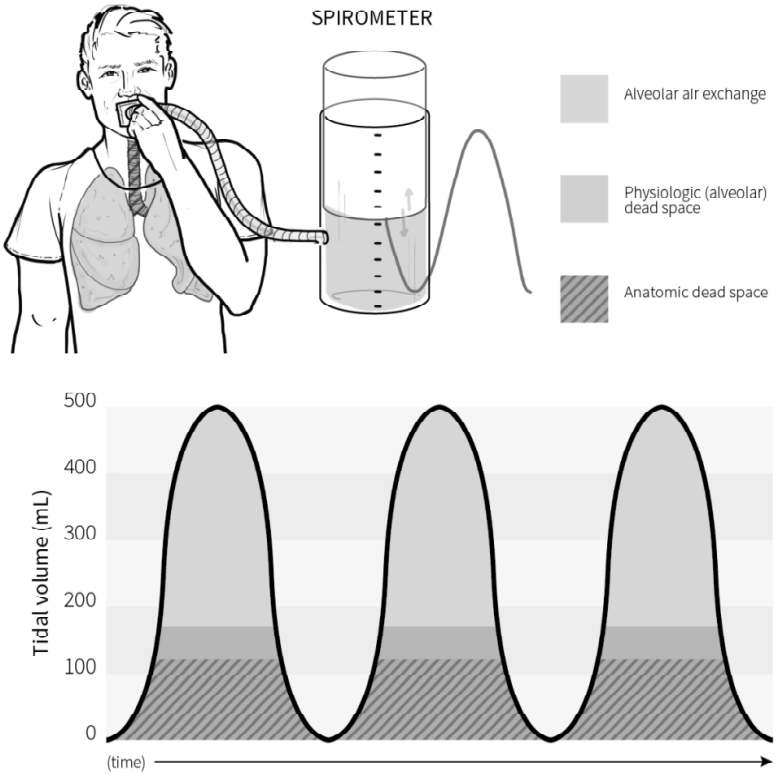


Figure. Tidal Volumes of a resting healthy individual. The portion of tidal

volume depicted in mint green represents the amount of space in the lungs that can actively inhale air and participate in gas exchange. Grey represents physiological dead space, which is the amount of alveolar tissue capable of participating in gas exchange but unable to because of some physical factor (*e.g.* lack of blood flow to a region of the lung). Purple shows the amount of anatomical deadspace: this is the portion of the airway that conducts air to the alveoli but cannot participate in gas exchange due to its specific anatomy (*e.g.* trachea, main bronchi). In a healthy individual the physiologic dead space (grey) is minimized and the alveolar airspace (mint) is large compared to the anatomical deadspace (purple).

Figure illustrates resting tidal volume, divided into the volumes associated with alveolar ventilation (V_A), which participates in gas exchange and deadspace ventilation (V_D), which does not participate in gas exchange.

With Acute Exercise

In any sort of physical exertion, light or strenuous, the body must compensate for the increased oxygen demand. To get more oxygen into the body during exercise, various sensors within the body will tell the central controller in the brain to increase minute ventilation, this means taking more breaths per minute as well as larger volumes of air per breath. Minute ventilation can increase to over 100 L/min with heavy exercise! This concept is illustrated by Figure.

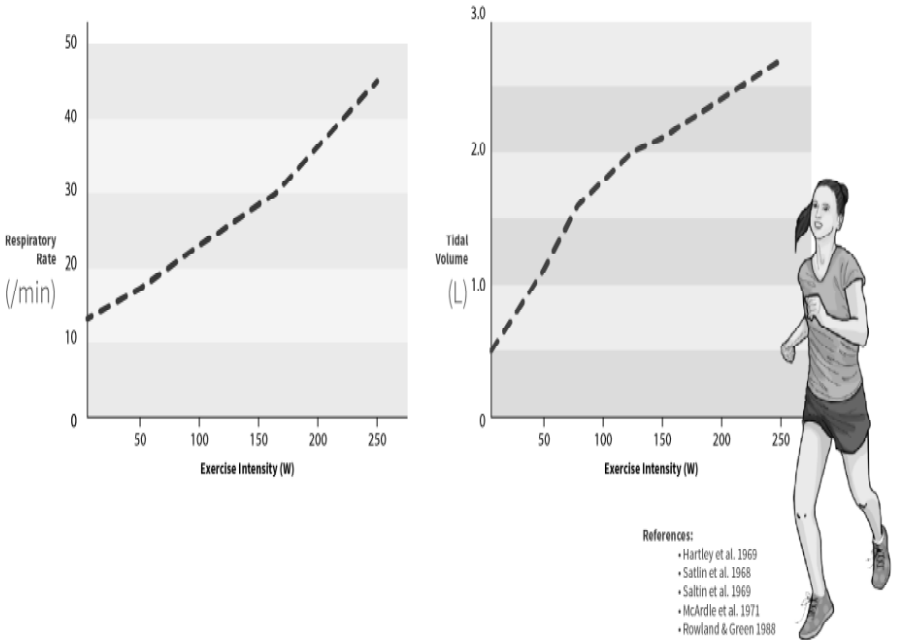


Figure. Tidal volume and breathing frequency of an individual running on a

treadmill. Both frequency and tidal volumes increase as velocity of treadmill (*i.e.* intensity of exercise) increases.

Change in Lung Volumes with Acute Exercise

As previously described the minute ventilation of an individual will increase with an increased demand for oxygen during exercise, due to an increase in tidal volume and breathing frequency. The increase in tidal volume comes at the expense of certain volumes within the lungs, such as expiratory and inspiratory reserve volumes. These changes are illustrated in Figure.

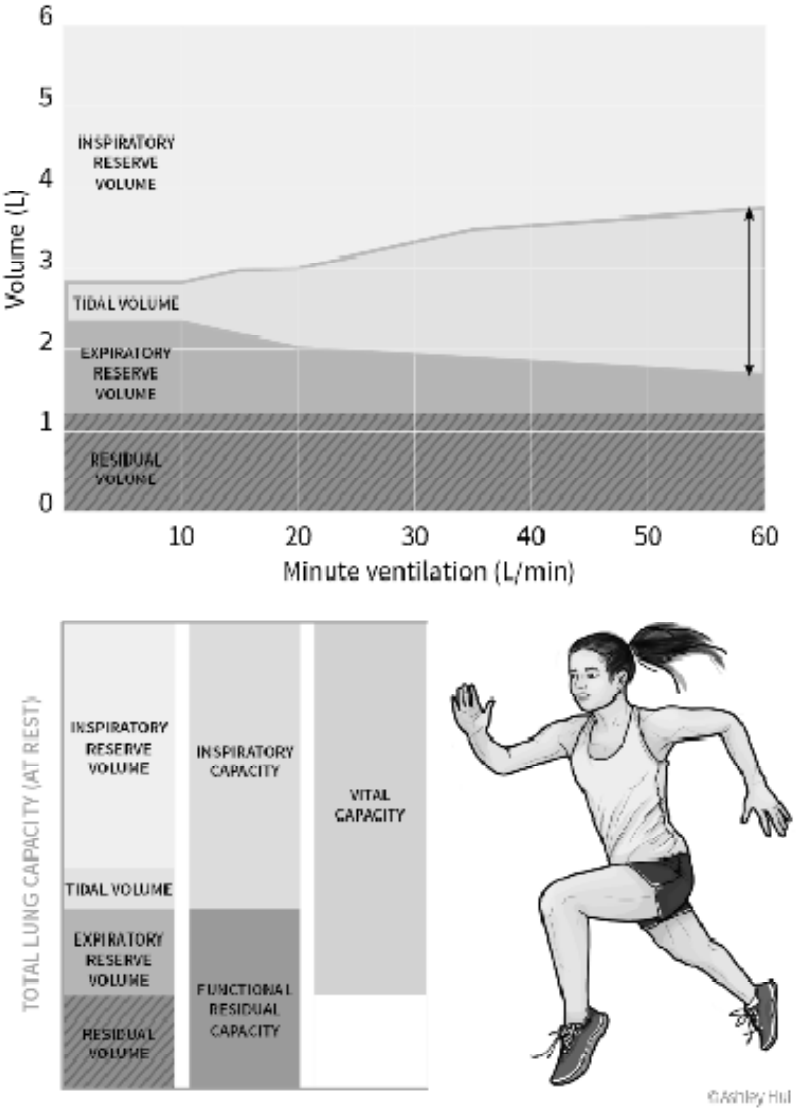


Figure. Illustration of residual, tidal, expiratory reserve, and inspiratory reserve volumes with increasing minute ventilation during exercise.

With exercise, there is a need to increase tidal volume to get more air to participate in alveolar ventilation and increase oxygenation of the blood. “Space” is needed in the lungs to accommodate this extra volume of inhaled air. This extra space comes from out of the inspiratory reserve volume (IRV). The IRV acts as a reservoir of extra lung volume that can become inflated with air as we need it, such as when there is a demand for more oxygen inhalation and CO_2 exhalation during exercise. Therefore with exercise, there is a decrease in IRV as tidal volume increases and takes over this “space” in the lung. Eventually the IRV can be used up, coinciding with physical size/ stretch of the lungs, however this limit is rarely approached by typical, healthy individuals during exercise.

Essentially we also sacrifice some of our expiratory reserve volume (ERV) in order to accommodate more tidal volume. The ERV decreases during exercise, since there is need to expire more air from the lungs that we typically do at rest. This is because we need a larger volume of lung to be involved in gas exchange with new air coming in with each breath. We also need to expire the increasing amount of CO_2 (and heat) that is being produced by the working muscles. The decrease in ERV can be seen in Figure.

There is a limit however as to how much we can breathe out. There is a small amount of air that needs to remain in the lungs to keep them inflated, called the residual lung volume. Residual volume does not change very much (if any) during exercise even with increasing tidal volume. At rest we usually don’t need to use our expiratory reserve volume. The ERV and the residual volume together make up the functional residual capacity (FRC); that is the amount of air contained in our lungs after a normal exhalation.

3.2 DIFFUSION OF GASES—EXCHANGE OF GASES IN THE LUNGS—EXCHANGE OF GASES IN THE TISSUES—CONTROL OF VENTILATION —VENTILATION AND THE ANAEROBIC THRESHOLD

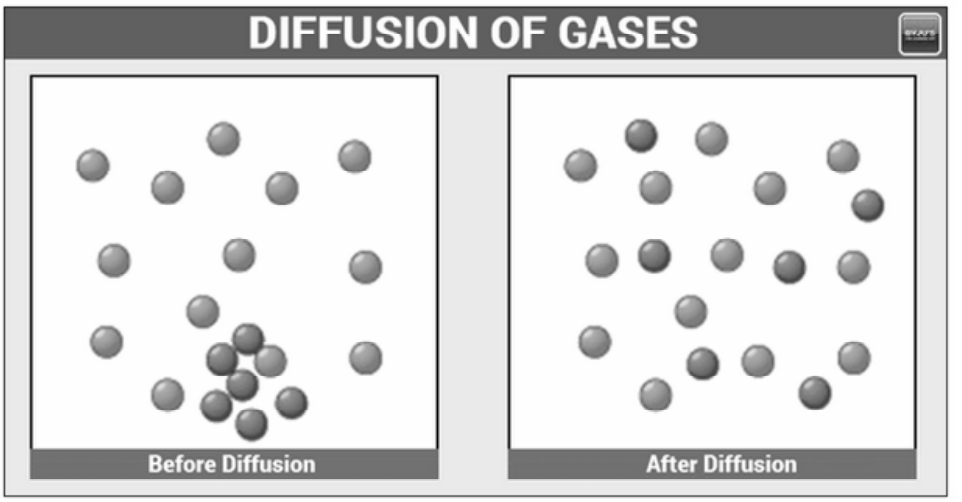
DIFFUSION OF GASES

Before discussing about the diffusion of gases, let’s know a bit about what is diffusion? The diffusion is a net movement of atoms or molecules from

high concentrated region to low concentration region. In other words, the movement of atoms or molecules from high chemical potential region to the low chemical potential region.

The word diffusion is derived from a Latin word – diffundere, to spread out. Which means, a substance that spreads out or moving from an area to another. Diffusion should not be confused with other transport phenomena like advection or convection, where it use move particles from one place to another in a bulk motion. The movement of molecules in solids is very small, relatively large in liquids and very large in gases. And this movement of molecules has lead to a phenomenon called as diffusion.

Diffusion of Gases



The thermal motion of gas particles at above absolute zero temperature is called molecular diffusion. The rate of this phenomenon movement is a function of viscosity of the gas, temperature and size of the particles. The result of diffusion is a slow mixing of materials where the distribution of molecules or atoms are uniform.

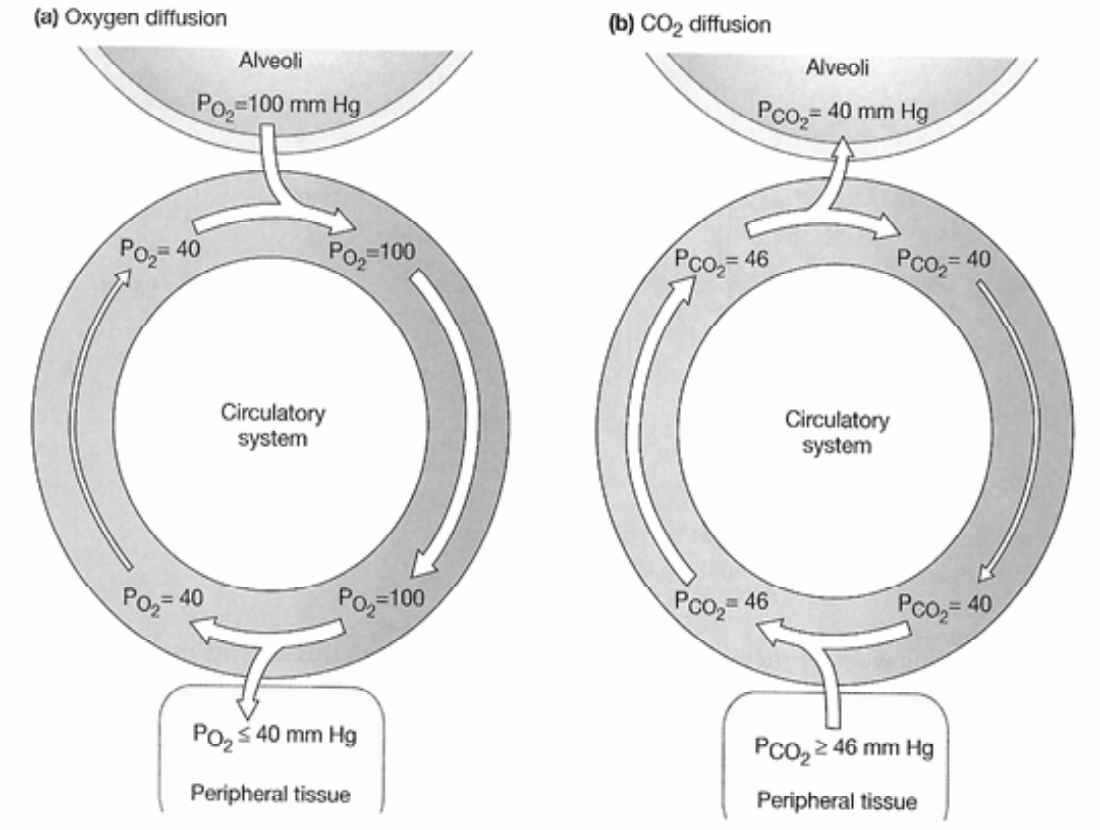
$$Rate\,of\ Diffusion = \frac{Amount\,of\ Gas\,Pas\sin g\,Through\,on\,Area}{Unit\,of\ Time}$$

Here is an example to understand the diffusion of gases. Take a container, separating it in two partition. Keep two gases A and B at same pressure in two parts of the container. The molecules of gas A and B are in continuous random motion in its respective compartments. Now, remove the partition of the container. The molecules of gas A will begin to stray into gas B due to the random motion. In the same way, the molecules of gas B will begin to stray into gas A due to the random motion. As time passes, the molecules of both gases continues to stary each other. In a period of time, the whole mass of gas in the container will be a homogeneous mixture of gas A and gas B and this results because of the phenomenon called as diffusion.

EXCHANGE OF GASES IN LUNGS AND TISSUES

The gas laws state that individual gases flow from regions of higher partial pressures to regions of lower partial pressure, and this rule governs the exchange of oxygen and carbon dioxide in the lungs and tissues. Normal alveolar P_{O2} is about 100 mm Hg. The P_{O2} of systemic venous blood arriving at the lungs is 40 mm Hg. Oxygen therefore moves down its partial pressure (concentration) gradient from the alveoli into the capillaries. Diffusion goes to equilibrium, and the P_{O2} of arterial blood leaving the lungs is the same as in the alveoli: 100 mm Hg.

When arterial blood reaches tissue capillaries, the gradient is reversed. Cells are continuously using oxygen for oxidative phosphorylation. In the cells of a person at rest, intracellular P_{O2} averages 40 mm Hg. Arterial blood arriving at the cells has a P_{O2} of 100 mm Hg. Because P_{O2} is lower in the cells, oxygen diffuses down its partial pressure gradient from plasma into the cells. Once again, diffusion goes to equilibrium, and as a result venous blood has the same P_{O2} as the cells it just passed.



Conversely P_{CO2} is higher in tissues than in systemic capillary blood because of CO_2 production during metabolism. Cellular P_{CO2} in a person at rest is about 46 mm Hg, compared to an arterial plasma P_{CO2} of 40 mm Hg. The gradient causes CO_2 to diffuse out of cells into the capillaries. Diffusion goes to equilibrium, and systemic venous blood averages a P_{CO2} of 46 mm Hg.

At the pulmonary capillaries, the process reverses. Venous blood bringing waste CO_2 from the cells has a P_{CO2} of 46 mm Hg. Alveolar P_{CO2} is 40 mm Hg. Because P_{CO2} is higher in the plasma, CO_2 moves format he capillaries into the alveoli. By the time blood leaves, the alveoli, it has a P_{CO2} of 40 mm Hg, identical to the P_{CO2} of the alveoli.

A Decrease in Alveolar P_{O2} Decreases Oxygen Uptake at the Lungs

The first requirement for adequate oxygen delivery to the tissues is

adequate oxygen intake from the atmosphere, as reflected by the P_{O2} of the alveoli. A decrease in alveolar P_{O2} will result in less oxygen entering the blood. There are two possible causes of low alveolar P_{O2}: either (1) the inspired air has abnormally low oxygen content or (2) alveolar ventilation is inadequate.

The main factor that affects the oxygen content of inspired air is altitude. The partial pressure of oxygen in air decreases along with total atmospheric pressure as you move form sea level (where normal atmospheric pressure is 760 mm Hg) to higher altitudes. For example, Denver, 1609 m above sea level, has an atmospheric pressure of about 628 mm Hg. The P_{O2} of dry air in Denver is 132 mm Hg, down from 160 mm Hg at sea level.

Unless a person is traveling, however, altitude remains constant. If alveolar P_{O2} is low but the composition of inspired air is normal, then the problem lies with alveolar ventilation. Low alveolar ventilation is also known as hypoventilation and is characterized by lower-than-normal volumes of fresh air entering the alveoli. Pathological factors that cause alveolar hypoventilation include decreased lung compliance and overdoses of drugs (including alcohol) that depress the central nervous system and slow ventilation rate and depth.

Changes in the Alveolar Membrane Alter Gas Exchange

In situations in which the composition of the air reaching the alveoli is normal but the P_{O2} of arterial blood leaving the lungs is low, some aspect of the exchange process between alveoli and blood is defective. The transfer of oxygen from alveoli to blood requires diffusion across the barrier created by type I alveolar cells and by the capillary endothelium.

Normally, the diffusion distance is small because the cells are thin and there is little or not interstitial fluid between the two cell layers. In addition, both oxygen and carbon dioxide are soluble in both water and lipids. Gas exchange in the lungs is rapid, blood flow through pulmonary capillaries is slow, and diffusion reaches equilibrium in less than 1 second. Pathological changes that adversely affect gas exchange include (1) a decrease in the amount of alveolar surface area available for gas exchange, (2) an increase in the

thickness of the alveolar membrane and (3) an increase in the diffusion distance between the alveoli and the blood.

Physical loss of alveolar surface area is dramatic in emphysema, a degenerative lung disease most often caused by cigarette smoking. The irritating effect of smoke in the alveoli activates alveolar macrophages that release proteolytic enzymes. These enzymes destroy the elastic fibers of the lung and induce apoptosis of cells, breaking down the walls of the alveoli. The result is a high-compliance/low-elastic recoil lung with fewer and larger alveoli and less surface area for gas exchange.

Pathological changes in the alveolar membrane that alter its properties slow gas exchange. For example, in fibrotic lung diseases, deposition of scar tissue thickens the alveolar membrane. Diffusion of gases through this scar tissue is much slower than normal. However, because the lungs have a built-in reserve capacity, one-third of the exchange epithelium must be incapacitated before arterial P_{O2} falls significantly.

One pathological condition in which the diffusion distance between alveoli and blood increases is pulmonary edema, characterized by excessive interstitial fluid volume in the lungs. Normally, only small amounts of interstitial fluid are present in the lungs, the result of low pulmonary blood pressure and effective lymph drainage. However, if pulmonary blood pressure rises for some reason, such as left ventricular failure or mitral valve dysfunction, the normal filtration/reabsorption balance at the capillary is disrupted. When capillary hydrostatic pressure increases, more fluid filters out of the capillary. If filtration increases too much, the lymphatics are unable to remove all the fluid and excess accumulates in the pulmonary interstitial space, crating pulmonary edema. In severe cases, fluid even leaks across the alveolar membrane, collecting inside the alveoli.

Oxygen has low solubility in body fluids and takes longer to cross the increased diffusion distance present in pulmonary edema, resulting in decreased arterial P_{O2}. Carbon dioxide, in contrast, is relatively soluble in body fluids, so the increased diffusion distance may not significantly affect carbon dioxide exchange. In some cases of pulmonary edema, arterial P_{O2} is low but arterial P_{CO2} is normal because of the different solubilities of the two gases.

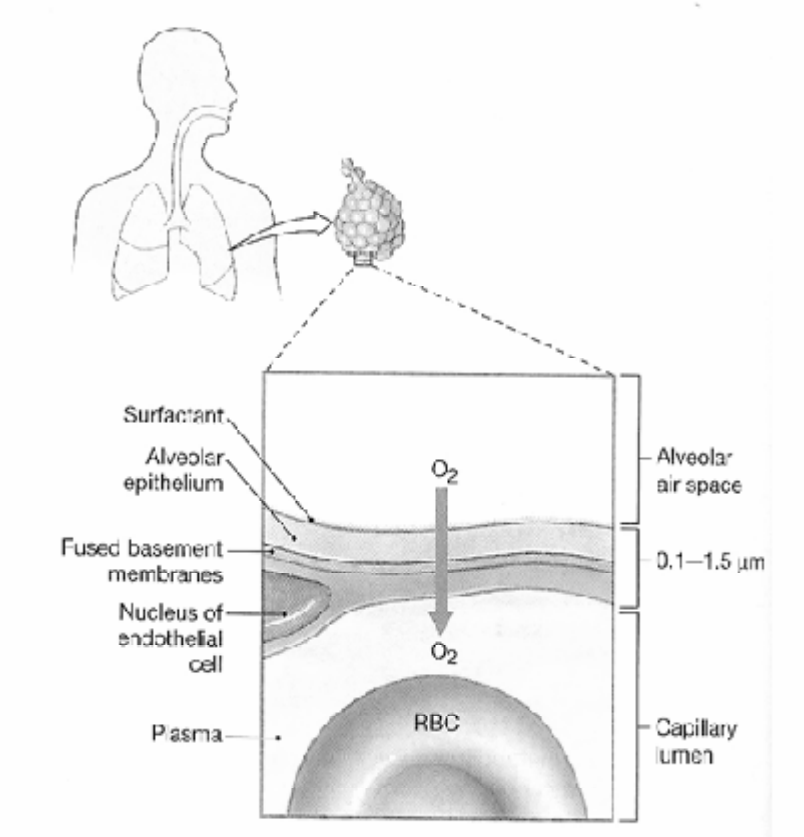


Fig: Oxygen Diffuses Across Alveolar Epithelial Cells and Capillary Endothelial Cells to Enter the Plasma

CONTROL OF VENTILATION

Control of ventilation refers to the physiological mechanisms involved in the control of breathing, which is the movement of air into and out of the lungs. Ventilation facilitates respiration. Respiration refers to the utilization of oxygen and production of carbon dioxide by the body as a whole, or by individual cells.

The most important function of breathing is blood gas homeostasis, *i.e.* the regulation of the partial pressures of oxygen and carbon dioxide in the arterial blood. The effector of this homeostat is centered primarily on the manner in which the lungs are ventilated. Under most conditions, the partial pressure of carbon dioxide (P_{CO2}) controls the respiratory rate.

The sensors for the arterial blood gas regulator are situated in the aortic and carotid bodies, which are primarily sensitive to the partial pressure of oxygen (PO_2) in the arterial blood, and the anterior and lateral surfaces of the

medulla oblongata in the brain stem which measures the P_{CO2} and pH of the cerebrospinal fluid and consequently the arterial blood.

Information from these sensors is conveyed along nerves to the respiratory centers in the brain stem. The respiratory centers are located in the medulla oblongata and the pons in the brainstem. There are four, two in the medulla and two in the pons.

1. Inspiratory center - reticular formation, medulla oblongata
2. Expiratory center - reticular formation, medulla oblongata
3. Pneumotaxic center - various nuclei of the pons
4. Apneustic center - nucleus of the pons

From the respiratory centers the skeletal muscles of ventilation, in particular the diaphragm, are alternately activated to cause air to move in and out of the lungs.

Involuntary Control of Respiration

Ventilatory Pattern

The pattern of motor stimuli during breathing can be divided into inspiratory and expiratory phases. Inspiration shows a sudden, ramped increase in motor discharge to the inspiratory muscles (including pharyngeal dilator muscles). Before the end of inspiration, there is a decline in motor discharge. Exhalation is usually silent, except at high minute ventilation rates.

The mechanism of generation of the ventilatory pattern is not completely understood, but involves the integration of neural signals by respiratory control centers in the medulla and pons. The nuclei known to be involved are divided into regions known as the following:

- Medulla (reticular formation)
  - Ventral respiratory group (nucleus retroambigualis, nucleus ambiguus, nucleus parambigualis and the pre-Bötzinger complex). The ventral respiratory group controls voluntary forced exhalation and acts to increase the force of inspiration. Regulates rhythm of inhalation and exhalation.
  - Dorsal respiratory group (nucleus tractus solitarii). The dorsal respiratory group controls mostly inspiratory movements and their timing.
- Pons
  - Pneumotaxic center.

- Coordinates speed of inhalation and exhalation.
- Sends inhibitory impulses to the inspiratory area.
- Involved in fine tuning of respiration rate.

* Apneustic center
  - Coordinates speed of inhalation and exhalation.
  - Sends stimulatory impulses to the inspiratory area – activates and prolongs inhalate (long deep breaths).
  - Overridden by pneumotaxic control from the apneustic area to end inspiration.

There is further integration in the anterior horn cells of the spinal cord.

Control of Ventilatory Pattern

Ventilation is normally unconscious and automatic, but with the possibility of partial or complete superimposition of voluntary, conscious alternative patterns of ventilation. Thus the emotions can cause yawning, laughing, sighing (etc.), social communication causes speech, song and whistling, while entirely voluntary overrides are used to blow out candles, and breath holding (to swim, for instance, underwater). Hyperventilation may be entirely voluntary or in response to emotional agitation or anxiety, when it can cause the distressing hyperventilation syndrome.

The ventilatory pattern is also temporarily modified by complex reflexes such as sneezing, straining, burping, coughing and vomiting.

Determinants of Ventilatory rate

Ventilatory rate (minute volume) is tightly controlled and determined primarily by blood levels of carbon dioxide as determined by metabolic rate. Blood levels of oxygen become important in hypoxia. These levels are sensed by blood gas chemoreceptors on the surface of the medulla oblongata for pH, and the carotid and aortic bodies for oxygen and carbon dioxide. Afferent neurons from the carotid bodies and aortic bodies are via the glossopharyngeal nerve (CN IX) and the vagus nerve (CN X), respectively.

Levels of CO_2 rise in the blood when the metabolic use of O_2,and the production of CO_2 is increased during, for example, exercise. The CO_2 in the

blood is transported largely as bicarbonate (HCO_3) ions, by conversion first to carbonic acid (H_2CO_3), by the enzyme carbonic anhydrase, and then by disassociation of this acid to H^+ and HCO_3". Build-up of CO_2 therefore causes an equivalent build-up of the disassociated hydrogen ions, which, by definition, decreases the pH of the blood. The pH sensors on the brain stem immediately sense to this fall in pH, causing the respiratory center to increase the rate and depth of breathing. The consequence is that the P_{CO2} does not change from rest going into exercise. During very short-term bouts of intense exercise the release of lactic acid into the blood by the exercising muscles causes a fall in the blood plasma pH, independently of the rise in the P_{CO2}, and this will stimulate pulmonary ventilation sufficiently to keep the blood pH constant at the expense of a lowered P_{CO2}.

Mechanical stimulation of the lungs can trigger certain reflexes as discovered in animal studies. In humans, these seem to be more important in neonates and ventilated patients, but of little relevance in health. The tone of respiratory muscle is believed to be modulated by muscle spindles via a reflex arc involving the spinal cord.

Drugs can greatly influence the control of respiration. Opioids and anesthetic drugs tend to depress ventilation, by decreasing the homeostat's response to raised carbon dioxide levels in the arterial blood. Stimulants such as amphetamines can cause hyperventilation.

Pregnancy tends to increase ventilation (lowering plasma carbon dioxide tension below normal values). This is due to increased progesterone levels and results in enhanced gas exchange in the placenta.

Feedback Control

Receptors play important roles in the regulation of respiration; central and peripheral blood gas chemoreceptors, and mechanoreceptors.

- Central chemoreceptors of the central nervous system, located on the ventrolateral medullary surface, are sensitive to the pH of their environment.
- Peripheral chemoreceptors act most importantly to detect variation of the P_{O2} in the arterial blood, in addition to detecting arterial P_{CO2} and pH.
- Mechanoreceptors are located in the airways and parenchyma, and are responsible for a variety of reflex responses. These include:

* The Hering-Breuer reflex that terminates inspiration to prevent over inflation of the lungs, and the reflex responses of coughing, airway constriction, and hyperventilation.
* The upper airway receptors are responsible for reflex responses such as, sneezing, coughing, closure of glottis, and hiccups.
* The spinal cord reflex responses include the activation of additional respiratory muscles as compensation, gasping response, hypoventilation, and an increase in breathing frequency and volume.
* The nasopulmonary and nasothoracic reflexes regulate the mechanism of breathing through deepening the inhale. Triggered by the flow of the air, the pressure of the air in the nose, and the quality of the air, impulses from the nasal mucosa are transmitted by the trigeminal nerve to the breathing centers in the brainstem, and the generated response is transmitted to the bronchi, the intercostal muscles and the diaphragm.

Voluntary Control of Respiration

In addition to involuntary control of respiration by respiratory neuronal networks in the brainstem, respiration can be affected by higher brain conditions such as emotional state, via input from the limbic system, or temperature, via the hypothalamus, or free will. Voluntary or conscious control of respiration is provided via the cerebral cortex, although chemoreceptor reflexes are capable of overriding it.

While breathing can obviously be controlled both consciously and unconsciously, other basic functions provided by the brainstem cannot be controlled voluntarily. Only conscious control of respiratory neuronal networks in the reticular formation can affect other basic functions regulated by the brainstem, because of the inter-meshed character of the reticular formation, *e.g.* the heart rate in yoga and meditation (“to take a deep breath”).

Many common parts of the body are cleverly used in this sensory-effector system to keep dissolved gases in a narrow physiologic range. Figure illustrates these areas:

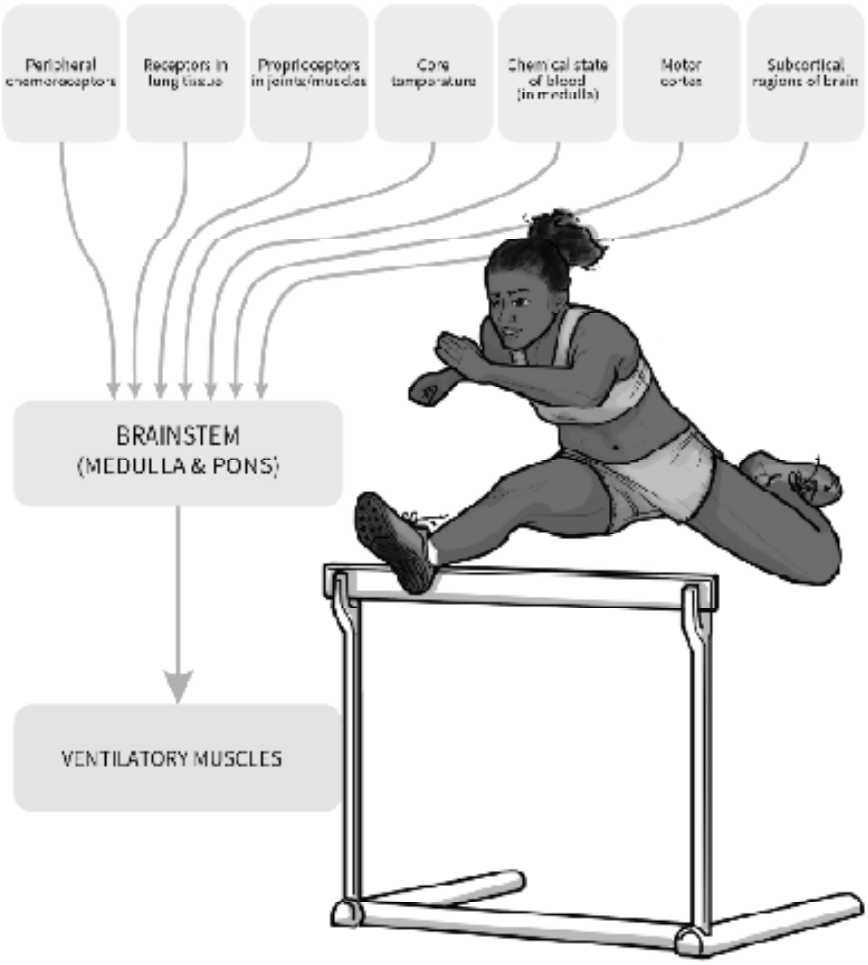


Figure. Schematic representation of factors that affect medullary control of pulmonary ventilation

As shown in Figure, the medial portion of the medulla is the central controller that regulates the normal respiratory cycle. This portion of the brain receives input from various "sensors" to either increase or decrease respiration (the amount of breaths), and the duration of each breath (how much air we take into the lungs). The overall goal of the central control mechanism is to maintain the correction oxygenation state of the blood to maximize oxygenation of body tissues.

VENTILATION AND ANAEROBIC THRESHOLD

Ventilatory Threshold

In kinesiology, the ventilatory threshold (VT1) refers to the point during

exercise at which ventilation starts to increase at a faster rate than VO_2 (V – volume, O_2 – oxygen). One's threshold is said to reflect levels of anaerobiosis and lactate accumulation. As the intensity level of the activity being performed increases, breathing becomes faster; more steadily first and then more rapid as the intensity increases. When breathing surpasses normal ventilation rate, one has reached ventilatory threshold. For most people this threshold lies at exercise intensities between 50% and 75% of VO_2 max. A major factor affecting one's ventilatory threshold is their maximal ventilation (amount of air entering and exiting lungs). This is dependent on their personal experience with the activity and how physically fit the person is. Comparison studies of more athletic people have shown that your ventilatory threshold occurs at a higher intensity if you are more active or have been training for that exercise; although, in some cases shorter continuous tests can be used because of rapid alterations in ventilation.

Methods

- Ventilation Curve – Plot VE vs. VO_2 or Watts or Time – The point at which there is a non-linear increase in ventilation
- V-Slope Method – Plot VO_2 vs. VCO_2 – The point at which the increase in VCO_2 is greater than the increase in VO_2
- Ventilatory Equivalents Method – Plot VE/VO_2 and VE/VCO_2 vs. Watts or time or VO_2 – Point at which VE/VO_2 increases while VE/VCO_2 decreases or stays the same

Sample Values

Frangolias DD, Rhodes EC School of Human Kinetics, University of British Columbia, Vancouver, Canada. Medicine and Science in Sports and Exercise [1995, 27(7):1007-1013]:

- A government experiment to test ventilatory threshold was held between November and December 2004. Subjects included 32 physically active males (age: 22.3; TV: 180.5; TM: 75.5 kg; VO_2max: 57.1 mL/kg/min) encountered a continuous test of increasing loads on a treadmill, cardiorespiratory and other variables were observed using ECG (recording of the electrical activity of the heart) and gas analyzer. During the test, subjects were asked to point at a scale from 6 to 20 reflecting their feeling of discomfort. The RPE threshold

was recorded as constant value of 12-13. Averages of ventilatory and RPE threshold were conveyed by parameters that were monitored and then compared by using t-test for dependent samples. No significant difference was found between mean values of ventilatory and RPE threshold, when they were expressed by parameters such as: speed, load, heart rate, absolute and relative oxygen consumption. The conclusion of this experiment was: the fixed value (12-13) of RPE scale may be used to detect the exercise intensity that corresponds to ventilatory threshold.

VO_2 Max Levels

Maximum oxygen intake, VO_2, is one of the best measures of cardiovascular fitness and maximal aerobic power. VO_2 max averages around 35–40 mL/(kg· min) in a healthy male and 27–31 mL/ (kg· min) in a healthy female. These scores can improve with training. Factors that affect your VO_2 max is age, sex, fitness, training, and genetics. While scores in the upper 80s and 90s have been recorded by legendary endurance athletes such as Greg Lemond, Miguel Indurain, and Steve Prefontaine, most competitive endurance athletes have scores in the mid to high 60s. Cycling, rowing, swimming and running are some of the main sports that push VO_2 levels to the maximum. Ventilatory threshold and lactate threshold are expressed as a percentage of VO_2 max; beyond this percentage the ability to sustain the work rate rapidly declines as high intensity but short duration energy systems such as glycolysis and ATP-PC are relied on more heavily.

The Anaerobic Threshold

The anaerobic threshold (AT), also called the “lactate threshold,” is the exertion level between aerobic and anaerobic training. The AT is the point during exercise when your body must switch from aerobic to anaerobic metabolism. The AT is a useful measure for deciding exercise intensity for training and racing in endurance sports.

During aerobic metabolism, your body creates energy by burning carbohydrates and fats in the presence of oxygen and produces carbon dioxide and water as by-products (breathing and sweating). Most of our daily activities are fueled by aerobic metabolism.

Anaerobic metabolism kicks in when exercise intensity is greatly increased, and the aerobic system can no longer keep up with the body’s energy demand.

This is the point at which we cross the AT. During anaerobic metabolism, the body burns stored sugars to supply the additional energy needed, and lactic acid is produced faster than it can be metabolized. Muscle pain, burning and fatigue make anaerobic energy expenditure difficult to sustain for longer than a few minutes.

The fitter you are, the longer you can fuel your body with the aerobic system before the anaerobic system needs to take over. You can improve your aerobic efficiency—and thus raise your AT—by doing high-quality aerobic work at a level just below your current AT. Monitoring your heart rate and finding your Training Heart Rate Range (THRR) will help you determine what your current AT is.

Workouts to Raise the AT

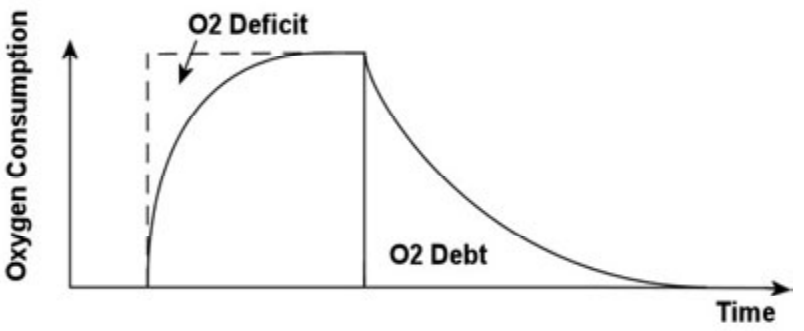
Interval workouts are effective for raising the AT. For the best results, vary your workouts between aerobic work (where duration takes priority over high intensity), and higher-intensity intervals (where you will be just under or at your Maximum Heart Rate (MHR)). Aerobic work should comprise the largest percentage of your training. Here are a few interval workouts to try. We recommend long sub-maximal intervals, with roughly equal rest. As always, warm-up well before starting your piece:

- 5 x 750 metres with 3 minutes rest
- 4 x 1000 metres with 3–4 minutes rest
- 4–5 x 5 minutes with 4 minutes rest
- 5 x 4 minutes with 4 minutes rest

OXYGEN DEBT

What is oxygen debt? When you have a short intense burst of exercise such as sprinting you generate energy for this anaerobically or without oxygen. When you stop exercising you are still breathing heavily. This is your body taking in extra oxygen to ‘repay’ the debt. Well, that is the simple solution but there is a little more to it if you want to look a bit deeper.

True, your body has worked anaerobically and will have produced energy without some of the oxygen it would normally have used performing low intensity exercise such as slow steady running. The difference between the oxygen the body required and what it actually managed to take in during the sudden sprint is called oxygen deficit.



When you stop sprinting and start to recover you will actually need more oxygen to recover than your body would have liked to use had enough been available. This is called Excess Post Exercise Oxygen Consumption.

So why does it Take More Oxygen to Recover then?

- You needed to replace the oxygen the body needed but couldn't get (oxygen deficit).
- Breathing rate and heart rate are elevated (to remove CO2) and this needs more oxygen.
- Body temperature and metabolic rate is increased and this needs more oxygen.
- Adrenaline and Noradrenaline are increased which increases oxygen consumption.

So after exercise there are other factors causing an increase in oxygen needs as well as repaying the lack of oxygen during exercise.

The chart below is often seen and shows how the amount of oxygen used by the body changes over time. At the beginning the body works anaerobically leaving an oxygen deficit. Over time the oxygen consumption levels out to a steady state. After exercise the oxygen is pain back (oxygen debt). Notice the area of oxygen debt is greater than the area of oxygen deficit for the reasons stated above.

What has Lactic Acid got to do with it?

Lactic acid is a by product of exercising without using oxygen (anaerobially). It is essential this is removed but it is not necessarily a waste product. It is recycled into other useful chemicals:

- During prolonged intensive exercise (*e.g.* 800m race) the heart may get half its energy from lactic acid. It is converted back to pyruvic acid and used as energy by the heart and other muscles.

- It is thought that 70% of lactic acid produced is oxidised, 20% is converted to glucose (energy) in the liver.
- 10% is converted to protein.

How Long does it take to Remove Lactic Acid?

- About 1 hour if cooling down with gentle exercise.
- It can take 2 hours or more if you dont warm down with gentle exercise.

LUNG VOLUMES AND CAPACITIES

Lung volumes and lung capacities refer to the volume of air associated with different phases of the respiratory cycle. The average total lung capacity of an adult human male is about 6 litres of air. Tidal breathing is normal, resting breathing; the tidal volume is the volume of air that is inhaled or exhaled in only a single such breath. The average human respiratory rate is 30-60 breaths per minute at birth, decreasing to 12-20 breaths per minute in adults.

Factors Affecting Volumes

Several factors affect lung volumes; some can be controlled and some cannot be controlled. Lung volumes vary with different people as follows:

Larger Volumes	***Smaller Volumes***
taller people	shorter people
people who live at higher altitudes	people who live at lower altitudes
non obese	obese

A person who is born and lives at sea level will develop a slightly smaller lung capacity than a person who spends their life at a high altitude. This is because the partial pressure of oxygen is lower at higher altitude which, as a result means that oxygen less readily diffuses into the bloodstream. In response to higher altitude, the body's diffusing capacity increases in order to process more air. Also, due to the lower environmental air pressure at higher altitudes, the air pressure within the breathing system must be lower in order to inhale; in order to meet this requirement, the thoracic diaphragm has a tendency to lower to a greater extent during inhalation, which in turn causes an increase in lung volume.

When someone living at or near sea level travels to locations at high

altitudes (*e.g.*, the Andes; Denver, Colorado; Tibet; the Himalayas) that person can develop a condition called altitude sickness because their lungs remove adequate amounts of carbon dioxide but they do not take in enough oxygen. (In normal individuals, carbon dioxide is the primary determinant of respiratory drive.)

Lung function development is reduced in children who grow up near motorways although this seems at least in part reversible . Air pollution exposure affects FEV1 in astmatics, but also affects FVC and FEV1 in healthy adults even at low concentrations.

Specific changes in lung volumes also occur during pregnancy. Functional residual capacity drops 18–20%, typically falling from 1.7 to 1.35 litres, due to the compression of the diaphragm by the uterus. The compression also causes a decreased total lung capacity (TLC) by 5% and decreased expiratory reserve volume by 20%. Tidal volume increases by 30–40%, from 0.5 to 0.7 litres, and minute ventilation by 30–40% giving an increase in pulmonary ventilation. This is necessary to meet the increased oxygen requirement of the body, which reaches 50 mL/min, 20 mL of which goes to reproductive tissues. Overall, the net change in maximum breathing capacity is zero.

Values

Average Lung Volumes in Healthy Adults

Volume	*Value (Litres)*	
	In Men	*In Women*
Inspiratory reserve volume	3.1	1.9
Tidal volume	0.5	0.5
Expiratory reserve volume	1.2	0.7
Residual volume	1.2	1.1

Lung Capacities in Healthy Adults

Volume	*Average Value (Litres)*		*Derivation*
	In Men	*In Women*	
Vital capacity	4.8	3.1	IRV + TV + ERV
Inspiratory capacity	3.5	2.4	IRV + TV
Functional residual capacity	2.3	1.8	ERV + RV
Total lung capacity	5.8	4.2	IRV + TV + ERV + RV

The tidal volume, vital capacity, inspiratory capacity and expiratory reserve

volume can be measured directly with a spirometer. These are the basic elements of a ventilatory pulmonary function test.

Determination of the residual volume is more difficult as it is impossible to "completely" breathe out. Therefore, measurement of the residual volume has to be done via indirect methods such as radiographic planimetry, body plethysmography, closed circuit dilution (including the helium dilution technique) and nitrogen washout.

In absence of such, estimates of residual volume have been prepared as a proportion of body mass for infants (18.1 mL/kg), or as a proportion of vital capacity (0.24 for men and 0.28 for women) or in relation to height and age ((0.0275* Age [Years]+0.0189*Height [cm]-2.6139) litres for normal-mass individuals and (0.0277*Age [Years]+0.0138*Height [cm]-2.3967) litres for overweight individuals). Standard errors in prediction equations for residual volume have been measured at 579 mL for men and 355 mL for women, while the use of 0.24*FVC gave a standard error of 318 mL.

Online calculators are available that can compute predicted lung volumes, and other spirometric parameters based on a patient's age, height, weight, and ethnic origin for many reference sources.

Restrictive and obstructive

The results (in particular FEV1/FVC and FRC) can be used to distinguish between restrictive and obstructive pulmonary diseases:

Type	*Examples*	*Description*	*FEV1/FVC*
restrictive diseases	pulmonary fibrosis, Infant Respiratory Distress Syndrome, weak respiratory muscles, pneumothorax	volumes are decreased	often in a normal range (0.8 - 1.0)
obstructive diseases	asthma or COPD or Emphysema	volumes are essentially normal but flow rates are impeded	often low (Asthma can reduce the ratio to 0.6, Emphysema can reduce the ratio to 0.78 - 0.45)

Increasing Lung Capacity

Lung capacity can be expanded through flexibility exercises such as yoga, breathing exercises, and physical activity. A greater lung capacity is sought by people such as athletes, freedivers, singers, and wind-instrument players. A stronger and larger lung capacity allows more air to be inhaled into the lungs. In using lungs to play a wind instrument for example, exhaling an expanded volume of air will give greater control to the player and allow for a clearer and louder tone.

EFFECTS OF EXERCISE AND TRAINING ON THE RESPIRATORY SYSTEM

Effects of physical activity and sports on the respiratory system mainly depend on changes in alveolar CO_2 levels. Here, after analyzing basics of oxygen transport (changes in CO_2 and O_2 concentrations in the blood and cells), we are going to provide clear and simple answers to the following questions:

- What are the exact criteria that determine the long-term positive effects of exercise on overall health and well-being?
- Are these criteria different in healthy and sick people?
- If exercise is healthy, why do thousands of sick people die every year from coronary-artery spasms, anginas, infarcts, strokes, exercise-induced asthma attacks and many other acute exacerbations of diseases during or following physical exercise?
- Is graded exercise therapy useful for all patients?
- What is going on with the respiratory system of these people during exercise?
- What are the short-term and long-term effects of exercise on the respiratory system?

Table. MV (Minute Ventilation) and Rf (Respiratory Frequency) at Rest

Condition	*MV, L/min*	*Rf, breaths/ min*	*Oxygen extraction, %*	*Breath Pattern*	*References*
Diseases*	12-18	>18	<12 %	Overbreathing	Over 40 studies
Healthy	6-7	10-12	25 %	Normal	Results of 14 studies
Norm	6	12	25 %	Normal	Medical textbooks

Super-health	2	3	>60 %	Ideal	Observations/yoga

*Chronic diseases include heart disease, diabetes, asthma, COPD, cystic fibrosis, cancer, and many others. Study Hyperventilation Syndrome for references and numbers.

As it is easy to observe, heavy breathing at rest results in relatively heavy breathing during exercise and that makes moderate or intensive exercise in the sick very difficult or impossible.

Table. Minute Ventilation during Moderate Exercise (15-fold Metabolism)

Condition	Minute ventilation	Short-term respiratory effects	Blood lactate	Duration of performance
Chronic diseases	About 150 L/min	Maximum mouth ventilation	Very high	A few minutes
Normal breathing	90 L/min	Heavy nose breathing	Elevated	1-2 hours
Super health states	30 L/min	Easy nose breathing	Nearly normal	Many hours

If you attend a typical mass running event or open marathon, you will notice numerous ambulances with paramedics, who are ready to provide rescue help and oxygen, regardless of the details of the chronic disease (heart disease, stroke, seizures, exercise-induced asthma, and so forth). Whatever the condition, low brain and heart oxygen levels are most likely physiological causes of possible deaths. Hence, the main questions then are: What are the factors that define effects of exercise on the respiratory system? What is going on with blood gases or O_2 and CO_2 in the blood and body cells? The answers depend on the pre-existing respiratory parameters and levels of blood gases before and after exercise.

Exercise and the Respiratory System in Healthy People

Consider the short-term effects of exercise in healthy people. Textbooks on exercise physiology suggest that, in fit and healthy people, arterial CO_2 levels rise slightly with light, moderate, medium and sub-maximum exercise intensity levels regardless of the route of breathing during exercise (mouth or

nasal or combined). Since CO_2 is the powerful vasodilation agent, expanded arteries and arterioles improve blood and O_2 delivery to all vital organs of the human body, including the heart and brain. Vasodilation ensures aerobic respiration in body cells making it possible for healthy people to enjoy all the benefits of aerobic exercise without any major problems related to tissue hypoxia causing excessive blood lactate, muscle spasms, injuries, low recovery rates, overexcitement, stress, poor sleep later, etc.

Hence, healthy people experience immediate positive effects of exercise on the respiratory system and blood gases. What happens after exercise (long-term effects of exercise on the respiratory system)? Since breathing is controlled by CO_2, the usual exercise effects for fit and healthy people are simple: breathing after exercise becomes lighter and slower due to an adaptation of the respiratory system and the breathing centre to higher CO_2 levels. As a result, the body-oxygen content increases for many hours after the exercise. This especially relates to the next-morning body oxygenation, and this is the main criterion of exercise efficiency, if someone decides to measure the exact long-term effects of exercise on the respiratory system.

However, when very healthy and healthy people do exercise with strictly nasal breathing, their blood gases during exercise are different in comparison with mouth breathing. Arterial CO_2 gets even higher, and arterial oxygen saturation becomes slightly less in a dose-dependent manner. Nasal breathing (in and out) slightly worsens the immediate performance and results, but is incomparably better in the long run. Why? Intermittent hypoxic hypercapnic training, as in case of nose breathing (in and out), is an excellent way to improve VO_{2max}, body-oxygen content and achieve adaptation of the breathing centre to higher CO_2.

VO_{2max} (definition)= the maximal oxygen uptake or the maximum volume of oxygen that can be utilized by the human body in one minute during maximal exercise. It is measured as milliliters of oxygen used in one minute per kilogram of body weight (ml/kg/min). VO_{2max} is usually ranged from 20-40 ml/kg/min (in unfit and ordinary subjects) and up to 80-90 ml/mg/min (in elite endurance athletes). Physiologically, it is the most significant parameter that predicts long-term endurance and performance in athletes.

One can try both these approaches (reduced nasal breathing on some days and heavy mouth breathing in others) and compare the effects of both types of exercise on your well-being. It is, for example, easy to discover that physical exercise with strictly nose breathing significantly reduces pulse for the same intensity level for any particular individual in comparison with mouth or combined breathing. Hence, the positive effects of physical exercise with nasal breathing only are immediate. They can be easily measured with sport watches and other devices that can record heart rate during exercise.

Exercise and the Respiratory System in Sick People

As analyzed before, sick people have heavy and deep breathing at rest

before exercise. Hence, their have abnormal blood gases prior to exercise. Usually they suffer from arterial hypocapnia (low CO_2 due to overbreathing) and (likely) mild arterial hypoxia, if they are chest breathers. (Chest breathing, as we discussed, reduces oxygen level in the arterial blood.). If they have problems with their lungs or ventilation-perfusion mismatch (as in a small group of patients with severe asthma, bronchitis, or emphysema), their arterial CO_2 is too high (up to 50-60 mm Hg), but blood oxygenation is low already at rest, causing dyspnea (shortness of breath sensation) even during low intensity exercise.

Overbreathing at rest reduces their body-oxygen levels. As a result, many people with diabetes, cancer, heart disease, chronic fatigue and many other conditions have elevated blood lactate level at rest, indicating the presence of cell hypoxia and anaerobic cellular respiration. Mild exercise generates even more lactic acid due to initial oxygen deficiency. (This is the common reason why the sick people do not like exercise.) As a result, since the lactic acid level is also controlled by the respiratory system, the body starts to remove bicarbonates (CO_2) from the blood by increased ventilation (metabolic acidosis). To maintain blood pH in the normal range, the breathing centre intensifies minute ventilation to remove some CO_2 from the body. The breathing becomes disproportionally heavier (the main short-term effect of exercise in the sick). This is possible to observe in many sick people during exercise: heavy panting, usually through the wide open mouth.

Mouth breathing, as we've previously discussed, further reduces the arterial and cellular CO_2, creating brain hypoxia and increasing heart rate. Nasal breathing, on the other hand, prevents CO_2 and nasal NO (nitric oxide) losses and improves brain and heart-oxygen content provided that the intensity of exercise matches oxygen delivery.

The overbreathing caused by mouth breathing during exercise can continue for many hours after exercise, if it is too intensive or anaerobic. Exercise with low intensities are better tolerated, but mouth breathing still negates any improvements in heart and body oxygen level canceling positive long-term effects of exercise on the respiratory system. It is normal then that severely-sick individuals can easily die due to moderate or intensive exercise combined with other hyperventilation-inducing lifestyle factors, including stress, overheating, overeating before the exercise, drop in blood glucose level, chest breathing, etc. It is not a surprise then that graded exercise therapy has conflicting results so far.

There are many coaches and fitness instructors these days who teach their athletes, students, and pupils to breathe in through the nose and out through the mouth in order to improve long-term effects of exercise on the respiratory system. This breathing technique for physical exercise is half-better than mouth breathing due to improved absorption of nitric oxide and some increase in arterial CO_2.

Which Exercise Programs have the Best Short-term and Long-term Effects on the Respiratory System and Body Oxygen Content?

Clinical experience of a large group of Soviet and Russian MDs suggests that nasal breathing during exercise is the key factor that maximizes positive short- and long-term effects of exercise on the respiratory system, and prevents any acute episodes, including coronary spasms, angina pains, infarcts, strokes, sport-induced asthma attacks, and seizures. Furthermore, nasal breathing ensures absorption of nitric oxide generated in the sinuses and inhaled into the lungs during nose breathing.

Consider how nasal breathing provided good health for people in the past. Physical exercise was the main factor that made the breathing and body-oxygen content of our predecessors much better. They were exercising up to 8-12 hours per day (including walking, gardening, and all type of activities where the whole body is involved in movement). Mouth breathing, as you can easily see in old photos and movies, was a socially unacceptable habit. Some evidence suggests that even competing athletes were breathing strictly through the nose (in and out) during training sessions and sport contests.

With the advance of the industrial revolution during the last 100 years, the amount of average exercise for people declined down to 10-60 min per day (this includes walking). Furthermore, mouth breathing during exercise leads to heart attacks, strokes, exercise-induced asthma attacks, and other exacerbations. As a result, physical exercise, instead of being a health benefit, became a serious hazard since we lost the habit of nose breathing. However, all the adverse long-term and short-term effects of exercise on the respiratory system can be virtually eliminated via the use of strictly nasal breathing (in and out).

Hence, the oldest or traditional exercise programs (physical activity with nasal breathing only) have the best effects on the respiratory system and body-

oxygen levels and general health of humans due to the high CO_2 production rate, arterial CO_2 increases, and adaptation of the breathing centre to higher CO_2 with slower and lighter automatic breathing for many hours later.

- "Physical work, sport, and exertion increase CO_2 production. Its level increases in the blood, while oxygen decreases. The higher the intensity, the stronger the excitement of the breathing centre and the deeper the breathing, but it is only deeper formally. Breathing becomes not deeper, but shallower: it is less in relation to metabolism. This is the reasoning behind the usefulness of exercise and sport! During prolonged intensive exercise the receptors, which control breathing, adapt to increased CO_2. If the person regularly works and toils, then he practically follows our method: he is decreasing his breathing using exercise". Dr. Buteyko lecture in the Moscow State University on 9 December 1969

Physical exercise, according to Dr. Buteyko, is the main factor that defines the long-term success of the student during breathing retraining due to positive effects of exercise on the respiratory system. Since a lack of physical exercise is the main cause of hyperventilation in modern man, it is normal that daily duration of physical activity has a correlation with personal-morning body-oxygen content (the CP - control pause). Indeed, Buteyko and his colleagues found that when their students achieved high CPs (*e.g.*, up to 60 s) and stopped doing breathing exercises, the stability of their CPs were dependent on the amount of their daily physical exercise.

4

Metabolism and Energy Transfer

METABOLISM

Definition

Metabolism is the set of life-sustaining chemical transformations within the cells of living organisms. The three main purposes of metabolism are the conversion of food/fuel to energy to run cellular processes, the conversion of food/fuel to building blocks for proteins, lipids, nucleic acids, and some carbohydrates, and the elimination of nitrogenous wastes. These enzyme-catalyzed reactions allow organisms to grow and reproduce, maintain their structures, and respond to their environments. The word metabolism can also refer to the sum of all chemical reactions that occur in living organisms, including digestion and the transport of substances into and between different cells, in which case the set of reactions within the cells is called intermediary metabolism or intermediate metabolism.

Metabolism is usually divided into two categories: catabolism, the breaking down of organic matter for example, the breaking down of glucose to pyruvate, by cellular respiration, and anabolism, the building up of components of cells such as proteins and nucleic acids. Usually, breaking down releases energy and building up consumes energy.

The chemical reactions of metabolism are organized into metabolic pathways, in which one chemical is transformed through a series of steps into another chemical, by a sequence of enzymes. Enzymes are crucial to metabolism because they allow organisms to drive desirable reactions that

require energy that will not occur by themselves, by coupling them to spontaneous reactions that release energy. Enzymes act as catalysts that allow the reactions to proceed more rapidly. Enzymes also allow the regulation of metabolic pathways in response to changes in the cell's environment or to signals from other cells.

The metabolic system of a particular organism determines which substances it will find nutritious and which poisonous. For example, some prokaryotes use hydrogen sulfide as a nutrient, yet this gas is poisonous to animals. The speed of metabolism, the metabolic rate, influences how much food an organism will require, and also affects how it is able to obtain that food.

A striking feature of metabolism is the similarity of the basic metabolic pathways and components between even vastly different species. For example, the set of carboxylic acids that are best known as the intermediates in the citric acid cycle are present in all known organisms, being found in species as diverse as the unicellular bacterium Escherichia coli and huge multicellular organisms like elephants. These striking similarities in metabolic pathways are likely due to their early appearance in evolutionary history, and their retention because of their efficacy.

Types

Metabolism refers to the dynamic changes of the molecules within a cell, especially those small molecules used as sources of energy and as precursors for the synthesis of proteins, lipids, and nucleic acids. These reactions occur in the steady state rather than all at once. Steady state refers to dynamic equilibrium, or homeostasis, where the individual molecules change but the rate at which they are made equals the rate at which they are destroyed. Concentrations of individual molecules in metabolic reactions are therefore kept relatively constant, while any individual molecules are present only for a brief time. Metabolism therefore is said to be an open chemical system. Metabolic reactions can be catabolic (directed toward the breakdown of larger molecules to produce energy), or anabolic (directed toward the energy–consuming synthesis of cellular components from smaller molecules).

ATP

Adenosine triphosphate (ATP) is a nucleotide (also called a nucleoside triphosphate) and is a small molecule used in cells as a coenzyme. It is often

referred to as the “molecular unit of currency” of intracellular energy transfer.

ATP transports chemical energy within cells for metabolism. Most cellular functions need energy in order to be carried out: synthesis of proteins, synthesis of membranes, movement of the cell, cellular division, transport of various solutes etc. ATP is the molecule that carries energy to the place where the energy is needed. When ATP breaks into adenosine diphosphate (ADP) and phosphate (P_i), the breakdown of the last covalent link of phosphate (a simple -PO_4) liberates energy that is used in reactions where it is needed.

It is one of the end products of photophosphorylation, aerobic respiration, and fermentation, and is used by enzymes and structural proteins in many cellular processes, including biosynthetic reactions, motility, and cell division. One molecule of ATP contains adenine, ribose, and three phosphate groups, and it is produced by a wide variety of enzymes, including ATP synthase, from adenosine diphosphate (ADP) or adenosine monophosphate (AMP) and various phosphate group donors. Substrate-level phosphorylation, oxidative phosphorylation in cellular respiration, and photophosphorylation in photosynthesis are three major mechanisms of ATP biosynthesis.

Metabolic processes that use ATP as an energy source convert it back into its precursors. ATP is therefore continuously recycled in organisms: the human body, which on average contains only 250 grams (8.8 oz) of ATP, turns over its own body weight equivalent in ATP each day.

ATP is used as a substrate in signal transduction pathways by kinases that phosphorylate proteins and lipids. It is also used by adenylate cyclase, which uses ATP to produce the second messenger molecule cyclic AMP. The ratio between ATP and AMP is used as a way for a cell to sense how much energy is available and control the metabolic pathways that produce and consume ATP. Apart from its roles in signaling and energy metabolism, ATP is also incorporated into nucleic acids by polymerases in the process of transcription. ATP is the neurotransmitter believed to signal the sense of taste.

The structure of this molecule consists of a purine base (adenine) attached by the 9 nitrogen atom to the 12 carbon atom of a pentose sugar (ribose). Three phosphate groups are attached at the 52 carbon atom of the pentose sugar. It is the addition and removal of these phosphate groups that inter-convert ATP, ADP and AMP. When ATP is used in DNA synthesis, the ribose sugar is first converted to deoxyribose by ribonucleotide reductase.

ATP was discovered in 1929 by Karl Lohmann, and independently by Cyrus Fiske and Yellapragada Subbarow of Harvard Medical School, but its

correct structure was not determined until some years later. It was proposed to be the intermediary molecule between energy-yielding and energy-requiring reactions in cells by Fritz Albert Lipmann in 1941. It was first artificially synthesized by Alexander Todd in 1948.

Physical and Chemical Properties

ATP consists of adenosine – composed of an adenine ring and a ribose sugar – and three phosphate groups (triphosphate). The phosphoryl groups, starting with the group closest to the ribose, are referred to as the alpha (α), beta (β), and gamma (ε) phosphates. Consequently, it is closely related to the adenosine nucleotide, a monomer of RNA. ATP is highly soluble in water and is quite stable in solutions between pH 6.8 and 7.4, but is rapidly hydrolysed at extreme pH. Consequently, ATP is best stored as an anhydrous salt.

ATP is an unstable molecule in unbuffered water, in which it hydrolyses to ADP and phosphate. This is because the strength of the bonds between the phosphate groups in ATP is less than the strength of the hydrogen bonds (hydration bonds), between its products (ADP and phosphate), and water. Thus, if ATP and ADP are in chemical equilibrium in water, almost all of the ATP will eventually be converted to ADP. A system that is far from equilibrium contains Gibbs free energy, and is capable of doing work. Living cells maintain the ratio of ATP to ADP at a point ten orders of magnitude from equilibrium, with ATP concentrations fivefold higher than the concentration of ADP. This displacement from equilibrium means that the hydrolysis of ATP in the cell releases a large amount of free energy.

Two phosphoanhydride bonds (those that connect adjacent phosphates) in an ATP molecule are responsible for the high energy content of this molecule. In the context of biochemical reactions, these anhydride bonds are frequently – and sometimes controversially – referred to as high-energy bonds (despite the fact it takes energy to break bonds). Energy stored in ATP may be released upon hydrolysis of the anhydride bonds. The primary phosphate group on the ATP molecule that is hydrolyzed when energy is needed to drive anabolic reactions is the ε-phosphate group. Located the farthest from the ribose sugar, it has a higher energy of hydrolysis than either the α-or β-phosphate. The bonds formed after hydrolysis—or the phosphorylation of a residue by ATP—are lower in energy than the phosphoanhydride bonds of ATP. During enzyme-catalyzed hydrolysis of ATP or phosphorylation by ATP, the available free energy can be harnessed by a living system to do work.

Any unstable system of potentially reactive molecules could potentially serve as a way of storing free energy, if the cell maintained their concentration far from the equilibrium point of the reaction. However, as is the case with most polymeric biomolecules, the breakdown of RNA, DNA, and ATP into simpler monomers is driven by both energy-release and entropy-increase considerations, in both standard concentrations, and also those concentrations encountered within the cell.

The standard amount of energy released from hydrolysis of ATP can be calculated from the changes in energy under non-natural (standard) conditions, then correcting to biological concentrations. The net change in heat energy (enthalpy) at standard temperature and pressure of the decomposition of ATP into hydrated ADP and hydrated inorganic phosphate is “30.5 kJ/mol, with a change in free energy of 3.4 kJ/mol. The energy released by cleaving either a phosphate (P_i) or pyrophosphate (PP_i) unit from ATP at standard state of 1 M are:

$ATP + H_2O \rightarrow ADP + P_i \quad \Delta G° = –30.5$ kJ/mol (–7.3 kcal/mol)

$ATP + H_2O \rightarrow AMP + PP_i \quad \Delta$ÄG° = –45.6 kJ/mol (–10.9 kcal/mol)

These values can be used to calculate the change in energy under physiological conditions and the cellular ATP/ADP ratio. However, a more representative value (which takes AMP into consideration) called the Energy charge is increasingly being employed. The values given for the Gibbs free energy for this reaction are dependent on a number of factors, including overall ionic strength and the presence of alkaline earth metal ions such as Mg^{2+} and Ca^{2+}. Under typical cellular conditions, ΔG is approximately –57 kJ/mol (–14 kcal/mol).

Ionization in Biological Systems

ATP (adenosine triphosphate) has multiple groups with different acid dissociation constants. In neutral solution, ionized ATP exists mostly as $ATP^{4"}$, with a small proportion of $ATP^{3"}$. As ATP has several negatively charged groups in neutral solution, it can chelate metals with very high affinity. The binding constant for various metal ions are (given as per mole) as Mg^{2+}(9554), Na+(13), Ca^{2+}(3722), K+(8), Sr^{2+}(1381) and Li+(25). Due to the strength of these interactions, ATP exists in the cell mostly in a complex with Mg^{2+}.

Biosynthesis

The ATP concentration inside the cell is typically 1–10 mM. ATP can be

produced by redox reactions using simple and complex sugars (carbohydrates) or lipids as an energy source. For complex fuels to be synthesized into ATP, they first need to be broken down into smaller, more simple molecules. Carbohydrates are hydrolysed into simple sugars, such as glucose and fructose. Fats (triglycerides) are metabolised to give fatty acids and glycerol.

The overall process of oxidizing glucose to carbon dioxide is known as cellular respiration and can produce about 30 molecules of ATP from a single molecule of glucose. ATP can be produced by a number of distinct cellular processes; the three main pathways used to generate energy in eukaryotic organisms are glycolysis and the citric acid cycle/oxidative phosphorylation, both components of cellular respiration; and beta-oxidation. The majority of this ATP production by a non-photosynthetic aerobic eukaryote takes place in the mitochondria, which can make up nearly 25% of the total volume of a typical cell.

Glycolysis

In glycolysis, glucose and glycerol are metabolized to pyruvate via the glycolytic pathway. In most organisms, this process occurs in the cytosol, but, in some protozoa such as the kinetoplastids, this is carried out in a specialized organelle called the glycosome. Glycolysis generates a net two molecules of ATP through substrate phosphorylation catalyzed by two enzymes: PGK and pyruvate kinase. Two molecules of NADH are also produced, which can be oxidized via the electron transport chain and result in the generation of additional ATP by ATP synthase. The pyruvate generated as an end-product of glycolysis is a substrate for the Krebs Cycle.

Glucose

In the mitochondrion, pyruvate is oxidized by the pyruvate dehydrogenase complex to the acetyl group, which is fully oxidized to carbon dioxide by the citric acid cycle (also known as the Krebs cycle). Every “turn” of the citric acid cycle produces two molecules of carbon dioxide, one molecule of the ATP equivalent guanosine triphosphate (GTP) through substrate-level phosphorylation catalyzed by succinyl-CoA synthetase, three molecules of the reduced coenzyme NADH, and one molecule of the reduced coenzyme $FADH_2$. Both of these latter molecules are recycled to their oxidized states (NAD^+ and FAD, respectively) via the electron transport chain, which generates additional ATP by oxidative phosphorylation. The oxidation of an NADH

molecule results in the synthesis of 2–3 ATP molecules, and the oxidation of one $FADH_2$ yields between 1–2 ATP molecules. The majority of cellular ATP is generated by this process. Although the citric acid cycle itself does not involve molecular oxygen, it is an obligately aerobic process because O_2 is needed to recycle the reduced NADH and $FADH_2$ to their oxidized states. In the absence of oxygen the citric acid cycle will cease to function due to the lack of available NAD^+ and FAD.

The generation of ATP by the mitochondrion from cytosolic NADH relies on the malate-aspartate shuttle (and to a lesser extent, the glycerol-phosphate shuttle) because the inner mitochondrial membrane is impermeable to NADH and NAD^+. Instead of transferring the generated NADH, a malate dehydrogenase enzyme converts oxaloacetate to malate, which is translocated to the mitochondrial matrix.

Another malate dehydrogenase-catalyzed reaction occurs in the opposite direction, producing oxaloacetate and NADH from the newly transported malate and the mitochondrion's interior store of NAD^+. A transaminase converts the oxaloacetate to aspartate for transport back across the membrane and into the intermembrane space.

In oxidative phosphorylation, the passage of electrons from NADH and $FADH_2$ through the electron transport chain powers the pumping of protons out of the mitochondrial matrix and into the intermembrane space. This creates a proton motive force that is the net effect of a pH gradient and an electric potential gradient across the inner mitochondrial membrane. Flow of protons down this potential gradient – that is, from the intermembrane space to the matrix – provides the driving force for ATP synthesis by ATP synthase. This enzyme contains a rotor subunit that physically rotates relative to the static portions of the protein during ATP synthesis.

Most of the ATP synthesized in the mitochondria will be used for cellular processes in the cytosol; thus it must be exported from its site of synthesis in the mitochondrial matrix. The inner membrane contains an antiporter, the ADP/ATP translocase, which is an integral membrane protein used to exchange newly synthesized ATP in the matrix for ADP in the intermembrane space. This translocase is driven by the membrane potential, as it results in the movement of about 4 negative charges out of the mitochondrial membrane in exchange for 3 negative charges moved inside. However, it is also necessary to transport phosphate into the mitochondrion; the phosphate carrier moves a proton in with each phosphate, partially dissipating the proton gradient.

Beta Oxidation

Fatty acids can also be broken down to acetyl-CoA by beta-oxidation. Each round of this cycle reduces the length of the acyl chain by two carbon atoms and produces one NADH and one $FADH_2$ molecule, which are used to

generate ATP by oxidative phosphorylation. Because NADH and $FADH_2$ are energy-rich molecules, dozens of ATP molecules can be generated by the beta-oxidation of a single long acyl chain. The high energy yield of this process and the compact storage of fat explain why it is the most dense source of dietary calories.

Fermentation

Fermentation entails the generation of energy via the process of substrate-level phosphorylation in the absence of a respiratory electron transport chain. In most eukaryotes, glucose is used as both an energy store and an electron donor. The equation for the oxidation of glucose to lactic acid is:

$C_6H_{12}O_6 \rightarrow 2\ CH_3CH(OH)COOH + 2\ ATP$

Anaerobic Respiration

Anaerobic respiration is the process of respiration using an electron acceptor other than O_2. In prokaryotes, multiple electron acceptors can be used in anaerobic respiration. These include nitrate, sulfate or carbon dioxide. These processes lead to the ecologically important processes of denitrification, sulfate reduction and acetogenesis, respectively.

ATP Replenishment by Nucleoside Diphosphate Kinases

ATP can also be synthesized through several so-called “replenishment” reactions catalyzed by the enzyme families of nucleoside diphosphate kinases (NDKs), which use other nucleoside triphosphates as a high-energy phosphate donor, and the ATP:guanido-phosphotransferase family.

ATP Production during Photosynthesis

In plants, ATP is synthesized in thylakoid membrane of the chloroplast during the light-dependent reactions of photosynthesis in a process called photophosphorylation. Here, light energy is used to pump protons across the chloroplast membrane. This produces a proton-motive force and this drives the ATP synthase, exactly as in oxidative phosphorylation. Some of the ATP produced in the chloroplasts is consumed in the Calvin cycle, which produces triose sugars.

ATP Recycling

The total quantity of ATP in the human body is about 0.2 moles. The majority of ATP is not usually synthesised de novo, but is generated from ADP by the aforementioned processes. Thus, at any given time, the total amount of ATP + ADP remains fairly constant.

The energy used by human cells requires the hydrolysis of 100 to 150 moles of ATP daily, which is around 50 to 75 kg. A human will typically use up his or her body weight of ATP over the course of the day. This means that each ATP molecule is recycled 500 to 750 times during a single day (100 / 0.2 = 500). ATP cannot be stored, hence its consumption closely follows its synthesis. However a total of around 5 g of ATP is used by cell processes at any time in the body.

Regulation of Biosynthesis

ATP production in an aerobic eukaryotic cell is tightly regulated by allosteric mechanisms, by feedback effects, and by the substrate concentration dependence of individual enzymes within the glycolysis and oxidative phosphorylation pathways. Key control points occur in enzymatic reactions that are so energetically favorable that they are effectively irreversible under physiological conditions.

In glycolysis, hexokinase is directly inhibited by its product, glucose-6-phosphate, and pyruvate kinase is inhibited by ATP itself. The main control point for the glycolytic pathway is phosphofructokinase (PFK), which is allosterically inhibited by high concentrations of ATP and activated by high concentrations of AMP. The inhibition of PFK by ATP is unusual, since ATP is also a substrate in the reaction catalyzed by PFK; the biologically active form of the enzyme is a tetramer that exists in two possible conformations, only one of which binds the second substrate fructose-6-phosphate (F6P). The protein has two binding sites for ATP – the active site is accessible in either protein conformation, but ATP binding to the inhibitor site stabilizes the conformation that binds F6P poorly. A number of other small molecules can compensate for the ATP-induced shift in equilibrium conformation and reactivate PFK, including cyclic AMP, ammonium ions, inorganic phosphate, and fructose-1,6- and -2,6-biphosphate.

The citric acid cycle is regulated mainly by the availability of key substrates, particularly the ratio of NAD^+ to NADH and the concentrations of calcium, inorganic phosphate, ATP, ADP, and AMP. Citrate – the molecule that gives its name to the cycle – is a feedback inhibitor of citrate synthase and also inhibits PFK, providing a direct link between the regulation of the citric acid cycle and glycolysis.

In oxidative phosphorylation, the key control point is the reaction catalyzed

by cytochrome c oxidase, which is regulated by the availability of its substrate – the reduced form of cytochrome c. The amount of reduced cytochrome c available is directly related to the amounts of other substrates:

$$\tfrac{1}{2} NADH + cytc_{ox} + ADP + P_i \rightleftharpoons \tfrac{1}{2} NAD^+ + cytc_{red} + ATP$$

Thus, a high ratio of [NADH] to [NAD^+] or a high ratio of [ADP][P_i] to [ATP] imply a high amount of reduced cytochrome c and a high level of cytochrome c oxidase activity. An additional level of regulation is introduced by the transport rates of ATP and NADH between the mitochondrial matrix and the cytoplasm.

Functions in Cells

Metabolism, Synthesis, and Active Transport

ATP is consumed in the cell by energy-requiring (endergonic) processes and can be generated by energy-releasing (exergonic) processes. In this way ATP transfers energy between spatially separate metabolic reactions. ATP is the main energy source for the majority of cellular functions. This includes the synthesis of macromolecules, including DNA and RNA, and proteins. ATP also plays a critical role in the transport of macromolecules across cell membranes, *e.g.* exocytosis and endocytosis.

Roles in Cell Structure and Locomotion

ATP is critically involved in maintaining cell structure by facilitating assembly and disassembly of elements of the cytoskeleton. In a related process, ATP is required for the shortening of actin and myosin filament crossbridges required for muscle contraction. This latter process is one of the main energy requirements of animals and is essential for locomotion and respiration.

Cell Signaling

Extracellular Signaling

Extracellular ATP (eATP) is also a signalling molecule. ATP, ADP, or adenosine are recognised by purinergic receptors, or purinoreceptors, which might be the most abundant receptors in mammalian tissues.

In humans, this signalling role is important in both the central and peripheral nervous system. Activity-dependent release of ATP from synapses, axons and glia activates purinergic membrane receptors known as P2. The

P2Y receptors are G protein-coupled receptors, which are metabotropic, and primarily modulate intracellular calcium and, to a lesser extent, cyclic AMP levels. Though named between $P2Y_1$ and $P2Y_{15}$, only nine members of the P2Y family have been cloned, and some are only related through weak homology and several ($P2Y_5$, $P2Y_7$, $P2Y_9$, $P2Y_{10}$) do not function as receptors that raise cytosolic calcium. The P2X ionotropic receptor subgroup comprises seven members ($P2X_1$–$P2X_7$), which are ligand-gated Ca2+-permeable ion channels that open when bound to an extracellular purine nucleotide, like ATP. In contrast to P2 receptors (agonist rank order of potency: ATP > ADP > AMP > ADO), purinergic nucleoside triphosphates like ATP are not strong agonists of P1 receptors, which are strongly activated by adenosine and other nucleosides (ADO > AMP > ADP > ATP). P1 receptors have A1, A2a, A2b, and A3 subtypes (the "A" is standard nomenclature for indicating an adenosine receptor subtype), all of which are G protein-coupled receptors, A1 and A3 being coupled to Gi, and A2a and A2b being coupled to Gs. All adenosine receptors were shown to activate at least one subfamily of mitogen-activated protein kinases. The actions of adenosine are often antagonistic or synergistic to the actions of ATP. In the CNS, adenosine has multiple functions, such as modulation of neural development, neuron and glial signalling and the control of innate and adaptive immune systems.

Intracellular Signaling

ATP is critical in signal transduction processes. It is used by kinases as the source of phosphate groups in their phosphate transfer reactions. Kinase activity on substrates such as proteins or membrane lipids are a common form of signal transduction. Phosphorylation of a protein by a kinase can activate a cascade such as the mitogen-activated protein kinase cascade.

ATP is also used by adenylate cyclase most commonly in G protein-coupled receptor signal transduction pathways and is transformed to the second messenger molecule cyclic AMP, which is involved in triggering calcium signals by the release of calcium from intracellular stores. This form of signal transduction is particularly important in brain function, although it is involved in the regulation of a multitude of other cellular processes.

DNA and RNA Synthesis

In all known organisms, the Deoxyribonucleotides that make up DNA are synthesized by the action of ribonucleotide reductase (RNR) enzymes on

their corresponding ribonucleotides. These enzymes reduce the sugar residue from ribose to deoxyribose by removing oxygen from the 22 hydroxyl group; the substrates are ribonucleoside diphosphates and the products deoxyribonucleoside diphosphates (the latter are denoted dADP, dCDP, dGDP, and dUDP respectively.) All ribonucleotide reductase enzymes use a common sulfhydryl radical mechanism reliant on reactive cysteine residues that oxidize to form disulfide bonds in the course of the reaction. RNR enzymes are recycled by reaction with thioredoxin or glutaredoxin.

The regulation of RNR and related enzymes maintains a balance of dNTPs relative to each other and relative to NTPs in the cell. Very low dNTP concentration inhibits DNA synthesis and DNA repair and is lethal to the cell, while an abnormal ratio of dNTPs is mutagenic due to the increased likelihood of the DNA polymerase incorporating the wrong dNTP during DNA synthesis. Regulation of or differential specificity of RNR has been proposed as a mechanism for alterations in the relative sizes of intracellular dNTP pools under cellular stress such as hypoxia.

In the synthesis of the nucleic acid RNA, adenosine derived from ATP is one of the four nucleotides incorporated directly into RNA molecules by RNA polymerases. The energy driving this polymerization comes from cleaving off a pyrophosphate (two phosphate groups). The process is similar in DNA biosynthesis, except that ATP is reduced to the deoxyribonucleotide dATP, before incorporation into DNA.

Amino Acid Activation in Protein Synthesis

Aminoacyl-tRNA synthetase enzymes utilize ATP as an energy source to attach a tRNA molecule to its specific amino acid, forming an aminoacyl-tRNA complex, ready for translation at ribosomes. The energy is made available by ATP hydrolysis to adenosine monophosphate (AMP) as two phosphate groups are removed. Amino acid activation refers to the attachment of an amino acid to its Transfer RNA (tRNA). Aminoacyl transferase binds Adenosine triphosphate (ATP) to amino acid, PP is released. Aminoacyl transferase binds AMP-amino acid to tRNA. The AMP is used in this step.

Amino Acid Activation

During amino acid activation the amino acids (aa) are attached to their corresponding tRNA. The coupling reactions are catalysed by a group of enzymes called aminoacyl-tRNA synthetases (named after the reaction product

aminoacyl-tRNA or aa-tRNA). The coupling reaction proceeds in two steps:

1. aa + ATP $\rightarrow$ aa-AMP + PP_i
2. aa-AMP + tRNA $\rightarrow$ aa-tRNA + AMP

The amino acid is coupled to the penultimate nucleotide at the 32-end of the tRNA (the A in the sequence CCA) via an ester bond (roll over in illustration). The formation of the ester bond conserves a considerable part of the energy from the activation reaction. This stored energy provides the majority of the energy needed for peptide bond formation during translation.

Each of the 20 amino acids are recognized by its specific aminoacyl-tRNA synthetase. The synthetases are usually composed of one to four protein subunits. The enzymes vary considerably in structure although they all perform the same type of reaction by binding ATP, one specific amino acid and its corresponding tRNA.

The specificity of the amino acid activation is as critical for the translational accuracy as the correct matching of the codon with the anticodon. The reason is that the ribosome only sees the anticodon of the tRNA during translation. Thus, the ribosome will not be able to discriminate between tRNAs with the same anticodon but linked to different amino acids. The error frequency of the amino acid activation reaction is approximately 1 in 10000 despite the small structural differences between some of the amino acids.

Binding to Proteins

Some proteins that bind ATP do so in a characteristic protein fold known as the Rossmann fold, which is a general nucleotide-binding structural domain that can also bind the coenzyme NAD. The most common ATP-binding proteins, known as kinases, share a small number of common folds; the protein kinases, the largest kinase superfamily, all share common structural features specialized for ATP binding and phosphate transfer.

ATP in complexes with proteins, in general, requires the presence of a divalent cation, almost always magnesium, which binds to the ATP phosphate groups. The presence of magnesium greatly decreases the dissociation constant of ATP from its protein binding partner without affecting the ability of the enzyme to catalyze its reaction once the ATP has bound. The presence of magnesium ions can serve as a mechanism for kinase regulation.

ATP Analogues

Biochemistry laboratories often use in vitro studies to explore ATP-

dependent molecular processes. Enzyme inhibitors of ATP-dependent enzymes such as kinases are needed to examine the binding sites and transition states involved in ATP-dependent reactions.

ATP analogs are also used in X-ray crystallography to determine a protein structure in complex with ATP, often together with other substrates. Most useful ATP analogs cannot be hydrolyzed as ATP would be; instead they trap the enzyme in a structure closely related to the ATP-bound state. Adenosine 5'–(γ–thiotriphosphate) is an extremely common ATP analog in which one of the gamma-phosphate oxygens is replaced by a sulfur atom; this molecule is hydrolyzed at a dramatically slower rate than ATP itself and functions as an inhibitor of ATP-dependent processes.

In crystallographic studies, hydrolysis transition states are modeled by the bound vanadate ion. However, caution is warranted in interpreting the results of experiments using ATP analogs, since some enzymes can hydrolyze them at appreciable rates at high concentration.

PC OR PHOSPHAGEN SYSTEM

A muscle cell has some amount of ATP floating around that it can use immediately, but not very much — only enough to last for about three seconds. To replenish the ATP levels quickly, muscle cells contain a high-energy phosphate compound called creatine phosphate. The phosphate group is removed from creatine phosphate by an enzyme called creatine kinase, and is transferred to ADP to form ATP. The cell turns ATP into ADP, and the phosphagen rapidly turns the ADP back into ATP. As the muscle continues to work, the creatine phosphate levels begin to decrease. Together, the ATP levels and creatine phosphate levels are called the phosphagen system. The phosphagen system can supply the energy needs of working muscle at a high rate, but only for 8 to 10 seconds.

ANAEROBIC METABOLISM

Glucose, a simple sugar, is the body's primary source of energy. Cells in the body can quickly and efficiently convert glucose to adenosine triphosphate, or ATP — the energy currency that enables all bodily functions to occur. Glucose breaks down to ATP by 2 pathways: aerobic metabolism, which requires oxygen, and anaerobic metabolism, which occurs without oxygen. Exercise can help increase the efficiency of anaerobic metabolism of glucose.

Anaerobic Metabolism of Glucose

Anaerobic metabolism of glucose is a step-wise biochemical process called

glycolysis or fermentation and can be performed by most cells in humans, animals and plants. Glycolysis occurs in the cytosol — the liquid portion of the cell — and produces energy quickly but not that efficiently. The anaerobic breakdown of 1 glucose molecule results in the production of 6 ATP molecules, 2 pyruvic acid molecules and 4 hydrogen ions, according to "Guyton and Hall Textbook of Medical Physiology." By comparison, aerobic metabolism of 1 glucose molecule results in 38 ATP molecules.

Intensity versus Duration

Muscle cells use anaerobic glycolysis to produce ATP very quickly, about 2.5 times faster than aerobic metabolism, enabling powerful bursts of activity. Historically this could fuel "fight or flight" survival activities, such as sprinting from predators or lifting heavy objects. Unfortunately, the intensity, or high power output, of these activities can only be maintained for short periods because of the quick use of the fuel source — glucose — and the production of acidic byproducts. On average, glycolysis can only produce ATP for 30 seconds to 1 minute, although with training this can be increased, according to a 2009 study published in "Sports Medicine." Activities that are sustained for more than 45 minutes increasingly use aerobic metabolism to produce ATP.

Byproducts

The pyruvic acid and hydrogen ions that are produced by anaerobic glycolysis must be managed. Pyruvic acid can undergo 2 different processes: It can enter the mitochondria, where it is further metabolized aerobically, or it can be converted to lactic acid. Conveniently, lactic acid can bind to hydrogen, creating lactate, which can exit the cell and eliminate buildup inside the muscle. Unfortunately, this process does not occur fast enough to balance the production of hydrogen ions by glycolysis, and the muscle cell becomes acidic, creating the burning sensation felt during intense exercise.

Training the Glycolytic System

Anaerobic training is an effort to increase the ability to produce ATP using the glycolytic pathway and to manage its byproducts. According to the American College of Sports Medicine, power training should consist of 30 to 45 seconds of intense exercise, such as weightlifting or sprinting, with 3 to 5 minutes of rest between sets. Individual physical capacity, training status and

target goals should be incorporated into any training regime. Speak to a doctor or personal trainer if you have any concerns about a new exercise regime.

AEROBIC METABOLISM

Aerobic metabolism is a way for your cells to convert fat, carbohydrate and sometimes protein into energy, but only in the presence of oxygen. Aerobic metabolism is slow, so it is useful for sustained activities like jogging or dancing rather than short bursts of effort like sprinting or weightlifting.

Function

Aerobic metabolism converts fat and carbohydrate into units of cellular energy called ATP. Aerobic metabolism is very efficient, producing 34 molecules of ATP from every molecule of glucose, compared to the two ATP molecules anaerobic metabolism generates. Aerobic metabolism is also the only means by which your cells can use fat for fuel, which is part of the reason why aerobic activities like swimming or cycling are such an effective means to lose weight.

Significance

Your body performs aerobic metabolism all day long to provide energy for activities of daily living. Because aerobic metabolism requires water and oxygen, it is the reason that humans breathe constantly and part of the reason why you need to drink water. Carbohydrates are a necessary ingredient for aerobic metabolism — even to burn fat. Because the muscles and liver can only store a limited amount of carbohydrate between meals, aerobic metabolism is also the reason why you need to eat carbohydrates every day. Although your body can metabolize protein for energy in the absence of carbohydrates, it is a slow and inefficient process. Aerobic metabolism in the absence of carbohydrate can only keep up with activities with a very low energy cost, leaving you feeling sluggish.

Effects

Aerobic metabolism produces carbon dioxide and water as byproducts. The extra carbon dioxide production from keeping up with the demands of exercise is what makes you breathe hard when you exercise. According to the American College of Sports Medicine, at their maximum exercise capacity, humans only use 75 percent of the oxygen they inhale, meaning that there is

no shortage of air coming in. Instead, it is the extra carbon dioxide buildup in the blood and the need to expel it that makes you short of breath.

Misconceptions

Activities aren't solely aerobic or anaerobic. In fact, anaerobic metabolism is the first step in aerobic respiration. Both types of metabolism carry on simultaneously in different proportions depending on your effort level. Even as you sit reading, your cells are still performing anaerobic metabolism. The reason that you aren't out of breath at rest is that your cells can easily clear anaerobic metabolism's byproducts as quickly as you produce them.

Time Frame

Aerobic metabolism can only sustain a certain level of activity before it can't process oxygen fast enough to keep up with the cells' demands. Anaerobic metabolism supports any additional activity beyond this point, producing lactic acid as a byproduct. As the Sports Fitness Advisor explains, eventually your body reaches a point where it is producing lactic acid faster than it can clear it, forcing you to slow down. The amount of time it takes for a person to hit that "wall" depends on the intensity of exercise and her individual fitness level.

AEROBIC AND ANAEROBIC SYSTEM DURING REST AND EXERCISE

While most people know that aerobic exercise is good for the heart and that resistance training helps build lean body mass, most people don't fully understand how these different types of exercise elicit very different responses within our bodies. A basic understanding of how our body uses energy during different forms of exercise is critical for designing an effective exercise program. We will focus on energy systems—*i.e.*, how the body utilizes fat, carbohydrate, and protein to produce energy—and how these energy systems are relied upon during different forms of exercise.

This article will give you a better understanding of how your body converts the food you eat into usable energy and how targeting specific energy systems will help you achieve your personal health and fitness goals.

Energy Systems Review

In general, there are three basic energy systems: (1) the phosphagen system

(also referred to as the immediate energy system), (2) the glycolytic energy system (also referred to as the nonoxidative or anaerobic system), and (3) mitochondrial respiration (also referred to as the oxidative or aerobic system).

Regardless of what energy system is used, the end result is the production of adenosine triphosphate (or ATP). ATP is extracted from the food we eat (fat, carbohydrate, and protein) and is required for the biochemical reactions involved in any muscle contraction. The intensity and duration of the activity dictates which foodstuffs are broken down as well as which energy system predominates. It is important to keep in mind, however, that no energy system acts alone.

The relative contribution from each system depends on the intensity and duration of the activity. The Phosphagen or Immediate Energy System The phosphagen system is active during all-out exercise that lasts about 5 to 10 seconds such as a 100-meter dash, diving, jumping, lifting a heavy weight, dashing up a flight of stairs, or any other activity that involves a maximal, short burst of power. This system relies on stored ATP and to a larger extent, creatine phosphate to provide immediate energy. For any maximal intensity exercise lasting longer than 10 seconds, assistance from other sources of energy is required.

Glycolytic Energy or Anaerobic System: The glycolytic energy system (also called glycolysis) involves the partial break down of glucose to a molecule called pyruvate. During this process, a relatively small amount of energy is produced. When oxygen demands exceed the oxygen supply, pyruvate is converted to lactate. Under these circumstances, glycolysis is often referred to as “fast” or “anaerobic” glycolysis. Anaerobic glycolysis is a key contributor to the total energy requirements for moderate to high intensity exercise lasting about one to two minutes. Although this system can provide a rapid source of energy, it is only about half as fast as the phosphagen system.

When there is enough oxygen to meet the oxygen demands of the activity, such as during prolonged light to moderate intensity exercise, glycolysis proceeds much slower and the pyruvate that is formed participates in the formation of additional energy via aerobic processes. In this case, glycolysis is sometimes referred to as “aerobic” or “slow” glycolysis.

We often think of low to moderate intensity aerobic exercise as a good way to burn a significant amount of fat. While this is true, aerobic energy can be derived from carbohydrates and to a much smaller extent, protein. In fact, most people don’t realize that even during light to moderate exercise,

carbohydrates can provide up to 40 to 60 percent of the total energy requirements. (See Table 1.) In contrast, protein is not a preferred source of energy during any form of exercise (assuming an adequate diet) and generally contributes less than 10 percent of the total energy requirements.

Monitoring Your Energy Usage

One of the most effective methods of determining the predominant energy system during a specific form of exercise is by monitoring your heart rate. Heart rate monitoring can help you determine the intensity of your workout as well as estimate the heart rate at which you transition from aerobic to anaerobic exercise (*i.e.*, from carbohydrate and fat usage to predominantly carbohydrate). While the transition point differs from person to person, you can get a general idea of where you transition from aerobic to anaerobic exercise by watching for substantial increases in heart rate, muscle fatigue, or in breathing depth and frequency. If you are truly engaging in anaerobic exercise, you will not be able to sustain the intensity of the exercise for longer than about one to two minutes.

If you notice your intensity dropping off, you were probably performing anaerobic exercise. In contrast, if you are able to sustain your exercise intensity longer than about two minutes, you are probably exercising aerobically. As your fitness improves, you will be able to perform higher intensity exercise for longer periods of time.

Exercise Mode and Energy Usage

Keep in mind that although resistance training doesn't necessarily burn a significant number of calories, it can provide significant health and fitness benefits. Not only does resistance training increase lean body mass (*i.e.*, muscle), which burns more calories than fat even while at rest, engaging in a regular resistance training can have positive effects on elements such as cholesterol, glucose metabolism, and bone density, to name a few.

Circuit Training Circuit training is sometimes considered a type of resistance training, but it is actually a compromise between resistance training and cardiovascular training. Essentially, circuit training can improve muscle endurance as well as provide modest gains in aerobic capacity. Because it is generally a low to moderate intensity workout that is sustained for an hour or more, circuit training is primarily an aerobic activity.

Aerobic Exercise

Walking, Jogging, Traditional Hi-Lo Aerobics, and Step Aerobics

"Aerobic" exercise is typically touted as a great way to burn a lot of fat. While this is not necessarily incorrect, it can be misleading. For example, at about 25 percent of aerobic capacity (*i.e.*, low intensity exercise), fat is the primary source of fuel, but you are not burning a significant number of calories. If your goal is to lose weight, the key consideration is the net deficit in calories, not where the calories come from. As exercise intensity increases, the number of calories burned also increases. Therefore, while it is true that fat contributes a greater percentage of the total energy during lower intensity exercise, at higher intensity exercise, the total quantity of fat utilized may be greater for exercise performed for an equivalent period of time.

So How Does Energy Usage Affect Your Workout?

If you don't have a specific goal in mind, but simply want to improve your overall health, the American College of Sports Medicine recommends moderate intensity physical activity performed for at least 20 to 30 minutes, excluding time spent warming up and cooling down, 3 to 5 times a week. If, on the other hand, you are training for some type of competitive event, make sure that your training program emphasizes the type of activity involved in that event.

For example, if you are training for a triathlon, engaging in a power lifting training program three days a week will not make the best use of your time. You need to actively engage in running, biking, and swimming. Finally, if your goal is to lose weight, caloric deficit is key. You should aim for a caloric deficit of about 500 calories a day through decreased energy intake, increased energy expenditure, or a combination of the two. Although there are numerous types of exercise that are effective for weight loss, a combination of regular aerobic exercise and resistance training is a good place to start.

SHORT DURATION HIGH INTENSITY EXERCISE

After setting your alarm for the fifth time this, and still not getting out of bed early to work out, you realize once again you're not going to workout. Don't give up just yet. With a few minutes of your time, its still possible to increase your heart rate and get your blood pumping.

Lets Get It Started

Before starting your workout, begin with at least a five minute warm up.

Your warm up should include a low intensity cardiovascular activity or activities such as jogging in place, jumping jacks or a light jog. Create a warm up that is specific to your program by using exercises that target specific muscles. An example would be using high knees, butt kicks, or lunges. There are many benefits to warming up including increased blood flow, increased heart rate, and warming up your muscles.

Nothing but the Basics

When you're short on time but still need to work out, grab a jump rope. Try various techniques when jumping rope such as high knees, side to side, and squat jumps. If it has been a while since you have jumped rope, start slowly aiming for 30 seconds. Try and perform as many 30 second sets as you can but, be sure to rest in between. If you don't have access to a jump rope, that's okay jumping jacks will do just fine. For more intense exercises try adding mountain climbers or bear crawls, these full body movements not only get your heart pumping but also work your entire body. Slowly increase your time while decreasing your rest time. A few sets and you'll be sweating in no time.

Go Outside

There are many activities you can do outside, including sprints and running. If you normally run outside, try changing your program. Instead of running long distances all week, use one day to run short distances for time. For example, instead of running a few miles, run one mile as fast as you can run. Sprints can also be added to your program including shuttle runs or running for a specified distance such as 40 yards 10 times. To increase your intensity add pushups in between your sprints.

Plyometrics

Plyometrics have been shown to improve power, strength and endurance. Squat jumps, burpee's, single leg hops, scissors, and box jumps are movements that you can do just about anywhere. For box jumps, use a stair if you don't have access to a box. Before beginning plyometrics be sure to try the movements first in order to practice the technique and form. You may find your heart rate increasing rapidly with these full body movements. Start slowly aiming for five to 10 repetitions, increasing the number once you're able to perform 10 repetitions with resting.

Variety is the Key

Don't be afraid to change your program often. If you're lifting weights, try using these exercises in between sets to increase your heart rate. On a strictly cardio day, aim for at least 25 to 30 minutes, if you don't have enough time, exercise for long as long as you can. Any amount is better than nothing.

HIGH INTENSITY EXERCISE LASTING SEVERAL MINUTES

The oxygen dissociation curve shifted less to the right in venous blood draining from muscle in eight insulin-deficient diabetics working at a constant submaximal workload than in seven normal controls (28.7 mm. Hg vs. 30.8 mm Hg; P less than 0.05). This diminution of the in-vivo Bohr effect at the muscle tissue level during exercise in diabetics was due to a significantly smaller decrease of venous blood pH (down to 7.33 vs. 7.27 in normals; P less than 0.05), probably a consequence of an latered muscle metabolism in insulin deficiency. Although no glucose was taken up, even during exercise, and less lactate was produced by insulin-deficient muscle (P less than 0.05), the differences in venous blood pH appeared to be brought about mainly by a different CO_2 production of the exercising muscle in the two groups. The response of Krebs cycle activity to exercise in insulin-deficient muscle might have been inadequate, as suggested by the increased 3-hydroxybutyrate/ acetoacetate ratio in the venous blood observed in the normal controls but not in the diabetics. Furthermore, proportionally less of the arterial ketone body concentration was utilized by the working muscle in the insulin-deficient diabetics. Changes in erythrocyte 2,3-diphosphoglycerate did not contribute to the differences in the in-vivo Bohr effect.

High Intensity and Long duration Exercise

High Intensity Training (HIT) is a form of strength training popularized in the 1970s by Arthur Jones, the founder of Nautilus. The training focuses on performing quality weight training repetitions to the point of momentary muscular failure. The training takes into account the number of repetitions, the amount of weight, and the amount of time the muscle is exposed to tension in order to maximize the amount of muscle fiber recruitment.

Principles

The fundamental principles of High Intensity Training (HIT) are that

exercise should be brief, infrequent, and intense. Exercises are performed with a high level of effort, or intensity, where it is thought that it will stimulate the body to produce an increase in muscular strength and size. Advocates of HIT believe that this method is superior for strength and size building to most other methods which, for example, may stress lower weights with larger volume (sets x reps).

As strength increases, HIT techniques will have the weight/resistance increased progressively where it is thought that it will provide the muscles with adequate overload to stimulate further improvements. There is an inverse relationship between how intensely and how long one can exercise. As a result, high intensity workouts are generally kept brief. After a High Intensity workout, as with any workout, the body requires time to recover and produce the responses stimulated during the workout, so there is more emphasis on rest and recovery in the HIT philosophy than in most other weight training methods. In any workout, not just HIT, training schedules should allow adequate time between workouts for recovery (and adaptation).

While many typical HIT programs comprise a single-set per exercise, tri-weekly, full-body workout, many variations exist in specific recommendations of set and exercise number, workout routines, volume and frequency of training. The common thread is an emphasis on a high level of effort, relatively brief and infrequent (*i.e.* not daily) training, and the cadence of a lift, which will be very slow compared to a non-HIT weight training routine.

Most HIT advocates stress the use of controlled lifting speeds and strict form, with special attention paid to avoiding any bouncing, jerking, or yanking of the weight or machine movement arm during exercise. Technical HIT advice varies from lifting the weights smoothly and at a natural pace, to timing the lifts, peaking at hold and descent. In extreme cases, it may take up to 30 seconds to complete a single repetition.

Also emphasized when near exhaustion in order to further exhaust the muscle or muscles exercised: doing static holds for periods of time, and negative reps (lowering the weight). This will stimulate further growth and strength because muscles are weakest in positive/contracting movements (sometimes referred to as first stage failure of a muscle). Although you may not be able to lift a weight for another rep you will almost certainly be able to hold it statically for a further period (second stage of failure) and finally lower a weight at a slow controlled speed (third stage of failure). Until all three (lifting, holding and lowering) parts of an exercise can no longer be completed

in a controlled manner a muscle cannot be considered thoroughly exhausted/ exercised.

Controversy

A large number of skeptics dispute the methods and results claimed by HIT advocates. Some of the criticism asserts that HIT violates much conventional "wisdom" in weight training. By always using a weight that one can lift 8-12 times, using 4 second negatives, and so on, it has flown in the face of the exercise establishment.

There exists also a controversy related to the development of HIT and its originality. Near the close of the 19th century, a medical doctor by the name of Gustav Zander developed a complete set of machines and a workout method remarkably close to that promoted by inventor and HIT enthusiast Arthur Jones in the early 1970s. Jones stated:

·So, in attempts to improve my exercise results, I designed and built a total of about twenty very sophisticated exercise machines, then believing that these were the first exercise machines ever built by anybody. But many years later, I learned that a doctor named Gustav Zander had designed and built a number of exercise machines in Europe nearly a hundred years before I built my first one; I did not copy Zander's work and learned nothing from him, was not even aware of his work until long after I had made the same discoveries that he had made. But if I had known about, and understood, Zander's work, it would have saved me a lot of time and a rather large fortune in money, because the man was a genius; his only problem was that he lived about a century ahead of his time, at a time when very few people cared about exercise and even fewer knew anything about it.

Regardless of who originally developed the systems (and machines) it is clear that through Arthur Jones and his company and a crew of HIT advocates, the principles and concepts of HIT became popularized.

HIT and other Training Routines

HIT will target a single body part with one or two exercises, and generally a single set of 6-10 reps for upper body exercises and either 8-15 or more commonly 12-20 reps for lower body exercises, done to momentary muscular failure. Deadlifts usually have a rep range of 1-5 reps.

Cadence for a HIT workout is supposed to be smooth, but not always Super Slow. A standard HIT cadence is usually 3-1-4-1. For clarity, here are two

examples of how the cadence would be for an exercise. On the Lat Pulldown exercise the cadence is as follows : 3 seconds pulling down (Positive movement), followed by a 1-second pause and squeeze (at full contraction), followed by a 4-second return (Negative movement), followed by a 1-second rest. This completes 1 rep.

On the Barbell Squat the cadence is as follows: 4 seconds lowering the bar (the Negative movement), followed by a 1-second pause (at the bottom), followed by 3 seconds raising up the bar (the Positive movement), followed by a 1-second rest at the top. This completes 1 rep.

HIT stresses intensity over repetition. Many weightlifters will use a HIT routine to help break a 'plateau' - meaning they will use HIT temporarily when another routine stops giving desired results. Some HIT trainees will use HIT exclusively as well - Arthur Jones believed HIT was all that was required.

Different strength training authors from Ellington Darden and Mike Mentzer to Dorian Yates and Gordon LaVelle have called their system HIT, with each individual having credited Arthur Jones for the formulation of its basic tenet principles. However, there has never been a clear and consistent guideline on how to utilize HIT. Darden advocated full body routines, while Yates recommended to split the workouts into four different sessions a week. Mentzer believed that no more than one set to muscular failure per body part was all that was required, yet Yates and LaVelle believed that more than one exercise per body part is necessary to get complete development as a bodybuilder.

Rest-pause

A former Mr. Universe, the late Mike Mentzer achieved his lifetime best condition from performing rest-pause, an old system of lifting involving single-rep maxima interspersed with brief (10 second) rest periods. Rest-pause has the advantages of old-school power training while also allowing for enough overall reps to be performed for hypertrophy and cardiovascular exercise purposes.

High-intensity Interval training

High-intensity interval training (HIIT), also called high-intensity intermittent exercise (HIIE) or sprint interval training (SIT), is a form of interval training, a cardiovascular exercise strategy alternating short periods of intense anaerobic exercise with less intense recovery periods. HIIT is the

concept where one performs a short burst of high-intensity (or max-intensity) exercise followed by a brief low-intensity activity, repeatedly, until too exhausted to continue. Though there is no universal HIIT session duration, these intense workouts typically last under 30 minutes, with times varying based on a participant's current fitness level.

HIIT workouts provide improved athletic capacity and condition as well as improved glucose metabolism. Compared with other regimens, HIIT may not be as effective for treating hyperlipidemia and obesity, or improving muscle and bone mass. However, research has shown that HIIT regimens successfully produced significant reductions in the fat mass of the whole-body. Some researchers also note that HIIT requires "an extremely high level of subject motivation" and question whether the general population could safely or practically tolerate the extreme nature of the exercise regimen.

Procedure

High-intensity interval training can be described as an exercise session composed entirely of HIIT techniques, or as a component of an exercise plan. HIIT exercise sessions generally consist of a warm up period, then several repetitions of high-intensity exercise separated by medium intensity exercise for recovery, then a cool down period. The high-intensity exercise should be done at near maximum intensity. The medium exercise should be about 50% intensity. The number of repetitions and length of each depends on the exercise, but may be as little as three repetitions with just 20 seconds of intense exercise The specific exercises performed during the high-intensity portions vary.

There is no specific formula to HIIT. Depending on one's level of cardiovascular development, the moderate-level intensity can be as slow as walking. A common formula involves a 2 :1 ratio of work to recovery periods, for example, 30–40 seconds of hard sprinting alternated with 15–20 seconds of jogging or walking.

The entire HIIT session may last between four and thirty minutes, meaning that it is considered to be an excellent way to maximize a workout that is limited on time. Use of a clock or timer is recommended to keep accurate times, the number of rounds, and intensity.

Branch

Peter Coe Regimen

A type of high-intensity interval training with short recovery periods was

used in the 1970s by the athletics coach Peter Coe when setting sessions for his son Sebastian Coe. Inspired by the principles propounded by the German coach and university professor Woldemar Gerschler and the Swedish physiologist Per-Olof Åstrand, Coe set sessions involving repeated fast 200 metre runs with only 30 seconds recovery between each fast run.

Tabata regimen

A version of HIIT was based on a 1996 study by Professor Izumi Tabata *et al.* initially involving Olympic speedskaters. The study used 20 seconds of ultra-intense exercise (at an intensity of about 170% of VO_2max) followed by 10 seconds of rest, repeated continuously for 4 minutes (8 cycles). The exercise was performed on a mechanically braked cycle ergometer. Tabata called this the IE1 protocol. In the original study, athletes using this method trained 4 times per week, plus another day of steady-state training, and obtained gains similar to a group of athletes who did steady state training (70% VO_{2max}) 5 times per week. The steady state group had a higher VO_2max at the end (from 52 to 57 mL/(kg•min)), but the Tabata group had started lower and gained more overall (from 48 to 55 mL/(kg•min)). Also, only the Tabata group had gained anaerobic capacity benefits. It is important to note that in the original study from 1996, participants were disqualified if they could not keep a steady cycling pace of 85RPM for the full 20 seconds of work.

In popular culture, "Tabata training" has now come to refer to a wide variety of HIIT protocols and exercise regimens that may or may not have similar benefits to those found in Tabata's original study.

Gibala Regimen

Professor Martin Gibala and his team at McMaster University in Canada have been researching high-intensity exercise for several years. Their 2010 study on students uses 3 minutes for warming up, then 60 seconds of intense exercise (at 95% of VO_2max) followed by 75 seconds of rest, repeated for 8–12 cycles (sometimes referred to as "The Little Method"). Subjects using this method training 3 times per week obtained gains similar to what would be expected from subjects who did steady state (50–70% VO_2max) training five times per week. While still a demanding form of training, this exercise protocol could be used by the general public with nothing more than an average exercise bike.

Gibala's group published a less intense version of their regimen in a 2011 paper in Medicine & Science in Sports & Exercise. This was intended as a gentler option for sedentary people who had done no exercise for over a year. It included 3 minutes of warm-up, 10 repetitions of 60-second bursts at 60% peak power (80–95% of heart rate reserve) each followed by 60 seconds of recovery, and then a 5-minute cool-down.

Zuniga Regimen

Jorge Zuniga, assistant professor of exercise science at Creighton University, set out to determine how to fit the highest volume of work and oxygen consumption into the smallest amount of time. He found that intervals of 30 seconds at 90% of maximum power output followed by 30 seconds of rest allowed for the highest VO_2 consumption and the longest workout duration at specified intensity. Alternative protocols considered included 100% of maximum power output on the same interval schedule, similar to the Coe regimen, and 90% of maximum power output for three minutes, similar to traditional interval training.

Zuniga's protocol has been implemented to great success by his students participating in Creighton's Army ROTC program. Cadets completing the protocol twice a week saw greater improvements in APFT scores than in years past.

Vollaard Regimen

Dr Niels Vollaard at the University of Stirling proposed that when high-intensity intervals are done at 'all-out' intensities, associated health benefits plateau after performing 2 or 3 sprint repetitions. This led to the development of a 10-minute exercise routine consisting of easy pedalling interspersed with two 20-second 'all-out' cycling sprints. In a 2017 meta-analysis, Vollaard indeed showed that common protocols with as many as 6 to 10 repetitions of 30-second 'all-out' sprints do not improve aerobic fitness more than the '2x20-s' protocol. It is claimed that this short protocol may remove many of the drawbacks that make other high-intensity interval training protocols unsuitable for the general population.

In a BBC Horizon programme in February 2012, Jamie Timmons, professor of systems biology at the University of Loughborough, put Michael Mosley through this exercise bike regimen, but with three sprints instead of two. This was done three times a week for a total of 30 minutes of exercise per week (3 minutes of intense exercise), plus warm-up and recovery time.

Regimen Comparison

Wood *et al.* compared High-intensity interval training of eight 1-minute bouts at 85% Wmax interspersed with a 1-minute active recovery at 25% Wmax v Sprint interval training of eight 30-second bouts at 130% Wmax interspersed with 90-second active recovery at 25% Wmax. (Total time matched at 24 mins including warm up and cool down). Their conclusion was "HIIT is the recommended routine" but "the magnitude of differences in various parameters between regimens was small; therefore, preference for either modality may be up to the individual".

Health Effects

Cardiovascular Fitness

A 2015 systematic review and meta-analysis of randomized controlled trials found that HIIT training and traditional endurance training both lead to significantly improved cardiovascular fitness in healthy adults ages 18–45 but greater improvements in VO_2 max were seen in those participating in the HIIT exercise regimen. Another analysis also found that HIIT regimens of one month or longer effectively improve cardiovascular fitness in adolescents and lead to moderate improvements in body composition. Furthermore, a separate systematic review and meta-analysis of seven small randomized controlled trials found that HIIT (defined as four intervals of four minutes at 85–95% of max heart rate with three-minute intervals at 60–70% of max heart rate) was more effective than moderate-intensity continuous training at improving blood vessel function and markers of blood vessel health.

- ***Cardiovascular disease:*** A 2015 meta-analysis comparing HIIT to moderate intensity continuous training (MICT) in people with coronary artery disease found that HIIT leads to greater improvements in VO_2 max but that MICT leads to greater reductions in body weight and heart rate. A 2014 meta-analysis found that the cardiorespiratory fitness, as measured by VO_2 max, of individuals with lifestyle-induced chronic cardiovascular or metabolic diseases (including high blood pressure, obesity, heart failure, coronary artery disease, or metabolic syndrome) who completed a HIIT exercise program was nearly double that of individuals who completed a MICT exercise program.

Metabolic Effects

HIIT significantly lowers insulin resistance compared to continuous training or control conditions and leads to modestly decreased fasting blood glucose levels and increased weight loss compared to those who do not undergo a physical activity intervention.

LONG DURATION EXERCISE

Concordant with the functional roles of the brain structures that exhibit increased gray matter volumes, regular exercise over a period of several months has been shown to persistently improve numerous executive functions and several forms of memory. In particular, consistent aerobic exercise has been shown to improve attentional control, information processing speed, cognitive flexibility (*e.g.*, task switching), inhibitory control, working memory updating and capacity, declarative memory, and spatial memory. In healthy young and middle-aged adults, the effect sizes of improvements in cognitive function are largest for indices of executive functions and small to moderate for aspects of memory and information processing speed. It may be that in older adults, individuals benefit cognitively by taking part in both aerobic and resistance type exercise of at least moderate intensity. Individuals who have a sedentary lifestyle tend to have impaired executive functions relative to other more physically active non-exercisers. A reciprocal relationship between exercise and executive functions has also been noted: improvements in executive control processes, such as attentional control and inhibitory control, increase an individual's tendency to exercise.