Occasional article

Chemistry of marathon running

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Introduction

The upsurge of interest in the beneficial effects of exercise and participation in endurance events like marathon running, which started in the early 1980's, has been maintained, and the 22000 competitors who completed the 1989 London Marathon bear witness to the continuing involvement of a mass of ordinary men and women. Most who train and compete regularly undergo adaptive physiological changes, with improved physical fitness and benefits to long term health. For a few, rigorous exercise is not without its hazards to health.

This review briefly and selectively outlines the normal physiological responses, together with adverse pathological effects and their clinical consequences where appropriate.

General metabolism

The ability of a person to become a high performance, endurance athlete is inherited and is due primarily to the predominance of slow twitch fibres in skeletal muscle—unlike sprinters and jumpers who have a higher proportion of fast twitch fibres.

Slow twitch fibres have a low contractile speed, producing minimal but highly efficient force with low fatiguability. This is largely due to their low myosin adenosine triphosphatase content and the poor affinity of troponin for calcium. They have more capillaries, more mitochondria and greater oxidative capacity, more myoglobin and less glycogen than fast twitch fibres. Slow fibres, therefore, have a greater capacity to produce energy for long periods using aerobic metabolism, being less efficient under anaerobic conditions.¹

Regular aerobic exercise, which involves a progressive increase in cardiorespiratory and muscle activity, induces physiological changes which enable peak

performance to be reached. Intensive training increases the maximal cardiac output and blood volume of skeletal muscles, and by conditioning, increases the mitochondrial density, oxidative enzymes, and myoglobin in muscle cells. These adaptations combine to raise the maximal total body oxygen consumption ($\text{VO}_2 \text{ max}$), thus enabling greater workloads to be tolerated with a consequent improvement in endurance.²

During aerobic metabolism, intracellular muscle glycogen and triglyceride with extracellular glucose and free fatty acids (FFA) are oxidised to provide energy. As glycogen stores become depleted during prolonged exercise the relative contribution from FFA increases, and this ability to oxidise FFA at any intensity of exercise is an important adaptation of training. If tissue oxygenation becomes inadequate, anaerobic glycolysis occurs with the production of lactate.

During a marathon race, muscle glycogen stores become depleted at around 20 miles, fatigue occurs, and poorly prepared runners experience a state of exhaustion referred to as "hitting the wall". Whether this state is experienced depends on the degree of fitness, the intensity of exertion, the degree of hydration and the initial level of muscle glycogen. FFA become the major energy source and performance progressively deteriorates.

Many factors may contribute to exhaustion and fatigue. The untrained athlete is more likely to suffer from ketosis after exercise, and the increased production of pyruvate, acetoacetate, and 3-hydroxybutyrate can exert an antilipolytic and hypoglycaemic effect in high concentrations. The concentration of serum lactate is higher in this group in contrast to the conditioned athlete who shows a minimal increase. This is probably due to enhanced metabolism of lactate, either by muscle oxidation or hepatic gluconeogenesis.³ Hypoglycaemia can occur in endurance events lasting more than four hours and the untrained person is more susceptible,⁴ but its presence does not

necessarily limit endurance if FFA are readily available.

To prevent or delay collapse from exhaustion the amount of stored muscle glycogen can be increased by dietary manipulation before the race. This is referred to as "carbohydrate loading". It involves depletion of muscle glycogen before the race by a combination of exercise and a diet high in protein and fat, but low in carbohydrate for three days. This is followed by a diet high in complex carbohydrates, forming 80% of the total calorie consumption for a similar period before the event. Glycogenesis is stimulated and glycogen in the leg muscles can be doubled compared with that obtained on a mixed conventional diet. This manoeuvre significantly increases the time exercise can be maintained, improving endurance, and delaying the onset of fatigue.⁵ Carbohydrate loading, which in an average man involves the storage of 700 g of glycogen, requires 2 litres of water for intracellular storage which may, incidentally, delay the effects of dehydration. Caffeine taken as strong coffee before a race, by stimulating lipolysis and release of FFA, has a glycogen sparing action and contributes to better endurance.

Lipoproteins, atherosclerosis, and ischaemic heart disease

Investigations to assess the effect of endurance exercise on serum lipoproteins have shown variable and inconsistent results. The weight of evidence indicates that serum triglyceride (TGL), total and low density lipoprotein cholesterol (LDL-C) are reduced and that high density lipoprotein cholesterol (HDL-C) is increased. Many studies have been inconclusive due to the difficulty of determining whether these changes are directly attributable to exercise, rather than a change in lifestyle which incorporates healthy eating with a reduced fat intake, reduction in obesity, and abstinence from tobacco and alcohol.²

When compared with sedentary people, endurance runners, skiers, and cyclists are able to maintain significantly lower LDL-C and TGL and higher HDL-C serum concentrations. It is also evident that those at risk from premature ischaemic heart disease who have high TGL, LDL-C and low HDL-C concentrations benefit favourably from regular exercise, thereby reducing the risk.⁶

The mechanisms for the change in serum lipid profile remain undetermined. Attention has focused on the induction of higher activities of lipolytic enzymes such as lipoprotein lipase in muscle and adipose tissue after exercise, but similar changes occur with weight loss alone, which is also associated with an increase in HDL-C. It might be anticipated that a sustained reduction in LDL-C associated with an

increase in HDL-C through exercise conditioning would help to delay the development of ischaemic heart disease and premature coronary thrombosis.

Although various studies in several species of animals indicate that the development of atherosclerosis is reduced by regular exercise, it remains speculative whether it is beneficial in man in the primary prevention of ischaemic heart disease.⁷ Epidemiological studies have failed to provide conclusive proof that regular aerobic exercise offers protection from the morbidity and mortality associated with ischaemic heart disease because of the difficulty of long term projects in controlling the multiple risk factors involved. Nevertheless, there are several reports^{8,9} covering a variety of sports where a reduced incidence of ischaemic heart disease has been observed with improved longevity in athletes who regularly participate. Life expectancy may be increased by up to three years, but to achieve this it has been estimated that a comparable time would have to be dedicated to exercise! This would involve running or jogging 20 miles a week with an energy expenditure of 2000 kilocal on a regular basis, indefinitely.

Sudden death and myocardial infarction

Sudden death during or while recovering from strenuous exercise is rare. Participation during the incubation period of a viral illness can aggravate and cause death from myocarditis. Most reported cases are due to cardiac arrhythmias secondary to underlying coronary artery disease. Myocardial ischaemia in the face of an increased oxygen demand predisposes to ventricular fibrillation. The only practical screening procedure to detect ischaemic heart disease before regular high level exercise is undertaken is electrocardiography, but the high incidence of abnormal tracings in 10% of well trained but otherwise normal athletes makes interpretation very difficult.

Bundle branch block, pseudo-ischaemic T waves, an increase in ST-segment and postero-inferior ischaemic patterns are not unusual,¹⁰ but the development of coronary thrombosis, which depends on the presence of pre-existing atherosclerosis, is unpredictable. It also requires the presence of a hypercoagulable state, which may be stimulated by physical stress or exercising in conditions of extreme heat and humidity.

The diagnosis of myocardial infarction in a "collapsed" runner with an abnormal ECG can cause diagnostic problems. The increased activity in serum "cardiac enzymes" may be difficult to interpret as severe exercise results in significant increases of creatine kinase (CK), lactate dehydrogenase, aspartate, and alanine aminotransferase activities which are released from skeletal muscle.¹¹ Increased muscle cell membrane permeability can be induced by hypoxia,

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dehydration, hyperpyrexia, ionic and pH changes.

After a marathon, serum total CK activity, which is predominantly due to release of the MM isoenzyme from muscle, and its normally undetectable "heart specific" isoenzyme CK-MB, are increased, becoming maximal 24 hours later. The percentage of CK-MB to total CK activity has been observed to vary between 1%–18%. Values greater than 6% are usually associated with myocardial infarction, but after strenuous exercise the measurement of CK-MB can be misleading.¹² Although long regarded as a sensitive and specific indicator of myocardial damage, small amounts of CK-MB have been found in skeletal muscle. A biopsy specimen of thigh muscle from trained runners has nearly three times the CK-MB activity of muscle from untrained people and approaches the concentration found in heart muscle.¹³ Interpretation of the results of CK enzyme assays in these circumstances should be made with caution. Myocardial scintigraphy with technetium-99m pyrophosphate, a specific diagnostic technique for myocardial infarction, can be used in difficult cases.

Heat exhaustion and heat "stroke"

Hyperthermia is a hazard when exercise is performed in hot and humid conditions, especially by unacclimatised persons.¹⁴ Prolonged exposure to heat from radiation and convection with inefficient dissipation combined with heat generated from metabolic activity predisposes to heat exhaustion which may culminate in "heat stroke". Although heat exhaustion can be due to either dehydration or salt depletion, they may be difficult to distinguish.¹⁵

Heat exhaustion due to predominant water depletion which follows excessive sweating causes intense thirst, fatigue, weakness, incoordination and mental impairment. The severe dehydration is associated with hypernatraemia and a hyperosmolar state. If, however, fluid losses due to sweating are replaced by adequate water but no salt, heat exhaustion due to salt depletion can occur with hyponatraemia. Signs of dehydration and thirst are usually absent, but fatigue, weakness, headache, giddiness, muscle cramp, diarrhoea and vomiting occur with hypotension and tachycardia. In contrast to heat exhaustion due to water depletion, body temperature usually remains normal.

Profound hyphosphataemia has been observed in runners who have collapsed on completion of severe exercise, and is associated with muscle weakness, dyspnoea, confusion, convulsions and coma.¹⁶ This is believed to be due to the intracellular shift of phosphate induced by stress and catecholamine release, symptoms developing with a serum phosphate concentration below 0.3 mmol/l.

"Heat stroke" which is invariably accompanied by collapse has a high mortality.¹⁷ It is characterised by a rectal temperature greater than 41°C (106°F), anhidrosis, delirium and coma. In fatal cases histopathological findings include myocardial fragmentation, subendocardial haemorrhages, acute tubular necrosis, cerebral oedema with congestion, petechial haemorrhages and generalised parenchymal changes in the central nervous system, fatty infiltration of the liver with hepatocellular degeneration and rhabdomyolysis.

Biochemical changes reflect the multisystem involvement.¹⁸ Myocardial, skeletal muscle, and liver damage result in large increases in the serum activity of creatine kinase, the aminotransferases, and lactate dehydrogenase. Jaundice may occur a few days after collapse. If acute oliguric renal failure supervenes the associated hyperkalaemia may be exacerbated by the extensive muscle damage which releases potassium, and hypocalcaemia may be precipitated by calcium becoming sequestered in devitalised muscle. Survival into the second week may be accompanied by hypercalcaemia, consistent with compensatory secondary hyperparathyroidism.¹⁵

Circulatory shock with poor muscle and liver perfusion contribute to hyperlactaemia and eventually to severe lactic acidosis. In fatal heat stroke disseminated intravascular coagulation is common and the generalised tissue destruction may well be secondary to the occlusion of the microcirculation. There is also evidence that hyperpyrexia can cause thermal cell damage.

Training in hot and humid conditions can reduce the risk of developing heat exhaustion. The body adapts by increasing the sweat volume and rate, enhancing heat loss. Sweat sodium concentration is reduced and the plasma volume expands, probably in response to the increased production of antidiuretic hormone and aldosterone. Together with an increase in stroke volume of the heart, more efficient heat loss from the skin can occur and improved oxygen transfer to muscles and other organs can be better maintained.

Endocrine effects

Endogenous opioid peptides, β -endorphin, and its precursor lipotrophin are released from the anterior pituitary in response to exercise, together with met-enkephalin originating from the adrenal medulla, sympathetic nervous system, and the gut.¹⁹ They are part of the adaptive changes that contribute to the "runner's high" which is a period of temporary euphoria with dulling of the senses to pain and fatigue. They also depress gonadotrophin release at the hypothalamic level in women in whom regular strenuous exercise can be associated with menstrual distur-

bances in about 20% of female athletes. These include delay of the menarche and secondary oligo/amenorrhoea which are a result of anovulation or deficient luteal activity, with low activities of progesterone.² The situation is reversible by reducing the amount of exercise.

Attention has been focused on the similarity between the build and personality of dedicated female runners and women with anorexia nervosa.²⁰ As reduction in body fat is often accompanied by oligo/amenorrhoea, and because adipose tissue produces and fixes oestrogen, its reduction may contribute to irregular menstrual function. As the amounts of oestrogen produced by fat are small in relation to that of ovarian origin this seems an unlikely explanation, but it is thought that women require an optimal amount of body fat to preserve menstrual function.

Although modest exercise maintains the mineral density of bone, in some women there is a risk of developing osteoporosis as a consequence of reduced quantities of circulating oestrogens.

Haematological effects

Regular and prolonged exertion is associated with a variable reduction in haematocrit and haemoglobin concentration. This is usually due to an increase in plasma volume following enhanced sodium retention and is a physiological "pseudo-anaemia".²¹ Some athletes develop an actual increase in haemoglobin mass, which, together with an increase in red cell 2, 3 diphosphoglycerate, might be regarded as a compensatory mechanism to improve oxygen uptake by the tissues. No "shift to the right", however, of the oxygen dissociation curve which might be expected has been observed. The benefits to performance from the compensatory polycythaemia obtained by high altitude training and "blood doping" using autologous blood transfusion indicate that the oxygen carrying capacity is suboptimal for peak performance.

Pathological anaemia may be caused by occult gastrointestinal bleeding. Minor reductions in serum iron and ferritin concentrations are found in trained runners, but may reflect iron translocation from storage sites to red cells. It has been suggested that increases in circulating C-reactive protein and interleukin-1, part of the acute phase inflammatory response following severe exercise, may depress erythropoiesis.

In susceptible subjects running on hard surfaces can cause mechanical destruction of red cells (march haemoglobinuria), a rare cause of anaemia, with haemolysis, reduced serum haptoglobins, haemoglobinuria and hyperbilirubinaemia. Prolonged exertion severe enough to cause muscle damage may provoke rhabdomyolysis with myoglobinuria

and myoglobinuria, followed by acute oliguric renal failure.²²

During exercise there is an activation of the coagulation mechanism, with a shortened kaolin-activated partial thromboplastin time, increased factor VIII, and a raised platelet count.²³ This is balanced by an increased fibrinolytic activity and reduced platelet aggregation, which may contribute to the preventive effect of exercise on ischaemic heart disease, as they persist at rest after exercise.²⁴

Effects on the immune system

There is evidence that moderate exercise in animals and man actually stimulates the immune system and recreational runners seem to be less susceptible to respiratory infections. In contrast, high performance athletes in a variety of sports under intense training are more susceptible to glandular fever, toxoplasmosis, infective hepatitis, viral and other opportunistic infections that may progress to the debilitating post viral fatigue syndrome.²⁵

Exercising to exhaustion temporarily suppresses cell mediated immunity with reduced in vitro response to T and B cell mitogens, reduction in lymphocyte CD4:CD8 ratio (helper:suppressor cells), reduced natural killer cell activity and lymphocyte function. These effects persist throughout the resting phase immediately after exercise. Humoral immunity is also compromised and reductions in serum immunoglobulins, salivary IgA secretion, and total lymphocyte counts have also been observed, effects which become cumulative with regular training. Changes in neutrophil function indicate that non-specific immunity is also depressed.

The physical and psychological stress of competition and repeated exhaustion stimulating release of corticosteroids and catecholamines, which are both immunosuppressive, may contribute to the process of increased susceptibility. On the other hand, interferon α and interleukin 1 both increase during exercise, enhancing the immune process.²⁶ Further investigations are required to determine the optimal amount of exercise which is beneficial to a person and the factors contributing to immune deficiency in professional athletes.

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