PERTURBATIONS OF FLOW 3

EMBOLISM

- **embolus** (plural, **emboli**) = an intravascular, solid, liquid or gaseous mass that is transported by the blood to a site distant from its point of origin

- **embolism** = the blockage of a downstream vessel by an embolus arising upstream

THROMBOEMBOLISM

- the **vast majority of emboli are thromboemboli**
- as a thromboembolus moves downstream, it inevitably encounters a blood vessel smaller than its diameter and becomes impacted → partial or complete occlusion of the vessel
- thromboemboli also commonly lodge at sites of vessel bifurcation (= **saddle thromboemboli**) (e.g. at the distal end of the aorta)

- once impacted, a thromboembolus causes local endothelial hypoxia and coagulation and therefore becomes anchored to the vessel wall
- it may then begin to propagate, give rise to further thromboemboli, undergo fibrinolysis or become organised in a manner akin to a thrombus
- in many cases, it can be very difficult to establish if an attached intravascular blood clot is a thrombus that has developed locally or a thromboembolus; a thorough search for a possible thrombus upstream is necessary to distinguish these two possibilities

- the clinical consequences of thromboembolism depend on whether the thromboembolus lodges in the pulmonary or systemic circulation and on whether it is **bland** (sterile) or **septic** (containing infectious agents, particularly bacteria)
- septic thromboembolism can lead to new foci of infection

Pulmonary Thromboembolism

- venous thromboemboli arising from thrombi in the gastrointestinal, splenic or pancreatic mesenteric veins or the portal vein itself are likely to become trapped in the **vascular bed of the liver** after being transported there via the portal vein
- however, **venous thromboemboli arising from thrombi elsewhere in the body are most likely to lodge in the vascular bed of the lungs**

- pulmonary thromboembolism is an important condition in humans, especially following extended anaesthesia, with more than 95% of cases resulting from deep leg vein thrombosis proximal to the knee
- pulmonary thromboembolism rarely results from anaesthesia in animals but can occur with right-sided vegetative endocarditis, the nephrotic syndrome, heavy heartworm infestations, malignant tumours of the adrenal gland or kidney, prolonged recumbency of large animals etc

- depending on its size, a pulmonary thromboembolus may occlude the main pulmonary artery, impact across the bifurcation of the right and left pulmonary arteries, or pass into the smaller arterial branches

- sudden embolic obstruction of ≥ 60% of the pulmonary circulation → sudden death or hypertensive right heart disease (**cor pulmonale**)
- multiple episodes of pulmonary thromboembolism over time may also cause pulmonary hypertension and cor pulmonale

- however, because the lungs have a **dual arterial blood supply** (pulmonary and bronchial arteries), embolic obstruction of medium-sized pulmonary arterial branches **usually does NOT cause pulmonary infarction** unless the oxygen supply to the lungs was already compromised (e.g. by pre-existent anaemia)
- conversely, embolic obstruction of small pulmonary arterial branches can result in small (but usually clinically insignificant) pulmonary infarcts

Systemic Thromboembolism

- systemic thromboemboli travel in the systemic arterial circulation
- systemic arterial thromboemboli may be **widely distributed** (e.g. to brain, myocardium, kidneys, spleen, liver, intestines) and are **likely to cause tissue infarction**

- e.g. thromboemboli arising from mitral or aortic vegetative valvular endocarditis
- e.g. in horses, thromboemboli arising from a thrombus in the root of the cranial mesenteric artery caused by *Strongylus vulgaris* larvae (verminous arteritis) may impact in the cranial mesenteric, caecal or colic arteries supplying the large intestine
- e.g. thromboemboli arising from thrombi in the left atrium in cats with cardiomyopathy often lodge as saddle thromboemboli at the aortic trifurcation

OTHER TYPES OF EMBOLI

- the following emboli are **less common than thromboemboli** but their impaction in blood vessel branches may have the same consequences

- **bacterial colonies and fungal hyphae**

- **malignant neoplastic cells**

- **lipid**

- e.g. traumatic fracture of long bones or pelvic bones with release of lipid from marrow adipocytes
- e.g. soft tissue trauma with rupture of subcutaneous adipocytes
- e.g. rupture of lipid-laden hepatocytes in diabetes mellitus
- e.g. embolism from sites of atherosclerosis

- lipid emboli are usually numerous and only detectable microscopically
- seldom cause infarction but can prove fatal by release of free fatty acids that damage endothelium and trigger widespread microthrombosis (disseminated intravascular coagulation)
- lipid embolism may cause unexpected death very soon after a traumatic accident

- **gas bubbles**

- venous **air embolism** is a rare complication of pneumocystography, laparoscopy, cryosurgery or chest injury
- air embolism may also occur when traumatic or surgical wounds rupture large blood vessels and the pumping action of muscles or respiration sucks air into the bloodstream
- generally, more than 100 mL of gas is needed to cause a problem
- air bubbles may coalesce to form frothy masses that can occlude large blood vessels and even outflow from the right ventricle

- gas embolism also occurs in **decompression sickness** in divers who ascend too rapidly, in passengers in unpressurised aircraft that have ascended rapidly, and in passengers of pressurised aircraft that suffer sudden explosive depressurisation
- abrupt drop in atmospheric pressure → nitrogen gas expands and bubbles out of solution → embolism to skeletal muscles and periarticular tissues ("**the bends**") or lungs ("**chokes**")
- in chronic decompression sickness, gas emboli in bone → multifocal ischaemic necrosis (especially heads of the femurs, tibia and humeri) ("**caisson disease**")

- **foreign bodies**

- e.g. broken needles and hairs introduced at venipuncture, broken-off catheters, bullets etc

- **parasites**

- embolic parasites may be larval or adult, and alive or dead
- e.g. adult heartworm (*Dirofilaria immitis*) in dogs and cats
- e.g. large strongyle (*Strongylus vulgaris*) larvae in horses

- **fibrocartilage**

- e.g. intervertebral disc protrusion in dogs, pigs and humans → arterial or venous embolism of fragments of fibrocartilage derived from the nucleus pulposus of the disc → spinal cord infarction

- **amniotic fluid**

- e.g. women in the periparturient period
- tears in placental membranes and uterine veins → pulmonary embolism of procoagulant amniotic fluid containing foetal epithelial squames, hair, fat and/or mucus → pulmonary oedema +/- microthrombosis → high mortality rate

- **egg yolk** - in birds

- **tissue cells**

- e.g. tissue trauma → embolism of individualised or small clusters of hepatocytes or of bone marrow haematopoietic cells

- **agglutinated clumps of erythrocytes** - e.g. in immune-mediated haemolytic anaemia

ISCHAEMIA AND INFARCTION

- thrombi, thromboemboli and other types of emboli are of significance because they can occlude vessel lumina downstream to cause ischaemia and tissue infarction

- **ischaemia = hypoxic or anoxic tissue injury resulting from a local reduction in blood flow**

- **infarction = the process by which ischaemic necrosis of a localised area of tissue develops**

- **infarct = the area of tissue which has undergone infarction**

NB - A strict definition of ischaemia involves a local reduction in blood flow. However, many doctors and vets use the term ischaemia more loosely to refer to any type of hypoxic/anoxic tissue injury (e.g. tissue hypoxia induced by severe pneumonia, severe anaemia, methaemoglobinaemia, carbon monoxide poisoning, cyanide poisoning etc).

CAUSES OF ISCHAEMIA AND INFARCTION

- thrombosis, thromboembolism or embolism
- arteriosclerosis
- atherosclerosis
- congestive heart failure
- shock
- dehydration
- impaired venous return to the right heart (e.g. ruminal bloat, gastric dilation-volvulus)
- sustained arteriolar vasoconstriction in frostbite, ergotism and fescue toxicosis
- external compression of vessels (especially veins) (e.g. from a neoplasm, abscess, torniquet or tight bandage, or the body weight of a large recumbent animal, or strangulation of veins by torsion or by a hernial ring)

- **most infarcts result from occlusion of arterial branches by thrombi or especially thromboemboli**
- **arterial infarcts are far more common than venous infarcts** because many tissues lack a collateral arterial blood supply whereas collateral venous channels may be numerous

- **venous infarcts are usually due to venous thrombosis or external compression of veins**
- venous infarcts due to thrombosis are most likely to develop in organs with a single venous outflow channel (e.g. testes, ovaries, kidneys)

FACTORS THAT INFLUENCE THE PROGNOSIS

- reduced blood flow may have no or minimal effect on tissues, or it may cause tissue degeneration, atrophy or necrosis, or even death of the animal

- **cerebral, myocardial, intestinal and pulmonary infarcts can be fatal**
- however, infarcts in many tissues and especially small infarcts may be asymptomatic or responsible for only transient clinical signs (e.g. fever and malaise)

- healed infarcts are common incidental findings at necropsy, especially if the affected organ retains adequate functional mass (e.g. renal infarcts)

- the following factors determine the consequences of ischaemia

Presence of an Alternative Oxygen Supply

- the **availability of an alternative supply of oxygen** is the **most important factor** determining whether decreased arterial blood flow will cause significant tissue damage

- most tissues have one of **three basic patterns of arterial blood supply**:

- **functional end arteries**

  - the arterial supply to many tissues is limited to a single vessel that then ramifies into smaller and smaller branches
  - e.g. **spleen** and **kidneys**
  - e.g. **cerebrum** and **heart**
  - occlusion of end arteries almost invariably leads to infarction unless the occluded vessel is an extremely small one

- **parallel arteries**

  - some organs and tissues have separate but parallel systems of arterial supply, often with substantial functional and/or structural anastomoses
  - e.g. **skeletal muscles** and **intestines**
  - the arterial supply to the intestines includes many anastomoses near the mesenteric border; occlusion of such arterial vessels rarely causes infarction
  - however, if a mesenteric artery is occluded near its origin from the abdominal aorta (e.g. in verminous arteritis and thrombosis of the root of the cranial mesenteric artery in horses due to *Strongylus vulgaris* larvae), arterial infarction of the large intestine can occur

- **dual blood supply**

  - e.g. the **lungs** are supplied with blood by the pulmonary and bronchial arteries
  - e.g. the **liver** receives blood from both the hepatic artery and the portal vein
  - infarction of the liver or lung is unusual unless the oxygen supply is already compromised (e.g. by concurrent severe anaemia or pre-existent passive congestion)
  - the same holds true for the **distal forelimbs** which are perfused by both the radial and ulnar arteries

Rate of Development and Degree of Occlusion

- sudden and complete occlusion of an **artery** usually causes infarction

- slowly developing or incomplete occlusion of a **vein** is less likely to cause venous infarction of tissues upstream because there is time for development or enlargement of **collateral venous channels**
- e.g. sudden and complete blockage of the portal vein → rapidly fatal venous infarction of the intestines

- gradual or incomplete obstruction of the portal vein may permit development of collateral veins draining the splanchnic viscera to the caudal vena cava and/or renal or gonadal veins (**acquired portosystemic shunting**)

Size of the Affected Vessel

- the smaller the occluded vessel, the less significant are the consequences
- e.g. sudden obstruction of the pre-hepatic portal vein → usually fatal venous infarction of the intestines
- sudden obstruction of a large intra-hepatic branch of the portal vein → infarction of a large wedge of liver parenchyma
- sudden obstruction of a small intra-hepatic portal vein branch → infarction of several hepatic acini

Cell Vulnerability to Hypoxia and Duration of Hypoxia

- cells vary in their susceptibility to hypoxia

- **brain neurons** undergo necrosis if deprived of oxygen for approximately 3-4 minutes
- cerebellar Purkinje cells and neurons of the deep laminae of the cerebral cortex, the hippocampus and basal ganglia are particularly vulnerable to hypoxia

- **myocardial fibres** can only survive approximately 20-30 minutes of hypoxia

- **renal proximal tubular epithelium** can only survive approximately 2 hours of hypoxia

- in the **small intestine**, 5-10 minutes of hypoxia causes sloughing of epithelial cells from the tips of the villi and progressing towards the base
- crypt epithelial necrosis commences 2-4 hours after onset
- by 30-60 minutes post-onset, there is necrosis of serosal mesothelium
- smooth muscle necrosis does not begin until after 6 hours of hypoxia
- the colon is less sensitive to hypoxia than the small intestine, at least in the dog and horse

- because mesenchymal cells such as fibroblasts are relatively resistant to hypoxia, the stromal framework of tissues may survive despite loss of the more sensitive parenchymal cells
- the stroma provides a scaffold on which tissue repair by regeneration of labile or stable cells may occur if the animal survives

Oxygen Content of Blood

- the overall cardiovascular and haematological health of an individual can play a decisive role in determining the outcome of an episode of vascular occlusion
- any factor that reduces the oxygen content of the blood increases the likelihood that vascular occlusion will cause infarction
- e.g. partial obstruction of blood flow in a small vessel in an anaemic or hypoxaemic animal could cause infarction whereas it might cause no injury in an animal that has a normal blood oxygen concentration
- e.g. generalised circulatory disorders such as congestive heart failure or shock may allow tissue infarction to occur in the case of an otherwise inconsequential vessel blockage

Miscellaneous Factors

- reperfusion injury following restoration of blood flow, the ability of infarcted tissue to undergo repair (i.e. tissues composed of permanent versus stable versus labile cell populations), the degree of local accumulation of metabolic waste products (e.g. lysosomal enzymes, lactic acid) and the presence of secondary bacterial infection (e.g. gut ischaemia → bacterial invasion or absorption of bacterial toxins into the general circulation) also influence the outcome of ischaemia

MICROSCOPIC APPEARANCE OF ISCHAEMIA

- in almost all tissues, ischaemic necrosis is of **coagulative** type, with the basic microscopic outline of the dead cells persisting for at least several days until they are liquefied or phagocytosed by leukocytes
- the initial hypoxic/anoxic insult (+/- subsequent intracellular acidosis) denatures both structural and enzymatic proteins, blocking cell autolysis
- the necrotic cells appear hypereosinophilic, with the nuclei pyknotic (shrunken and hyperchromatic), karyolytic (faded) or karyorrhectic (fragmented)

- in the brain and spinal cord, ischaemic necrosis is of **liquefactive** type and results in softening of the affected area (**malacia**)

GROSS APPEARANCE OF INFARCTS

- infarcts are usually **wedge-shaped**, with the occluded vessel at the apex
- if the base of the wedge is a serosal surface, there is often fibrinous exudate over the surface
- when viewed from the base, the infarct may be of rhomboid or diamond shape

- infarcts can be classified on the basis of their colour into **red** or **haemorrhagic infarcts** or **white** or **anaemic infarcts**
- infarcts can also be classified on the basis of presence or absence of microbial infection into **septic** or **bland infarcts**

Red or Haemorrhagic Infarcts

- red infarcts occur:

  - with **venous occlusion**, e.g. haemorrhagic infarction of the intestines following mesenteric torsion (both passive congestion of and continued arterial blood flow into the area contribute to the red appearance)

  - in **loose spongy tissues** (e.g. spleen, lungs) that allow blood to seep from viable marginal tissue into the infarcted zone

  - in **tissues with dual circulations** (e.g. lung or liver), with blood flow from viable vessels into the necrotic zone (but with the latter flow being insufficient to prevent ischaemic necrosis)

- in **tissues in which blood flow is re-established** after a critical period of tissue hypoxia (e.g. surgical correction of a mesenteric torsion); reflow of blood permits generation of reactive oxygen species (free radicals) and entry of leukocytes that magnify the tissue damage (= **reperfusion injury**)

- red infarcts may protrude slightly above the surrounding tissues and may feel firmer than viable adjacent tissue
- red infarcts become paler over time as the extravasated erythrocytes lyse or are phagocytosed by macrophages
- over time, red infarcts may become grossly discoloured yellow-brown due to haemosiderin accumulation within macrophages

White Infarcts

- white infarcts occur:

- with **arterial occlusion**

- in **solid organs** (e.g. myocardium) in which the solidity of the tissue limits the amount of haemorrhage that can seep into the ischaemic zone from adjacent capillary beds

- white infarcts become demarcated from adjacent viable tissue by a narrow rim of haemorrhage and hyperaemia
- white infarcts become paler and more sharply defined over time

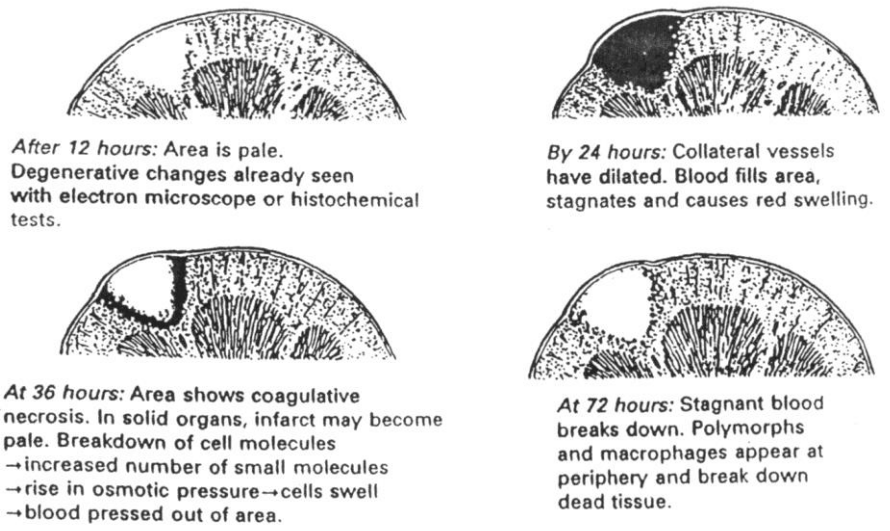
Age of Infarct

- the gross appearance of an infarct is influenced by its age (Figure 1 illustrates the evolution of a renal infarct over time)
- all infarcts are initially poorly defined but become more sharply demarcated by reactive events in the adjacent viable tissue
- ultimately, ischaemic tissue is removed by fragmentation and by invasion by phagocytic leukocytes (chiefly macrophages) that release proteolytic enzymes into the necrotic zone to liquefy the mummified cells

- **peracute infarcts** - may be invisible to the naked eye and only recognisable by electron microscopy

- **acute infarcts** (> 12 hours) - the infarcted tissue appears friable
- white infarcts become more obvious due to abnormal tissue pallor and red infarcts become more obvious due to haemorrhage into the infarct
- in both red and white infarcts, a narrow zone of acute inflammation (characterised by hyperaemia and neutrophilic infiltration) appears at the border between necrotic and viable tissue; the cream-white band of infiltrating leukocytes lies immediately internal to the red marginal band of hyperaemia

Figure 1



Reference: "Pathology Illustrated" – A.D.T. Govan, P.S. Macfarlane, R. Callander, 4th edition, Churchill Livingstone, Edinburgh, 1995

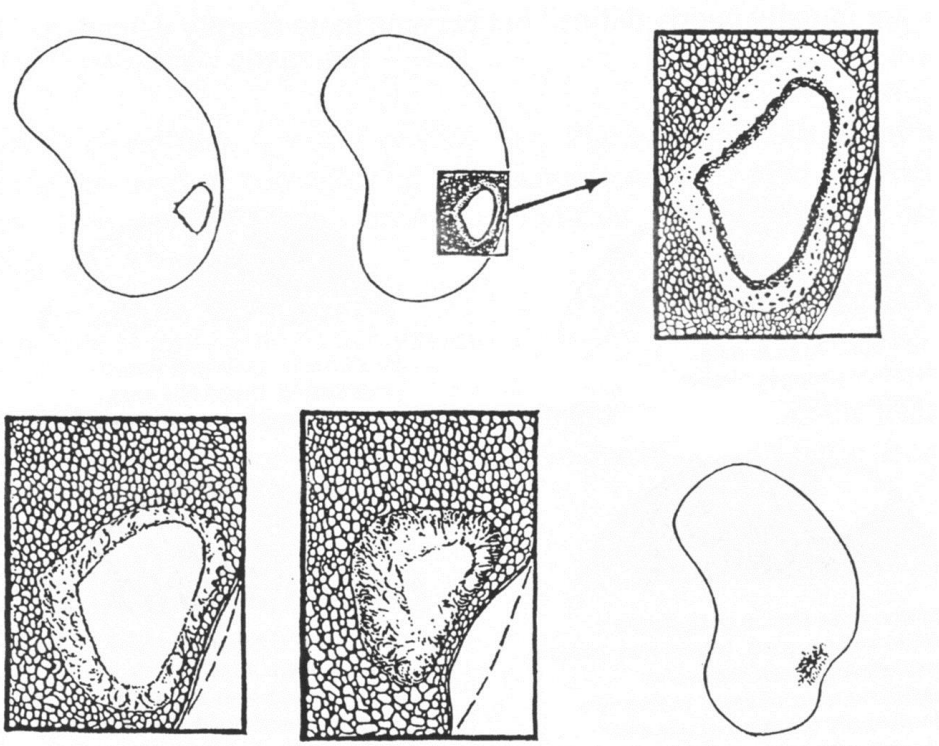
- **subacute infarcts** - peripheral inflammation becomes more prominent from 24-48 hours post-insult and advances inwards
- reactive inflammation is followed by fibroplasia from the infarct margins
- in stable or labile tissues, some parenchymal regeneration may commence at the periphery if a supporting connective tissue scaffold remains intact

- **chronic infarcts** - leukocyte invasion leads to progressive liquefaction and phagocytosis of the necrotic debris, with new collagen gradually filling in from the periphery (Figure 2)
- removal of necrotic tissue debris may take ≥ 2-3 weeks
- ultimately, most infarcts are replaced by scar tissue with the zone remaining as a firm, cream-white, contracted, wedge-shaped zone of fibrosis

Septic Infarcts

- septic infarcts may arise from initial bacterial embolism or septic thromboembolism (e.g. from valvular endocarditis) or alternatively by secondary microbial colonisation of an originally sterile infarct
- if the animal survives, the infarct will be converted into an abscess by recruitment of neutrophils

Figure 2



Diagrammatic representation of the resorption of an infarct. *Top left*, Discrete pale area surrounded by a white line. *Top center and right*, Necrotic tissue in the middle, with zone of neutrophils around the edge and connective tissue nearest the renal tissue. *Lower left*, Necrotic tissue is resorbed as the connective tissue increases. Note depression from the surface. *Lower center*, Further growth of connective tissue, resorption of necrotic tissue, and depression of the lesion below the surface. *Lower right*, A healed depressed scar.

Reference: "General Veterinary Pathology" – R.G. Thomson, 2nd edition, W.B. Saunders Company, 1984

VETERINARY BIOSCIENCE: CARDIOVASCULAR SYSTEM