Disorders of the lymph circulation: their relevance to anaesthesia and intensive care

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The lymphatic system is known to perform three major functions in the body: drainage of excess interstitial fluid and proteins back to the systemic circulation; regulation of immune responses by both cellular and humoral mechanisms; and absorption of lipids from the intestine. Lymphatic disorders are seen following malignancy, congenital malformations, thoracic and abdominal surgery, trauma, and infectious diseases. They can occasionally cause mortality, and frequently morbidity and cosmetic disfigurement. Many lymphatic disorders are encountered in the operating theatre and critical care settings. Disorders of the lymphatic circulation relevant to anaesthesia and intensive care medicine are discussed in this review.

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Applied anatomy

In the human body the lymphatic system is organized in the form of lymphatic vessels, lymph nodules, and nodes. The lymphatic vessels begin as blind-ended lymphatic capillaries and ends at the subclavian veins. In disease states with altered Starling forces and increased capillary permeability, the amount of fluid filtered out of the systemic capillaries may greatly increase in volume and overwhelm this system to produce oedema.

Disturbances of the lymph circulation are less well recognized than those of the arterial and venous circulation. The lymphatic vessels, unlike the arteries and veins, are not easily seen during dissection or surgery. Damage to the lymphatics is generally not followed by any obvious immediate consequences and it is often believed that they are expendable in surgical practice. In the clinical setting, lymphatic pathways can be disrupted by many different causes including congenital anomalies, infection, malignancy, radiation, surgery, and trauma. The effects of blockage/leakage become problematic when the usual compensatory mechanisms are overwhelmed.

Dynamics of lymph flow

The lymphatic circulation is devoid of any central pump. Lymph flow depends, predominantly, on local pressure effects and intrinsic contraction of the larger lymphatics. Any factor that increases the interstitial tissue pressure by 2 mm Hg tends to increase lymph flow in lymphatic vessels. Conversely, if the interstitial tissue pressure is greater than 2 mm Hg above atmospheric pressure, then lymph flow may...
It has been shown that increased sympathetic stimulation of the greater splanchnic nerve (sympathetic) appears to increase lymphangion contractility and lymph flow. The contraction of a lymphangion can be as high as 25 mm Hg. Sympathomimetic agents, such as norepinephrine, can markedly increase lymph flow, but it can markedly increase after a meal rich in long chain triglycerides. Normally, the liver contributes one-third of the lymph flow in the thoracic duct in a resting adult. Varying the pressure within the thoracic duct can alter each organ’s contribution to thoracic duct flow and thereby affect the composition of chyle. A raised pressure in the thoracic duct can decrease lymph flow but not effect on the hepatic lymph flow.

### Chyle

Chyle is a mixture of lymph and chylomicrons from intestinal lymphatics. It is normally found in the mesenteric lymphatics, the cisterna chilii, and the thoracic duct. The lymphatic outflow and pumping have been shown to decrease as a result of compression of the lymphatic vessels. The anterograde flow of lymph is further facilitated by the presence of numerous microscopic and macroscopic bi-leaflet valves, which exist at least every few millimetres to prevent retrograde flow. To achieve a continuous local lymph output, external intermittent compression of the lymphatics is essential from: (i) contraction of muscles; (ii) movement of body parts; (iii) arterial pulsations; and (iv) compression of the tissues by forces outside the body. Lymph veins have contractile smooth muscles and the segment of the vessel between successive valves is called a lymphangion. The lymphangion contracts when it is stretched with lymph and empties proximally into successive lymphangions. The contraction of a lymphangion can generate a pressure as high as 25 mm Hg.

The exact mechanisms of lymphatic smooth muscle contractility are unclear. Sympathomimetic agents, including alpha and beta agonists, appear to mediate lymphatic truncal contraction, as do the by-products of arachidonic acid including thromboxane and prostaglandins. There is evidence for the presence of G proteins, adenylyl cyclase, and phospholipase C activities in lymphatic smooth muscle cell membranes. Lymphatic endothelial cells produce nitric oxide, which in turn relaxes lymphatic smooth muscles, via accumulation of guanosine 3′,5′ cyclic monophosphate. Angiotensin II appears to increase lymph flow by a direct effect on lymphatic vessels, while 5-hydroxytryptamine has an opposite action by inhibiting spontaneous contractility.

The contractility of the mesenteric lymphatics is suppressed in a dose-dependent manner by halothane. The effects of other anaesthetic agents are not known. Stimulation of the greater splanchnic nerve (sympathetic) appears to increase lymphangion contractility and lymph flow. It has been shown that increased sympathetic activity gives rise to peripheral lymphoedema, which shows improvement after sympathectomy. This has been proposed to be one mechanism for reflex sympathetic dystrophy and its treatment.

In the thoracic duct, lymph flow is dependent on: (i) pressure gradients generated by contractile elements in the lymphatics; (ii) the intrathoracic pressure; and (iii) the venous backpressure in the subclavian vein. These interactions have not been studied in any detail, compared with the large amount of work on ventilatory/circulatory interactions in venous and arterial systems. PEEP and positive pressure ventilation appear to increase lymph flow through the thoracic duct. Conversely, excessively high intrathoracic pressure and a high PEEP can impede the thoracic duct flow both by direct pressure on the duct and venous hypertension.

Lymphatic outflow and pumping have been shown to increase in the setting of hypovolaemic shock in order to restore the blood volume. After major burn injury, lymph flow from the injured area increases and transports a large amount of hyaluronan, a connective tissue component of the interstitial matrix. Clinical and radiological studies have demonstrated markedly raised thoracic duct flow, with gross dilatation and increased pressures, in patients with cirrhosis. It is not understood whether such changes are a cause or secondary effect of the underlying pathology.

### Formation of oedema

Oedema results when tissue fluid accumulates faster than the lymphatic system can remove it. Ascites, pleural, and...
pericardial effusions are localized fluid collections formed by similar mechanisms. Most clinical presentations of oedema are thought to be due, primarily, to disturbances in the arterial or venous circulation, for example the pulmonary oedema seen in heart failure or ARDS. The role of the lymphatics in such disorders has not been well studied clinically because of inherent difficulties in measuring lymph flow. Pulmonary lymph flow has been shown to increase in animal models of ARDS, and has been used as an index of alveolar-capillary membrane permeability. Lymphatic endothelial cells appear to be affected by the inflammatory process, and histology of lungs from patients with ARDS has shown a marked disruption of lymphatic as well as pulmonary capillaries. Lymphatic damage may therefore have a role in the pathogenesis of the interstitial oedema of ARDS.

Widespread tissue oedema is common in critically ill patients. Multiple factors are involved including increased systemic capillary permeability, alterations in plasma oncotic forces, and altered lymphatic transport. The exact role of the lymphatics is uncertain. A significantly raised intrathoracic pressure in mechanically ventilated critically ill patients can increase the impedance to lymph flow in the thoracic duct and other larger lymphatics. In addition, alterations in lymphangion contractility and lymphatic capillary permeability may be important in critically ill patients.

**Lymphoedema**

Lymphoedema is defined as accumulation of lymph in the extracellular space as a result of lymphatic block or dysfunction. Many cases follow chronic lymphatic obstruction but it can develop acutely in any organ following surgery. The early oedema seen in surgically transposed free flaps, or transplanted visceral organs, for example bowel, lungs, and heart, is in part a result of accumulation of lymph as a result of transected lymphatics. Surgeons usually make no attempt to anastomose lymphatic vessels during such procedures.

Acute lymphoedema has been shown to affect the heart and lungs following thoracic surgery. It can depress
myocardial function and cause pulmonary hypertension as a result of perivascular oedema. Acute lymphoedema typically settles over a few days and studies have shown early restoration of lymphatic collaterals.

Chronic lymphoedema is usually seen as a complication of radical cancer surgery or radiotherapy in the Western world. In tropical and subtropical countries, filariasis, a parasitic infection, is responsible for lymphoedema in more than 90 million people. Lymph slowly accumulates in the tissues distal to the site of damage over weeks, months or years. In the initial stage the oedema is soft, pitting and temporarily reduced by elevation and a compression bandage (Fig. 2). Pain may occur from stretching of soft tissues and be related to conditions such as infection, thrombosis, and nerve entrapment syndromes. If left untreated, an inflammatory state develops with collagen deposition and soft tissue overgrowth. At this stage, the tissue becomes less pitting, more firm or brawny, and elevation of the limb no longer results in reduction of the oedema. Superimposed occult or overt infection (lymphangitis) commonly contributes to progressive limb deformity and elephantiasis (Fig. 3).

Early diagnosis is essential to prevent worsening of the condition and to help relieve the psychological impact of the disease. There is no effective drug treatment. Current options include education of patients in prevention of infection, limb positioning, exercise, compression garments and bandages, pneumatic pumps, and lymphatic massage. Prevention of acute inflammation including lymphangitis and cellulitis is crucial as the swelling tends to worsen after each episode. Surgery is occasionally undertaken to de-bulk excessive tissue or to bypass local lymphatic defects by lympho-venous anastomosis, in patients with severe deformity. During anaesthesia, neither arterial nor venous cannulation should be attempted in the lymphoedematous limbs. Non-invasive measurement of arterial pressure is often not possible.

**Drug absorption**

Protein-based drugs are broken down when administered by the enteral route and therefore have poor bioavailability. Therefore, the s.c. or i.m. route is widely used for delivery of protein drugs. The lymphatics are responsible for the absorption of subcutaneously or intramuscularly injected protein drugs including certain vaccines, human growth hormone and insulin. These drugs are not absorbed by the systemic capillaries because of their large molecular size. Liposomes, injected subcutaneously, can potentially act as carriers for the delivery of therapeutic and diagnostic agents for lymphatic disorders. Liposomes, on reaching the lymph nodes, will be phagocytosed by the macrophages, releasing the drugs to be concentrated in the lymph nodes. This route of administration may prove useful in the treatment of metastatic malignancies and parasitic infestations including filariasis.

Some oral medications including digoxin may also be absorbed by the mesenteric lymphatics. In a recent case report, a patient who was receiving oral digoxin developed an unrelated chylothorax. The patient’s plasma digoxin concentration was measured as near to zero, but that in chyle, collected from the chylothorax, was at therapeutic levels. It is not known which other medications are absorbed via the mesenteric lymphatics into the systemic circulation.

Lymphatics play a major role in systemic dissemination of toxins in cases of snake and spider bites. Firm pressure bandaging is an effective means of restricting the lymphatic transport of toxins, provided the bandage is applied within a defined pressure range of 5–9 kPa. Strict limb immobilization is necessary to minimize lymphatic flow, and walking after upper or lower limb envenomation will inevitably result in systemic envenomation despite other first-aid measures.

**Mesenteric lymph and organ dysfunction**

Recently, there has been an increase in the understanding of the gut mucosal barrier, and the pathophysiology of sepsis and multiple organ dysfunction, beyond the original
description of bacterial translocation. Bacterial translocation has been shown to occur in animal models but data from human studies are less convincing. Recent work failed to demonstrate any bacteria or endotoxin in the portal blood, mesenteric lymph, and chyle in patients with multiple organ dysfunction secondary to sepsis or multiple trauma. New reports suggest that mesenteric lymph has a significant role in the generation of remote organ injury in the presence of dysfunctional gut. Shock, trauma or sepsis-induced gut injury can result in the generation of cytokines and other pro-inflammatory mediators in the gut. Mesenteric lymph appears to be the route of delivery of inflammatory mediators from the gut to remote organs. These toxic mediators have been demonstrated in mesenteric lymph, but not in the systemic or portal circulation. Acute lung injury, endothelial damage, haemopoietic failure, and activation of white cells, have been shown to be caused by these toxic products carried in mesenteric lymph. Division or ligation of lymphatics in the gut mesentery before induction of shock prevents the increase in lung permeability and limits shock-induced pulmonary neutrophil recruitment.

Thoracic duct drainage has been proposed as a means of removing these substances before they reach the pulmonary and systemic circulation. Preliminary trials in patients with pancreatitis were promising in reducing the severity of acute lung injury. This may be because the lung is the first organ exposed to mesenteric lymph. Further work needs to be performed in this area before recommending this approach for clinical use.

**Sentinel node biopsy**

Sentinel node biopsy is increasingly performed to decide whether a patient requires a regional lymph node clearance following removal of breast or other cancers. The sentinel node is the first node to receive lymph from a primary tumour and therefore the most likely to have metastatic cells. A blue dye or a radioactive compound is injected around the primary tumour and becomes concentrated in the sentinel node to help in its identification.

Anaesthetists should be aware of some practical implications of this procedure. Patent V dye absorbs light wavelength at 640 nm, which corresponds to the wavelength of red light used in pulse oximeters. When this dye ultimately reaches blood, the percentage of deoxygenated haemoglobin is overestimated, that is the pulse oximeter reads a lower SaO2 than the actual value. This decrease in SaO2 reading can occur between 30 s to 20 min following injection, and can last several hours. Arterial blood gas analysis is recommended during the procedure. There are reports of other adverse reactions to patent V dye including: anaphylactic and anaphylactoid reactions; discolouration of urine; and tattooing of skin around the injection site.

**Other lymphatic disorders**

Disorders associated with the lymphatic system are principally seen in relation to congenital malformations, the spread of infection or invasion by tumour cells, and the effects of lymphatic obstruction or leak.

**Airway compromise**

Many lymphatic tumours including lymphomas progressively enlarge without any pain or tenderness and are often noticed first in the neck. They can present as symptomatic or asymptomatic mediastinal masses. They can result in upper and lower airway compression as well as superior vena caval obstruction. The anaesthetic implications of these conditions have been reviewed. Induction of anaesthesia can result in the ‘cannot intubate, cannot ventilate’ situation or complete loss of the airway. Some slow growing lymphatic tumours including lymphangiomatas can involve several organs in the neck and the mediastinum and can present with acute airway obstruction because of encroachment on the tongue base, parapharyngeal space, or the larynx. Cystic hygroma is a lymphatic tumour seen in infants and children, and airway management remains a challenge during induction of anaesthesia.
**Chylothorax**

Chylothorax is defined as an accumulation of chyle within a pleural cavity. A milky appearance of pleural fluid is considered typical. The condition results from either obstruction or damage of the central lymphatics, including the thoracic duct or cisterna chyli. Such damage can result from trauma, or surgery involving the oesophagus, thoracic spine, and aorta. Traumatic chylothorax is seen after blunt or penetrating chest injuries (Fig. 4). A significant number of such cases can be associated with a fracture dislocation of the thoracic spine. 56 Sudden hyperextension of the spine has been suggested as the cause of thoracic duct injury in this setting. Spontaneous chylothorax has been reported after minor trauma such as coughing or stretching following ingestion of a fatty meal.

Chylothorax, right, left, or bilateral, is a recognized complication of central venous cannulation, and stellate ganglion, and coeliac plexus blocks. This may result from direct damage to the thoracic duct or thrombosis of the superior vena cava, innominate, or subclavian veins.

The clinical presentation of a chylothorax may be delayed from the time of injury if the patient is not receiving enteral feeding or is receiving continuous gastric suction. The probability of chylothorax is increased if the effusion increases in size with resumption of enteral feeding. The diagnosis can be confirmed by demonstrating a typical chylous composition (Table 1).

The principles of management include: (i) pleural drainage with appropriate fluid and nutritional replacement; (ii) measures to reduce the production of chyle; (iii) treatment of the underlying cause; and (iv) obliteration of the pleural space or ligation of a demonstrated thoracic duct leak. Conservative therapy is usually tried first for 2–3 weeks, after which surgical/radiological intervention is considered.

Decompression of the pleural space by continuous tube drainage relieves symptoms and accurately monitors chyle loss. Fibrin clots can block the chest drains. Occasionally multiple chest drains are required, if there are multiple loculations and re-accumulation. Placement of a chest drain may be difficult in the presence of a frail segment in patients with multiple trauma. Ultrasound or CT guided insertion of chest drains is helpful in these situations.

Replacement of daily losses of fluid, calories, proteins and electrolytes is essential to avoid severe hypovolaemia, hypoalbuminaemia, and malnutrition. Continuous loss of lymphocytes leads to immunosuppression and an increased susceptibility to infections. Chyle has been re-transfused into patients to prevent the loss of lymphocytes and proteins, but this procedure has inherent technical difficulties. Oral or enteral nutrition may increase lymph flow and therefore is not generally encouraged. Commercially available enteral feeds with a fat content less than 1 g litre⁻¹, which are rich in medium chain triglycerides, may be suitable for some patients. Total parenteral nutrition at the outset is now considered to be the optimal approach in critically ill patients.

In isolated case reports, chylothorax has been successfully treated with octreotide, and etilefrine. The exact mechanism of the action of octreotide is not clear. Octreotide is used in patients with high output gastrointestinal fistulae because of its inhibitory effect on gastric and pancreatic secretion. If gastrointestinal volume and enzymes are reduced by octreotide, it may subsequently decrease chyle flow in the thoracic duct. Etilerine is a sympathomimetic agent used in the management of postural hypotension. It is thought to cause smooth muscle contraction of the thoracic duct and may thereby reduce the leak.

There have been case reports in children where persistent thoracic duct leaks have been reduced by the application of very high intrathoracic pressures over a number of days. Also, the reduction of venous hypertension, secondary to pulmonary arterial hypertension, by inhaled nitric oxide has been found to be helpful in such cases.

It may take several weeks for a chylothorax to resolve. A high volume chyle output predicts failure of continuing conservative management. The decision to abandon conservative management is frequently difficult. However, an operative intervention is usually indicated if the average daily chyle loss exceeds 1500 ml in adults, or chyle drainage is unchanged after 2 weeks of conservative management.

The thoracic duct can be tied off surgically to prevent leakage of chyle into the body cavities. Interventions including videoassisted thoracoscopic, thoracotomy, or pleurectomy have to be individualized depending on the primary cause. It may be helpful to administer nasogastric olive oil or cream before surgery in order to increase chyle flow and help identify the site of the leak. Alternatively methylene blue, injected between the toes, helps outline the thoracic duct. Percutaneous transabdominal catheterization of the cisterna chyli or thoracic duct has been used to embolize chylous fistulae. Following such interventions, lymph is thought to return to the venous circulation via collateral channels.

Although the mortality from chylothorax is decreasing, significant morbidity continues as a result of lymphopenia, hypoalbuminaemia, malnutrition, and prolonged hospitalization. Prolonged central venous catheterization, total parenteral nutrition, multiple chest drain insertions, and additional surgical procedures contribute to the risk.

**Chylous ascites**

In chylous ascites, chyle accumulates in the peritoneal cavity. It results from an obstruction or leak in either the cisterna chyli or its large afferent lymphatics. It has a similar aetiology to chylothorax. Lymphomas account for more than half of the cases. Abdominal and retroperitoneal surgical procedures can damage the lymphatics. In post-surgical cases, the diagnosis is often delayed because the...
peritoneal fluid is initially serous until enteral feeding is reintroduced.\textsuperscript{35} The diagnosis of chylous ascites is based on the chemical content of the peritoneal fluid. Peritoneal fluid in this condition is very rich in proteins, usually 50\% greater than that of plasma. Management of chylous ascites is similar to that of chylothorax. Repeated paracentesis is performed for patient comfort and to minimize the risk of development of the abdominal compartment syndrome.\textsuperscript{35} Persistent chylous ascites following several weeks of conservative treatment warrants a more aggressive approach including insertion of a peritoneovenous shunt, percutaneous embolization,\textsuperscript{27} or direct surgical repair of the cisterna chilii.\textsuperscript{35}

Chylopericardium

Chylopericardium is a rare disorder in which chyle accumulates in the pericardial cavity. It can be congenital or secondary to pericarditis, pancreatitis, cardiac or thoracic surgery, or malignancies. Chylopericardium is seen in children undergoing cardiac surgery with development of cardiac tamponade. The principles of management include: pericardial drainage, a low lipid diet, and surgery in persistent cases.

Conclusions

The lymphatic circulation is important in health and disease but its functions are poorly understood and often overlooked. Clinicians need to be aware of lymphatic disorders, which have direct relevance to anaesthesia and intensive care medicine. It is likely that future research will uncover other functions for the lymphatic circulation.

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