

Physiological effects of exercise

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The physiological response to exercise is dependent on the intensity, duration and frequency of the exercise as well as the environmental conditions. During physical exercise, requirements for oxygen and substrate in skeletal muscle are increased, as are the removal of metabolites and carbon dioxide. Chemical, mechanical and thermal stimuli affect alterations in metabolic, cardiovascular and ventilatory function in order to meet these increased demands.

Immediate energy sources

Adenosine triphosphate

Adenosine triphosphate (ATP) is the common chemical intermediate that provides energy for all forms of biological work and is essential for muscle contraction. Some enzymes (ATPase) are able to use the energy stored in the bond between adenosine diphosphate (ADP) and inorganic phosphate (P_i). As water is involved this is called hydrolysis.



Each mole of ATP releases 7.3 kcal (30.7 kJ), and a small amount of ATP is stored in the muscle. If enough ATP was stored to fuel daily resting metabolism, it would amount to more than half of an individual's body mass. Therefore it is essential that ATP can be resynthesized rapidly from energy-dense molecules, and, at rest, the ATP requirement of muscles is readily supplied from the oxidative metabolism of glucose and fatty acids. However, at the onset of exercise there is an immediate requirement for increased supply of energy and there is only enough ATP stored for 1–2 seconds of work and therefore rapid ways to resynthesize ATP are required.

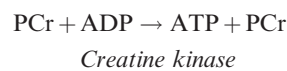
The adenylate kinase reaction

One alternative source is the adenylate kinase reaction, which results in ATP production from the conversion of two molecules of adenosine diphosphate (ADP) to adenosine monophosphate (AMP) and ATP. However, of

greater quantitative importance is the utilization of phosphocreatine stored in the muscle.

Phosphocreatine system

Phosphocreatine (PCr) is another high-energy compound containing a high-energy phosphate bond that can be hydrolysed to provide energy and resynthesize ATP:



Skeletal muscle stores of PCr provide quantitatively the greatest contribution to energy provision in the first 10 s of high intensity activities such as sprinting. PCr stores are rapidly depleted but they provide an important buffer in the first few seconds of exercise before other aspects of metabolism are activated.

Resynthesis of ATP from energy-dense substrates

Glycolysis

Glycolysis is the pathway by which glycogen and glucose are converted to two pyruvate molecules. In the presence of oxygen, pyruvate enters the Krebs cycle via acetyl CoA. Each turn of the Krebs cycle produces hydrogen carriers that enter the electron transport chain (ETC) and ultimately donate H^+ to oxygen to form water, allowing the ETC to proceed. However, when oxygen is not present, the ETC cannot proceed which prevents flux through the Krebs cycle and results in a build up of pyruvate. If this was allowed to continue then glycolysis would stop and no further ATP would be resynthesized. Fortunately, pyruvate can accept the hydrogen carrier, forming lactic acid via lactate dehydrogenase (LDH). The conversion of glycogen to lactic acid yields only 3 mol ATP per molecule of glycogen, but this can occur in the absence of oxygen and the maximum rate of glycolysis can be reached within a few seconds of the onset of exercise. In contrast, complete breakdown of glycogen via glycolysis, the Krebs cycle and the ETC yields 39 ATP per molecule of glycogen.

Key points

Adenosine triphosphate (ATP) is the principal high-energy phosphate molecule that enables muscle contraction.

Energy supplies to muscle are initially provided from the immediate energy sources of ATP and phosphocreatine before other aspects of metabolism are activated.

Muscle fibres are classified as type I, type IIa and type IIb fibres.

Pulmonary ventilation increases because of a rise in tidal volume and respiratory rate to meet increased oxygen demands.

Oxygen delivery during strenuous exercise is limited by cardiovascular function.

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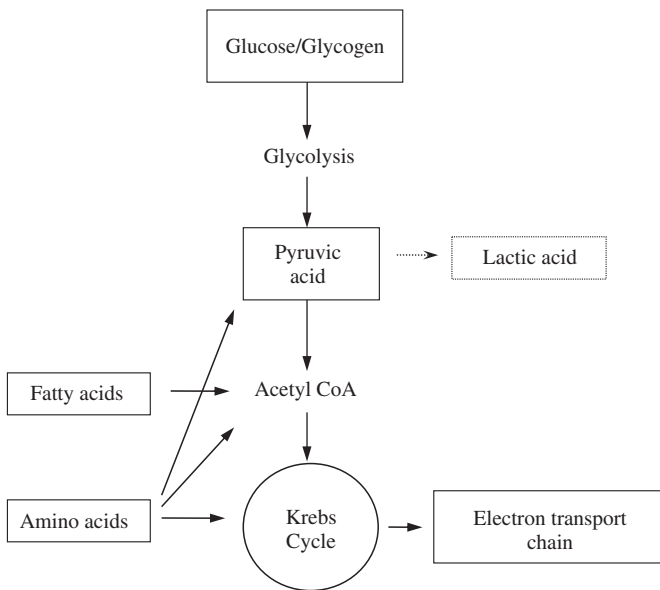


Fig. 1 An overview of substrate metabolism.

Fat metabolism

Fatty acids are more energy dense than glycogen and there are very large stores of fat in adipose tissue. In fact, if all of the energy stored as fat were stored as glycogen, body mass would increase by ~50 kg. Fatty acids are catabolized via β -oxidation and then entry to the Krebs cycle and the ETC. If it is fully oxidized a typical fat (palmitate) yields 129 molecules of ATP. Given that stores of fat in the body are so vast, they would allow exercise at a maximal intensity (i.e. sprinting) to continue for >1 h. However, the rate of ATP resynthesis from fat is too slow to be of great importance during high intensity activity. Therefore, although fat is the preferred substrate and dominates the energy contribution to resting metabolism, carbohydrate stores are available when energy requirements increase, for example at the onset of exercise. As exercise continues, however, fat metabolism may become more important, particularly if muscle glycogen stores become depleted.

Traditionally, protein is not considered to contribute to energy provision except under conditions of starvation or in ultra-endurance events. This is unsurprising on the basis that most of the protein in the body is functional in nature, for example contractile proteins in skeletal muscle.

Muscle types

Muscle fibres can be classified as type I, type IIa and type IIb fibres. Characteristics of type I (slow twitch) and type IIb (fast twitch) fibres are summarized in Table 1. The proportion of type I and type II fibres varies in different muscles, with greater proportions of type I fibres in postural muscles. Type I fibres are more suited to prolonged activity as they are more efficient than type II fibres and have a greater reliance on oxidative metabolism of fatty acids and glycogen. Therefore, during prolonged, low intensity

Table 1 Characteristics of Type I and II muscles

Characteristic	Type I	Type II
Time to peak tension	~110 ms	~50 ms
Macroscopic colour	Red	White
Capillary supply	High	Low
Main energy system	Aerobic	Anaerobic
Myoglobin levels	High	Low
Number of mitochondria	High	Low
Oxidative enzymes levels	High	Low
Resistance to fatigue	Low	High
Type of exercise suited	Endurance/long-distance runner	High intensity/sprinter

activity, type I fibres will be recruited. However, as the force required increases, larger type II fibres are recruited. If the speed of contraction is rapid, only type II fibres can contribute to force generation since type I fibres cannot produce force at as fast a rate as type II fibres. There are hereditary differences in the proportion of each type of fibre in a given muscle, which determine to some degree the athletic capabilities of the individual. For example, some people appear to be more suited to marathon running (type I predominant) whereas others are born to sprint and jump (type II predominant).

Respiratory system

During exercise, ventilation might increase from resting values of around 5–6 litre min^{-1} to >100 litre min^{-1} . Ventilation increases linearly with increases in work rate at submaximal exercise intensities. Oxygen consumption also increases linearly with increasing work rate at submaximal intensities. In an average young male, resting oxygen consumption is about 250 ml min^{-1} and in an endurance athlete oxygen consumption during very high intensity exercise might reach 5000 ml min^{-1} . The increase in pulmonary ventilation is attributable to a combination of increases in tidal volume and respiratory rate and closely matches the increase in oxygen uptake and carbon dioxide output. Breathing capacity, however, does not reach its maximum even during strenuous exercise and it is not responsible for the limitation in oxygen delivery to muscles seen during high intensity activity. Haemoglobin continues to be fully saturated with oxygen throughout exercise in people with normal respiratory function.

Changes in arterial blood gases

The changes which occur in arterial pH, P_{O_2} and P_{CO_2} values during exercise are usually small. Arterial P_{O_2} often rises slightly because of hyperventilation although it may eventually fall at high work rates. During vigorous exercise, when sufficient oxygen for flux through the Krebs cycle is not available, the increased reliance on glycolysis results in increased accumulation of lactic acid, which initially leads to an increase in $P_{a_{CO_2}}$. However, this is counteracted by the stimulation of ventilation and as a result $P_{a_{CO_2}}$ is decreased. This provides some respiratory compensation for

further lactic acid production and prevents a decline in blood pH, which remains nearly constant during moderate exercise.

Changes in ventilation

Ventilation increases abruptly in the initial stages of exercise and is then followed by a more gradual increase. The rapid rise in ventilation at the onset of exercise is thought to be attributable to motor centre activity and afferent impulses from proprioceptors of the limbs, joints and muscles. The mechanism of stimulation following this first stage is not completely understood. Arterial oxygen and carbon dioxide tensions are not sufficiently abnormal to stimulate respiration during exercise. Suggestions have been made that the sensitivity of peripheral chemoreceptors to oscillations in $P_{a_{O_2}}$ and $P_{a_{CO_2}}$ is responsible for increasing ventilation, even though the absolute values remain stable. Central chemoreceptors may be readjusted to increase ventilation to maintain carbon dioxide concentrations. Other theories are that the rise in body temperature may play a role, or that collateral branches of neurogenic impulses from the motor cortex to active muscles and joints may stimulate the brain stem and respiratory centre leading to hyperpnoea. Overall, a number of factors have been suggested for the increase in ventilation, which occurs with exercise. The respiratory rate might remain elevated after heavy exercise for up to 1–2 h.

Cardiovascular system

Substrate and oxygen requirements of working skeletal muscles are dramatically elevated above resting requirements. Resting blood flow to muscle is usually $2\text{--}4\text{ ml} \cdot 100\text{ g muscle}^{-1}\text{ min}^{-1}$, but might increase to nearly $100\text{ ml} \cdot 100\text{ g muscle}^{-1}\text{ min}^{-1}$ during maximal exercise. This occurs in part because of vasodilatory metabolites such as AMP, adenosine, H^+ , K^+ and PO_4^{3-} acting on pre-capillary sphincters, which override the vasoconstrictor effects of norepinephrine. In addition, decreased pH and increased temperature shift the oxygen dissociation curve for haemoglobin to the right in exercising muscle. This assists in unloading more oxygen from the blood into the muscle. During muscular contraction, blood flow is restricted briefly but overall it is enhanced by the pumping action of the muscle.

Whilst muscle and coronary blood flow increase, cerebral blood flow is maintained constant and splanchnic flow diminishes. However, essential organs such as the bowel and kidneys must be protected with some blood flow maintained. An additional demand on blood flow during exercise is the requirement to increase skin blood flow in order to enable heat dissipation.

Circulatory changes

The increase in blood flow to muscles requires an increase in the cardiac output, which is in direct proportion to the increase in oxygen consumption. The cardiac output is increased by both a rise in the heart rate and the stroke volume attributable to a more complete emptying of the heart by a forcible systolic contraction.

Table 2 Comparison of cardiac function between athletes and non-athletes

	Stroke volume (ml)	Heart rate (beats min^{-1})
At rest		
Non-athlete	70	70
Trained athlete	100	50
Maximum exercise		
Non-athlete	110	190
Trained athlete	160	180

These chronotropic and inotropic effects on the heart are brought about by stimulation from the noradrenergic sympathetic nervous system. The increase in heart rate is also mediated by vagal inhibition and is sustained by autonomic sympathetic responses and carbon dioxide acting on the medulla.

The efficacy of systolic contraction is particularly important in trained athletes who can achieve significant increases in cardiac output as a consequence of hypertrophy of cardiac muscle. Table 2 shows that increased maximal cardiac output in endurance trained athletes is a function of greater stroke volume rather than an increase in maximal heart rate, which is, in fact, lower in these athletes.

Heart rate and stroke volume increase to about 90% of their maximum values during strenuous exercise and cardiovascular function is the limiting factor for oxygen delivery to the tissues. Oxygen utilization by the body can never be more than the rate at which the cardiovascular system can transport oxygen to the tissues. There is only a moderate increase in blood pressure secondary to the rise in cardiac output. This is caused by stretching of the walls of the arterioles and vasodilatation, which in combination reduce overall peripheral vascular resistance. There is a large increase in venous return as a consequence of muscular contraction, blood diversion from the viscera and vasoconstriction.

Maximum oxygen consumption

As work rate is increased, oxygen uptake increases linearly. However, there is an upper limit to oxygen uptake and, therefore, above a certain work rate oxygen consumption reaches a plateau. This is termed the maximal oxygen uptake ($\dot{V}O_{2\text{max}}$). A considerable amount of research has focused on the factors that limit $\dot{V}O_{2\text{max}}$.

The pulmonary system

Pulmonary limitations to $\dot{V}O_{2\text{max}}$ are evident in some situations, such as when exercising at high altitudes and in individuals with asthma or other types of chronic obstructive pulmonary disease. However, in most individuals exercising at sea level the lungs perform their role of saturating arterial blood with oxygen extremely effectively as described previously.

Cardiac output

As described previously, endurance training results in increased cardiac output through increased stroke volume.

This is considered to be a very important factor determining $\dot{V}O_{2\max}$ in the normal range of $\dot{V}O_{2\max}$ values. In addition, β -blockade reduces cardiac output and results in a concomitant reduction in $\dot{V}O_{2\max}$. During maximal exercise, almost all of the available oxygen in the blood is extracted by skeletal muscle, and for this reason it appears that delivery of oxygen through increased blood flow is the most important factor limiting $\dot{V}O_{2\max}$.

Oxygen carrying capacity of the blood

A reduction in the oxygen carrying capacity in conditions such as anaemia produces fatigue and shortness of breath on mild exertion. Some athletes have tried to increase red blood cell levels by removing, storing and then reinfusing them. This method of 'blood doping' has been shown to improve $\dot{V}O_{2\max}$ by up to 10%. More recently, there has been evidence of erythropoietin abuse in sport in order to increase red blood cell levels. The improvements in $\dot{V}O_{2\max}$ observed when employing these methods provide good evidence that oxygen delivery is a limiting factor for $\dot{V}O_{2\max}$.

Skeletal muscle limitations

The factors listed above can be considered as 'central' factors in the same way that potential limitations in the skeletal muscle are considered 'peripheral' factors limiting $\dot{V}O_{2\max}$. Peripheral factors include properties of skeletal muscle such as levels of mitochondrial enzymes and capillary density. As mitochondria are the sites of oxygen consumption (in the final stage of the ETC), doubling the number of mitochondria should double oxygen uptake in the muscle. However, this is not the case, suggesting that the number of mitochondria are not limiting to $\dot{V}O_{2\max}$. Capillary density is known to increase with endurance training, with the effect of increasing transit time of blood through the muscle, and improving oxygen extraction from the muscle. It has been suggested that there is a relationship between capillary density and $\dot{V}O_{2\max}$.

In summary, a reduction in any of the factors involved in the delivery and utilization of oxygen will decrease $\dot{V}O_{2\max}$. However, in healthy individuals carrying out whole-body maximal exercise

at sea level, the ability of the cardiorespiratory system to deliver oxygen to the working muscles rather than the ability of the muscles to consume the oxygen is limiting.

Body temperature

The maximum efficiency for the conversion of energy nutrients into muscular work is 20–25%. The remainder is released in a non-usable form as heat energy, which raises the body temperature. In order to dissipate the extra heat generated as a result of increased metabolism during exercise, blood supply to the skin must be increased. This is achieved with vasodilatation of cutaneous vessels by inhibition of the vasoconstrictor tone. Evaporation of sweat is also a major pathway for heat loss and further heat is lost in the expired air with ventilation.

The hypothalamus is responsible for thermoregulation and it is important that this process is effective. However, during exercise in hot, humid conditions evaporative heat loss through sweating might not be able to remove sufficient heat from the body. Regulation of body temperature may fail and temperatures may be high enough to cause heat stroke. This presents with symptoms of extreme weakness, exhaustion, headache, dizziness eventually leading to collapse and unconsciousness.

Key references

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See multiple choice questions 136–138.