Underwood: Chapter 6: Thrombosis, Embolism and Infarction

Thrombo-embolic phenomena are a major cause of morbidity and mortality in the UK and other developed countries. Common and serious disorders in which Thrombo-embolic mechanisms participate include:

- myocardial infarction

- cerebral infarction

- pulmonary embolism.

One of the commonest sequences of vascular disaster is thrombosis leading to embolism leading to infarction. However, infarction may be due to causes other than embolism, and embolism may have antecedent causes other than thrombosis.

Clot

When blood stagnates due to cessation of the pumping action of the heart, or if blood is allowed to stand in a bottle or test tube, then the clotting process is set in action. A complex series of enzymatic steps is activated, resulting in the formation of a fibrin meshwork that entraps the cells into a solid but elastic clot. When this process occurs in the body after death, the red cells tend to settle out before the clot forms, so that these post-mortem clots have two layers: a lower, deep red layer (resembling redcurrant jelly) and an upper, clearer layer with the appearance of chicken fat, with platelets evenly distributed throughout. Since these clots have formed within the body and represent the blood content of the vessel during life, they are moulded to the shape of the vessels in which they have formed. Some time after death, the various blood cells and the cells of the vessel wall begin to release their hydrolytic enzymes and the clot is dissolved.

Thrombosis

- A thrombus is a solid mass of blood constituents formed within the vascular system

- Predisposing factors (Virchow's triad): abnormalities of the vessel wall; abnormalities of blood flow; abnormalities of blood constituents

- Arterial thrombosis is most commonly superimposed on atheroma

- Venous thrombosis is most commonly due to stasis

- Clinical consequences include: arterial thrombosis (tissue infarction distally); venous thrombosis (oedema, due to impaired venous drainage), and embolism.

A thrombus is a solidification of blood contents that forms within the vascular system during life and is therefore different in concept from a clot.

Role of Platelets

The mechanism for closing small gaps in vessel walls brought about by trauma involves the platelets. Platelets are smaller than red blood cells, rather angular in appearance and have no nucleus. They are derived from large, multinucleated cells in the bone marrow called megakaryocytes. Although platelets have no nucleus, they are highly structured internally and contain a variety of organelles, some of which are specific to them. As well as mitochondria and the various cytoskeletal elements found in most cells, platelets also contain alpha granules and dense bodies. The alpha granules contain several substances involved in the process of platelet adhesion to damaged vessel walls (fibrinogen, fibronectin, platelet growth factor and an antiheparin as well as less well-defined substances), and the dense granules contain substances such as adenosine diphosphate (ADP) which causes platelets to aggregate.

Platelets are activated and the contents of their granules are released when the platelets come into contact with collagen, as may be found in damaged vessel walls, or with polymerising fibrin. The platelets change shape and extend pseudopodia; their granules release their contents and the platelets form a mass that covers the vessel wall defect until the endothelial cells have regenerated and repaired the vessel permanently. However, if this process is activated within an intact vessel, it results in a thrombus.

Thrombus Formation

There are three predisposing situations that may result in thrombus formation. These were described originally by Virchow and are known as *Virchow's triad.* The three factors are:

- changes in the intimal surface of the vessel

- changes in the pattern of blood flow

- changes in the blood constituents.

Not all three are needed for thrombosis to occur, but any one of them may result in thrombosis in a particular place.

Arterial Thrombosis

In its earliest phase the atheromatous plaque may consist of a slightly raised fatty streak on the intimal surface of any artery, such as the aorta. With time, the plaque enlarges and becomes sufficiently raised to protrude into the lumen and cause a degree of turbulence in the blood flow. This turbulence eventually causes loss of intimal cells, and the denuded plaque surface is presented to the blood cells, including the platelets. The turbulence itself will predispose to fibrin deposition and to platelet clumping and the bare luminal surface of the vessel will have collagen exposed and platelets will settle on this surface. Thus we have two of the factors described in Virchow's triad operating in an atheromatous plaque. If this plaque exists in the aorta of a smoker or someone with a high cholesterol and high levels of low density lipoprotein - common risk factors for atheroma - then the third of Virchow's

factors is introduced, since these changes in blood constituents are well known to predispose to thrombus formation. This process, once begun, may be self-perpetuating since it has been shown that platelet-derived growth factor, which is contained in the alpha granules, causes proliferation of arterial smooth muscle cells, which are an important constituent of the atheromatous plaque.

Thus, the first layer of the thrombus is a platelet layer. Formation of this layer in turn causes the precipitation of a fibrin meshwork in which red cells are trapped and a layer of this meshwork is developed on top of the platelet layer. This cmplex structure now protrudes even further into the lumen, causing more turbulence and forming the basis for further platelet deposition. The normal flow of blood within the vessels is laminar; the cells move in the swifter central lane and the plasma runs along the walls. Therefore, the greatest degree of turbulence occurs at the downstream side of arterial thrombi as the blood passes over the thrombus and on the upstream side of venous thrombi for the same reason. Thrombi will therefore grow in the direction of blood flow; this process is known as *propagation.*

Venous Thrombosis

In veins, however, the blood pressure is lower than in arteries and atheroma does not occur; so what initiates venous thrombus formation? Most venous thrombi seem to begin at valves. Valves naturally produce a degree of turbulence since they protrude into the vessel lumen and they may be damaged by trauma, stasis, and occlusion. However, thrombi can also form in veins of young, active individuals with no predisposing factors that can be identified. Once they begin, the thrombi grow by successive deposition in the manner described previously and this process may produce a highly patterned, coralline growth. The alternating bands of white platelets and red blood cells in thrombi were first described by Zahn and are called the *lines of Zahn.*

Since normal flow within the vessels is laminar, most of the blood cells are kept away from atheromatous walls or from damaged vein valves. However, if the blood pressure is allowed to fall during surgery or following a myocardial infarction, then flow is slower through the vessels and thrombosis becomes a likely event. Similarly, the venous return from the legs is very reliant upon calf muscle contraction and relaxation which massages the veins and, because of the valves, tends to return the blood heartwards. So if elderly subjects are immobilised for any reason, they become at great risk from the formation of deep leg vein thromboses. The frequency with which deep vein thrombosis is found to occur following surgery is directly related to the enthusiasm with which it is sought (i.e., by the pathologist at postmortem examination) and the sensitivity of the methods used to demonstrate it. Postmortem studies on unselected medical and surgical patients show significant deep vein thrombosis in 34% of the former and 60% of the latter regardless of the cause of death.

When a vein becomes thrombosed it evokes an inflammatory reaction, a phenomenon known as *thrombophlebitis,* but the opposite process also occurs; a vein that is inflamed will often thrombose and this is known as *phlebothrombosis.* The end effect is the same, a thrombosed and inflamed vein, but clearly if there is a predisposing cause then the cause needs to be recognised and treated.

Clinical Effects

The effects of thrombosis are apparent only if the thrombus is sufficiently large to significantly affect the flow of blood. Arterial thrombosis reults in loss of pulses distal to the thrombus and all the signs of impaired blood supply: the area becomes cold, pale, painful and eventually the tissue dies and gangrene results. In venous thromboses, 95% of which occur in leg veins, the area becomes tender, swollen and reddened, since blood is still carried to the site by the arteries but cannot be drained away by the veins. The tenderness is due to developing ischaemia in the vein wall initially, but there is also general ischaemic pain as the circulation worsens.

Phlegmasia alba dolens (white painful leg) occurs with relatively slow thrombosis in the ileofemoral veins and is seen most commonly in medical patients or following pregnancy. The leg becomes white, swollen and painful and, if untreated, progresses over 2-6 weeks to a chronic cold, aching, oedematous limb that requires elastic stockings since the venous system within the limb is permanently disrupted.

Phlegmasia cerulea dolens (blue painful leg) is due to acute massive ileofemoral venous thrombosis and the pain is sharp enough to cause the patients great distress. Shock may develop and some degree of gangrene within the limb is common.

Thrombophlebitis migrans occurs in previously healthy veins in any area of the body. The thromboses appear and disappear changing site all the ttime and the condition may persist for months or even years. It is extremely ominous and usually indicates the presence of visceral cancer, commonly of the pancreas.

Strokes may be due to the formation of thrombus in a cerebral vessel although they may be also the result of haemorrhage or embolism.

Myocardial infarction is often associated with thrombus formation in coronary arteries and is responsible for numerous sudden deaths.

Fate of Thrombi

Various fates await the newly-formed thrombus. In the best scenario it may resolve; the various degradative processes available to the body may dissolve it and clear it away completely. A second possibility is that the thrombus may become *organised* intto a scar by the invasion of macrophages which clear away the thrombus, as fibroblasts replace it with collagen, occasionally leaving a mural nodule or web that narrows the vessel lumen. A third possibility is that the intimal cells of the vessel in which the thrombus lies may proliferate, and small sprouts of capillaries may grow into the thrombus and later fuse to form larger vessels. In this way the original occlusion may become *recanalised* and patent again. Another common result is that the thrombus affects some vital centre and causes death before either the body or tthe clinicians can make an effective response; this event is very common. Finally, fragments of the thrombus may break off into the circulation, a process known as *embolism.*

Embolism

- An embolus is a mass of material in the vascular system able to become lodged within a vessel and block its lumen

- Most emboli are derived from thrombi

- Other types of embolic material include: atheromatous plaque material, vegetations on heart valves (infective endocarditis), fragments of tumour (causing metastases), amniotic fluid, gas and fat

- Most common occurrence is pulmonary embolism from deep leg vein thrombosis.

An embolus is a mass of material in the vascular system able to lodge in a vessel and block its lumen. The material may have arisen within the body or have been introduced from outside. The material may be solid, liquid or gaseous. The end result of embolism are more dependent upon the final resting place of the embolic material than on its nature.

Pulmonary Embolism

Around 95% of venous thrombosis occurs in leg veins; the majority of the rest occur in pelvic veins and a very few occur in the intracranial venous sinuses. Therefore, most emboli from such thrombi will arrive in the pulmonary circulation - *pulmonary embolism.* The only possibility for such emboli to arrive in the arterial side of the circulation is if there is an arterial/venous communication such as a perforated septum in the heart (*paradoxical embolus*).

The effects of pulmonary emboli depend upon their size. Small emboli may occur unnoticed and be lysed within the lung or they may become organised and cause some permanent, though small, respiratory deficiency. Such a respiratory deficiency may only come to light with the eventual accumulation of damage from many such tiny embolic events. The accumulation of such damage over a long period may be the cause of so-called 'idiopathic' pulmonary hypertension.

A second class of pulmonary emboli may be large enough to cause acute repsiratory and cardiac problems that may resolve slowly with or without treatment. The main symptoms are chest pain and shortness of breath due to the effective loss of the area of lung supplied by the occluded vessel, which may even become infarcted. This occlusion puts some strain on the heart, which is evident on the ECG as right heart strain with deep S waves in lead 1 and the presence of Q waves and inverted T waves in lead 3 (S1, Q3, T3). This ECG pattern is one of the few that a pathologist will look for in the case notes before performing an autopsy on a patient suggested of having had a pulmonary embolus in life; without these findings the embolus is unlikely to have caused death. Although many patients recover from such episodes, their lung function is impaired and, of course, they are at risk from further emboli from the same source. Consequently, they require symptomatic therapy for the embolus as well as treatment for the causative thrombosis.

The third class of pulmonary emboli are massive and result in sudden death. These are usually long thrombi derived from leg veins and having the shape of the vessels in which they arose, tather than that of the vessels in which they are found at postmortem examination. They are often impacted across the bifurcation of one of the major pulmonary arteries as a 'saddle embolus', a descriptive term for their appearance. As with all thrombi, even if they have undergone embolisation, they retain the appearance of a thrombus with lines of Zahn and a granular, friable consistency. This consistency is distinct from the elastic, 'chicken fat and redcurrant jelly' appearance of postmortem clots.

Systemic Embolism

Systemic emboli arise in the arterial system and again their effects are due to their size and to the vessel in which they finally lodge. The thrombi from which they come generally form in the heart or on atheromatous plaque. In the heart, thrombi may form on areas of dead cardiac muscle as a result of myocardial infarction, since these areas will have lost their normal endothelial lining and will expose the underlying collagen to the circulating platelets. These areas of dead myocardium will also be adynamic and will disrupt the normal blood flow within the heart, creating turbulence and predisposing to thrombus formation at that site.

Another common cause of thrombosis within the heart is the presence of atrial fibrillation. This ineffectual movement of the atria causes blood to stagnate in the atrial appendages and thrombosis to occur. When the normal heart rhythm is re-established the atrial thrombus may be fragmented and emboli broken off.

Emboli from the heart are usually derived from thrombi on the left side of the circulation. These emboli may travel to the brain causing cerebrovascular incidents such as transient ischaemic attacks or strokes, or they may travel to any of the viscera, or to the limbs.

Larger emboli may lodge at the bifurcation of the aorta as a saddle embolus cutting off the blood supply to the lower limbs, a situation that requires rapid diagnosis if the embolus is to be removed before the changes in the limbs become irreversible. Smaller emboli may lodge in smaller vessels nearer the periphery and cause gangrene of the digits. Small emboli may travel into the kidneys or spleen and be relatively asymptomatic, even when they cause the death of tthe area of tissue distal to their site of impaction; such ischaemic scars are not uncommon findings at autopsy with no clinical history to lead one to suspect that such eventts had been occurring.

More dramatic consequences develop as a result of emboli travelling to the intestine, often passing down the superior mesenteric artery; this impaction can cause dath of whole sections of small bowel which, unlike kidneys or spleen, depends upon the whole organ to be intact in order to function. The death of even a small area of bowel means perforation and peritonitis, whereas the death of a small area of kidney or spleen means only a small scar.

Vegetations on the heart valves are an important source of emboli. Most seriously, in infective endocarditis the vegetations consist of micro-organisms, usually bacteria, and are extremely friable. Marantic vegetations, consisting of platelets and fibrin, occur on the heart

valves of patients who are severely debilitated, for example by cancer; these vegetations are often firmly adherent and are less likely to embolise.

Embolic Atheroma

Fragments of atheromatous plaque may embolise and these are frequently seen in the lower limbs of arteriopathic patients. The precise cause of such ischaemic toes is rarely investigated thoroughly enough to be sure of the cause. They may be recognised in histological preparations by the cigar-shaped clefts left behind when the cholesterol crystals dissolve out during histological processing.

Infective Emboli

Infected lesions within the blood stream, in particular the vegetations on rheumatic heart valves, may break off and lodge in small vessels in the usual way. But here, the usual effects of emboli are compounded by the infective agent presentt and this agent may weaken the wall of the vessel, causing the development of a *mycotic aneurysm.*

Fat Embolism

Fat embolism usually arises following some severe trauma with fracture to long bones. Fat from the bone marrow is released into the circulation and comes to lodge in various organs. A similar situation arises in severe burns and in extensive soft tissue injury. Much of the circulating fat enters the lungs and this indicates that it must travel by way of the venous system. However, fat globules are fluid and so small that many also enter the systemic arterial circulation, causing confusion or coma, renal impairment and skin petechiae. It has also been suggested that systemic effects of trauma, particularly burns, can cause changes in the stability of fat held in micellar suspension, resulting in free fat appearing in the circulation.

Gas Embolism

There are various causes of embolic events involving gas; several are iatrogenic. The classic form is *Caisson disease.*

Other causes of gas embolism are mainly surgical when some vessel is opened to the air. This also occurs in suicide attempts when the neck veins are cut, or accidentally when patients are disconnected from IV lines and air enters. The 'secret murders' by air injection so favoured by thriller writers are rare, since the volume of air needed to cause death in this fashion is around 100 ml.

The pathological signs of this condition at autopsy include visible bubbles in the vessels such as those of the meninges, and sometimes a frothy ball of fibrin and air in the right side of the heart occluding one of the valves.

Amniotic Embolism

With the vastly increased pressures in the uterus during delivery, the head engages and the pressure is transferred to the amniotic fluid which may be forced into the maternal uterine

veins. These amniotic fluid emboli travel in the circulation and lodge in the lungs, causing respiratory distress like other pulmonary emboli. They can be recognized histologically since they contain the shed skin cells of the infant.

Tumour Embolism

Tumour emboli are mainly small and break off as tumours which penetrate vessels. This mechanism is a major route of dissemination of malignancies.

Embolism of Foreign Matter

Particles of foreign matter may contaminate fluids injected intravenously. The foreign particles elicit a granulomatous reaction in the organs in which they lodge.

Infarction

- Ischaemic death (necrosis) of tissue

- Infarcts elicit an inflammatory reaction

- Gangrene is infarction of mixed tissues in bulk (i.e., gut wall, part of a limb)

- In some tissues, Ischaemic necrosis may result from impaired vascular flow short of total cessation.

Infarction is Ischaemic death of tissue within the living body. This means that death of tissue from other causes, such as toxins or trauma, are not infarction but are simply necrosis, which is the general term for death of tissue within the living organism. Only death of tissue due to restricted blood supply is infarction. The word infarction means 'stuffed full' and reflects the fact that the first types of infarction that were recognised were those in which the blockage was venous and the arterial supply continued to pump blood into the organ when the outlet was blocked. A similar effect may be seen in those cases where a second blood supply is present and although the arterial inflow is blocked, blood still enters the organ from this second supply; a good example of this is the lung, which has both pulmonary and bronchial arterial supplies. In the past, pathologists classically divided infarcts into grey and red infarcts, but these merely represent stages in the same process; not all infarcts in the same organ go through these stages, so the division is pointless.

Appearance of Infarcts

The appearance of infarcted areas depends upon the time that has elapsed between the infarct occurring and the lesion coming to the attention of the pathologist. If the tissue is examined within 24 hours of the infarct there will be no direct evidence of the event. Between 24 and 48 hours the dead tissue is beginning to evoke a response from the surrounding living tissue and inflammatory cells can be seen moving into the infarcted area. In routine histological sections stained with haematoxylin and eosin the cytoplasm contains proteins, which stain pink, and RNA which stains blue. In normal tissue, the cytoplasm therefore has a slightly purple tingle and in areas that have been dead a few hours the RNA is broken down

and the cytoplasm becomes bright pink. It should be borne in mind that all histological sections of tissue are 'dead' and that what we are looking at is the consequence of the time that has elapsed between the infarcted tissue dying and the rest of the tissue being killed by being dropped into formalin or some other fixative.

If the infarcted tissue has stayed in the living patient for some days before being removed (by biopsy or autopsy) then the degradative processes of the body in the form of macrophages and polymorphs will have begun to clear away the dead tissue, which will consequently have an amorphous, acellular appearance apart from the numerous inflammatory cells. At this stage, the tissue is at its weakest; myocardial infarction patients who have survived the acute episode 10 days previously may suddenly die with rupture of the healing infarct and consequent haemopericardium and cardiac tamponade. The gross appearance of the tissue at this time is very variable; if small blood vessels in the vicinity have also become Ischaemic they may die and blood will escape into the infarct, giving it a patchy or confluent red appearance. On the other hand, there may be no bleeding into the area, in which case it remains pale with a red hyperaemic rim, and grows progressively paler as healing takes place.

If the patient survive this danger period the damaged tissue either regenerates or repairs with the formation of a scar. Such a scar is apparent as a grey, contracted area consisting of collagenous fibrous tissue. A scar solves the tissue deficit in the sense that the organ is intact and the hole is mended, but the scarred area is no longer functional; a healed myocardial infarct is adynamic and can be the site of further problems for the patient. In the heart, this may take the form of an aneurysm as the scar is subjected to cyclic pressure loads and becomes stretched without any ability to contract again.

The overall shape of infarcts depends upon the territory of perfusion of the occluded blood supply; some classical appearances are the wedge-shaped infarcts seen in the lung and the triangular infarcts (conical in three dimensions) seen in the kidneys at autopsy. Other scarred infarcts such as those in spleen are less predictable since the blood supply is less regular and marked overlaps of vascular territories occur and because the soft tissue distorts as the scar contracts. In the brain the dead tissue is cleared away so efficiently that a fluid-filled cyst is often all that remains.

Gangrene

When the whole areas of a limb or a region of the gut have their arterial supply cut off and large areas of mixed tissues die in bulk, such a process is termed gangrene. Two types of gangrene are recognised:

- Dry gangrene - where the tissue dies and becomes mummified and healing occurs above it, so that eventually the dead area drops off. This is a sterile process, and is the common fate of gangrenous toes in the diabetic.

- Wet gangrene - where bacterial infection supervenes as a secondary complication, and in this case the gangrene spreads proximally and the patient dies of overwhelming sepsis.

Another mechanism that results in gangrene is torsion: the gut may twist on a lax mesentery, or an ovary or testis may twist on their pedicles, occluding the venous return. The

organ swells and the oedema further compresses the drainage. The arteries continue to pump blood into the organ, but ischaemia supervenes and infarction develops.

Gas gangrene is complicated by infection with gas-producing anaerobic bacteria such as *Clostridium perfringens.*

Capillary Ischaemia

In frostbite, the capillaries are damaged in exposed areas and contract so severely that the area they normally supply becomes Ischaemic and dies. Exposure to cold without freezing causes capillary contraction followed by a fixed dilatation; this is the mechanism of damage in 'trench foot' and related conditions.

Capillaries may also be blocked by parasites, by abnormal cells in sickle cell disease or by abnormal proteins that precipitate in the cold (cryoglobulinaemia) and these phenomena also lead to local ischaemia and infarction.

The balance of thrombotic and thrombolytic mechanisms is delicate and this balance may be secondarily disturbed by several different disease processes and, unfortunately, by some therapeutic interventions. In such cases, thrombosis may become activated without effective counterbalance, with the result that thrombi may form throughout the body and, consequently, bleeding may occur at multiple sites due to consumption of clotting factors; this phenomenon is called *disseminated intravascular coagulation or DIC*. It occurs as a complication of many disease states such as cancer or infection.

Susceptibility to Ischaemia

Different tissues show differing susceptibility to ischaemia for a variety of reasons. Some tissues have only one arterial supply and if this is blocked there is no possibility of collateral supplies taking over; one such 'end artery' situation is the retinal artery and thrombosis of this artery leads to inevitable blindness. Tissues also vary in the degree of ischaemia that they can tolerate, commonly as a function of differing metabolic needs, and even within a tissue different areas have different susceptibilities. Within the heart the sub-endocardial zone is at a watershed between the coronary supply from the outside and the diffusion zone from blood within the chambers. If the coronary arteries are narrowed by the presence of atheroma, these patients are at great risk of developing sub-endocardial infarctions if their systemic blood pressure drops for any reason. Consequently, such patients may develop the complication of sub-endocardial infarction following trauma, surgery or shock from infections.

Low-Flow Infarction

In some tissues, infarction may be due to impaired blood flow (or oxygenation) rather than an absolute cessation of flow. Tissues that are especially vulnerable to low-flow infarction include:

- 'watershed' areas

- tissues perfused by a portal vasculature

- tissues distal to pathological arterial stenoses

- metabolically active tissues.

'Watershed' Areas

Tissue at the interface between the adjacent territory of two arteries is prone to infarction if there is an impairment of blood or oxygen supply. The tissue is normally situated precariously on the fringes of the territories perfused by the arteries, with no collateral circulation to provide blood from alternative vessels.

Examples include:

- the splenic flexure of the colon; this is situated at the interface between the territories of the superior and inferior mesenteric arteries

- regions of the cerebral hemispheres at the interface between the territories of the major cerebral arteries

- the deep myocardium between the sub-endocardial myocardium (oxygenated directly from blood in the ventricles) and that which is perfused by the coronary arteries.

Patients who are severely shocked and hypotensive may develop Ischaemic lesions in these sites.

Portal Vasculature

Some tissues are perfused by blood which has already passed through one set of capillaries; this vascular arrangement is described as portal. Therefore, there is normally a drop in intravascular pressure across the first set of capillaries, rendering the tissue perfused by the second set of capillaries vulnerable to Ischaemic injury.

Examples include:

- the anterior pituitary, which is perfused by blood that has already perfused the median eminence of the hypothalamus

- the renal tubular epithelium, which is perfused by blood issuing from the glomerular capillaries

- some parts of the exocrine pancreas, which are perfused by blood that has already perfused islets of Langerhans in the vicinity.

These patterns of vascular microanatomy account for the pituitary infarction, renal tubular necrosis and acute pancreatitis that may occur in severely shocked patients.

Arterial Stenoses

Atheromatous narrowing or stenosis of arteries may be of insufficient severity to cause infarction distally in normotensive individuals. However, if the blood pressure and, therefore, blood flow falls, the tissue distal to the arterial stenosis may become infarcted. Thus, patients who become severely shocked may develop Ischaemic changes in various organs without there being any sign of *total* vascular occlusion.

Infarction and Metabolic Activity

Cells with large metabolic requirements are exceptionally vulnerable to Ischaemic damage and infarction. Cerebral neurones are the most at risk; irreversible damage occurs within a few minutes of cessation of blood flow and oxygenation. Cardiac myocytes also have a considerable requirement for oxygen and other nutrients; they may be irreversibly damaged if the coronary arteries, which may be narrowed by atheroma, cannot supply these requirements during tachycardia associated with exertion.