Haemodynamics of lymphoedema

Robert Dennis

The Starling hypothesis and available data on the physiology of the microcirculation provide a clear model for understanding how arterial, capillary and venous haemodynamics may affect the production of lymphatic fluid. This review considers the studies that have focused on venous and arterial haemodynamics and calf muscle pump function. Although the evidence base available is small, changes in the haemodynamics of lymphoedematous limbs have been identified. Arterial inflow appears to be increased, while venous outflow is decreased, both of which result in high hydrostatic pressures within the microcirculation. The pathophysiology of these changes remains unclear and, at present, there are few available interventions.

Key words

Lymphoedema
Haemodynamics
Venous outflow
Arterial inflow
Calf muscle pump

The Starling hypothesis and the available data on the physiology of the microcirculation provide a model for understanding the production of interstitial fluid. The Starling equation (*Table 1*) illustrates the forces which contribute to fluid movement (Berne and Levy, 1993).

Within this model, average values for capillary hydrostatic pressure (P_c) in human skin have been measured at 32mmHg at the arterial end and 15mmHg at the venous end. Plasma protein oncotic pressure (π_p) is approximately 25mmHg, and is predominantly produced by albumin. *In vivo*, albumin exerts an enhanced osmotic force due to the binding of sodium ions (known as the Gibbs-Donnan effect; Berne and Levy, 1993). Within the interstitial space, the small amount of albumin crossing the

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endothelium produces an interstitial fluid oncotic pressure (π_i) between 0.1–5mmHg, and interstitial fluid hydrostatic pressure (P_i) has been estimated to be between -1mmHg and -7mmHg. These values predict filtration of approximately 2% of the plasma into the interstitial space, and the classic conclusion to be gained from the Starling hypothesis is that filtration of fluid at the arterial end of the capillaries will lead to subsequent re-absorption of 85% of this fluid into the capillaries and venules. However, experimental studies have not observed these predicted rates of absorption or lymphatic production, which has led to a substantial re-evaluation of the Starling hypothesis. In the current model, it is not the hydrostatic and oncotic pressures within the interstitial space that principally define fluid movements, but rather those pressures in the subglycocalyx channels between endothelial cells (Levick, 2004). This current model predicts lower rates of net fluid filtration and that most of the filtrated fluid will be returned to the vascular system via the lymphatics.

Although changes to these factors may alter fluid movement, arterial and venous haemodynamics affect fluid movement by their influence on P_c. In the normal steady state, the most important variable factor controlling P_c is precapillary resistance. Changes

in arterial pressure per se have little influence on capillary filtration, since the myogenic autoregulation of the precapillary vessels means that the resistance changes to maintain a constant capillary pressure. Increased P_c attributed to raised venous pressure results in ankle swelling, lipodermatosclerosis and skin ulceration associated with venous hypertension. Considering these marked effects, it is unsurprising that the haemodynamics of lymphoedematous limbs have been of interest as potential initiating or aggravating factors, and also as potential areas of intervention.

Plethysmography

A variety of techniques have been used to study lymphoedema, including several used in everyday practice such as Doppler ultrasound. Less well-known

Table 1
Starling hypothesis
Fluid movement=k $[(P_c+\pi_i)-(P_i+\pi_p)]$
P_c = Capillary hydrostatic pressure P_i = Interstitial fluid hydrostatic pressure π_p = Plasma protein oncotic pressure π_i = Interstitial fluid oncotic pressure k = Filtration constant for the capillary membrane

in clinical practice is the technique of plethysmography, which has been used in many experimental studies to measure haemodynamics. The principle of this technique is to use the changing volume of a tissue to calculate blood flow.

Air plethysmography
The air plethysmography technique is based on the pressure changes within a sealed compartment around a limb. The patient stands on tiptoes, activating the calf muscle pump. This action reduces the venous volume within the leg, and is detected as a reduction in the pressure within the sleeve. The ejected volume from each contraction and the venous refilling time after 10 contractions can subsequently be deduced. The ejection volume provides information about the function of the calf muscle pump. The refilling time is reduced by venous outflow obstruction or the presence of venous incompetence and reflux.

Photoplethysmography
Photoplethysmography assesses variation in the light absorption of the skin by haemoglobin in the dermal venous plexuses. As the venous plexuses empty (for example, as a result of calf muscle pump activity), the amount of light reflected from the skin epidermis increases as the volume of haemoglobin decreases. As with air plethysmography, a shortened refilling time can be attributable to either outflow obstruction or venous reflux. A refilling time of less than 21 seconds has been shown to achieve a sensitivity of 100% and a specificity of 100% for deep vein thrombosis and outflow obstruction (Tan et al, 1999).

Venous occlusion plethysmography
The arterial inflow to a limb segment, in addition to certain venous characteristics, can be measured using venous occlusion plethysmography. Two cuffs are used to isolate a limb segment with uninhibited arterial inflow, but venous return remains occluded. The volume change in the limb segment is then used to calculate the arterial inflow. On releasing the pressure in the proximal cuff, the rate of decrease of the limb segment volume corresponds to the maximum venous outflow.

There are a number of different techniques for measuring the volume change of the limb segment.

Strain gauge plethysmography
Strain gauges are made of either mercury or an indium-gallium alloy sealed within a silastic tube. An important feature of the metal column within the gauge is that the resistance of the column is dependent on its length and is also inversely related

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to the cross-sectional area. As calf size increases, the accompanying change in resistance relates directly to the circumference change of the underlying limb segment. Strain gauge plethysmography has been widely used in the investigation of limb blood flow and has been validated against venography and direct venous pressure measurements (Mason et al, 1982).

Opto-electronic plethysmography
Opto-electronic plethysmography uses an infrared grid to measure the cross-sectional area of an object within the frame. The total volume of the limb segment at rest can be calculated as well as the changing cross-section of a single point on the limb during venous occlusion. One study has validated opto-electronic plethysmography against strain gauge plethysmography in the measurement of limb circumference during venous occlusion plethysmography (Stanton et al, 1998).

These techniques have been used to study haemodynamics in three main areas:
▶▶ Arterial haemodynamics
▶▶ Venous haemodynamics
▶▶ Calf muscle pump.

Changes in arterial inflow
In 1967 Jacobsson carried out an

in-depth study of 25 patients with upper limb lymphoedema following axillary surgery, and eight patients with lower limb lymphoedema (six with primary and two with secondary lymphoedema). Using venous occlusion plethysmography, arteriovenous pO2 differences and isotope clearance techniques, he showed a 42% increase in blood flow in the lymphoedematous limbs.

This observation of increased arterial inflow to oedematous limbs has also been made in three further studies. Martin and Foldi (1996) studied 48 women with upper limb lymphoedema and reported increased arterial flow in the oedematous arm. A study of 50 patients with upper limb lymphoedema following breast cancer treatment (Svensson et al, 1994) also showed increased arterial inflow in 68% of patients measured using the Doppler ultrasound. Yildirim et al (2000) similarly demonstrated increased arterial inflow with Doppler ultrasound after modified radical mastectomy.

Jacobsson's study (1967) showed increased flow in the skin and subcutaneous tissues only, while muscle blood flow was unchanged. However, he did observe that isotope clearance techniques were less consistent when assessing muscular blood flow, as the injections were performed with blinded muscular compartments. This observation of increased blood flow being limited to the skin and subcutaneous tissues is further supported by findings from Qvarfordt et al (1983). In this study, muscular blood flow in the deep compartments, measured using Xenon133 clearance, was shown to be decreased in seven patients with lower limb secondary lymphoedema during exercise (29.9 *versus* 32.4ml/min/100g, $P<0.05$). The authors attributed this reduced blood flow to raised intramuscular pressure.

Not all the evidence presented in the literature supports the theory of increased blood flow in oedematous limbs. Stanton et al (1998) compared the blood flow in oedematous arms following treatment for breast cancer, with the blood flow in the normal

arms of the same patients. Using a strain gauge and venous occlusion plethysmography, they found blood flow to lymphoedematous arms per unit volume was decreased (2.51 *versus* 3.77ml/100ml/min, *P*<0.05). The total blood flow to lymphoedematous and unaffected limbs, however, was the same (unaffected: 40.72ml/min; oedematous: 41.78ml/min), and the decrease in flow per unit volume was presumed to be due to a dilution effect of the increased volume of the lymphoedematous limb.

The causes for increased blood flow to the skin and subcutaneous tissues in lymphoedematous limbs are not clear. Jacobsson (1967) postulated that an increased volume of interstitial fluid increases diffusion distances; increased blood flow results either from vasodilatation secondary to the release of vasoactive factors, or from an increase in the density of capillaries. There is some histological evidence of an increased number of blood vessels within the skin and subcutaneous tissues (Roberts et al, 1994). These theories conclude that increased arterial inflow is a result of oedema, although it should be considered that there may also be a role for increased arterial inflow in the development of lymphoedema. Studies in patients with sympathetic dystrophy have suggested that increased arterial flow may be a consequence of decreased vasoconstrictor autoregulation, and that this might be related to the development of oedema (Brunning et al, 1980; Cooke et al, 1990). Damage to the autonomic nervous supply to a limb has been postulated as another causative factor in secondary lymphoedema following radiotherapy for breast cancer (Kühl and Molls, 1995).

Changes in venous outflow

Capillary haemodynamics are sensitive to changes in venous haemodynamics, as highlighted by the oedema associated with chronic venous hypertension and an increase in P_c. An initial study by Pflug et al (1971) noted an increase in venous blood flow by a 'factor of 2' using an indicator dilution technique. No subsequent *in vivo* studies have

supported these observations, however, and indicator dilution techniques have been criticised as measures of blood flow because the injection of the indicator itself increases blood flow (Rådegran, 1999).

In their study of arterial inflow, Qvarfordt et al (1983) measured venous emptying by strain gauge plethysmography. They observed significantly lower venous emptying in the oedematous leg (44.7 *versus* 61.4ml/

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min/100g), and presumed that raised interstitial pressure due to lymphatic obstruction might be responsible for partial compression of the veins, thereby reducing venous emptying. In this study, however, six of the seven patients had undergone radiotherapy to the inguinal lymph nodes for the treatment of malignant melanoma.

These figures are significant, as in a series of 81 patients with upper limb lymphoedema following breast cancer treatment, Svensson et al (1994) reported evidence of venous outflow obstruction in 57% of lymphoedematous limbs on colour Doppler imaging. Normal venous flow was observed in only 30% of patients. Szuba et al (2002) reported a 4.6% prevalence of concomitant venous obstruction in a group of patients being seen in a specialist lymphoedema clinic. Of this 4.6%, over half had been treated for malignant disease. Hence, there appears to be a significant incidence of direct damage to veins in secondary lymphoedema, resulting in outflow obstruction and venous hypertension. Venous outflow obstruction might, therefore, contribute significantly to secondary lymphoedema and duplex scanning may be indicated. Intervention for venous outflow obstruction has

had a role in patients with measured evidence of outflow obstruction and in whom there are severe symptoms of venous insufficiency (Lees and Redwood, 2006). A long saphenous vein graft can be used as either a femoro-femoral bypass for iliac vein obstruction (Palma operation), or a femoro-popliteal graft for occluded deep thigh veins. Relief of symptoms and long-term patency is reported in up to 70% of cases (Lees and Redwood, 2006). Endovascular stenting has been performed more recently, but long-term patency rates have not been compared to surgery.

Changes in venous outflow have also been observed in primary lymphoedema. Christenson et al (1985) studied eight patients with unilateral primary lymphoedema. Venous anatomy and function was studied with venography, Doppler studies and photo-plethysmography. Venography was unremarkable in two patients and four patients showed dilated, tortuous patent veins without postphlebitic changes. Doppler studies demonstrated an incompetent popliteal vein in four patients, although these findings are not quoted in relation to the presence of varicose veins on the venogram. Photoplethysmography showed a shortened refilling time in the oedematous legs compared with that of the healthy legs (20 *versus* 9.4 seconds). These results would suggest an association between lymphoedema and the development of venous hypertension and venous reflux. Such an association is also supported by Struckmann et al (1986) in a study using strain gauge plethysmography and refilling time to differentiate oedema of venous and lymphatic origin. Although mean refilling time was shown to be normal in patients with primary lymphoedema (56 seconds), refilling time was significantly shortened in two patients compared to normal patients (36 and 34 seconds *versus* 42–96 seconds, respectively). These two patients are noted as having clinical evidence of venous incompetence with mild varicose veins, and venography showed a normal deep venous system and no evidence of thrombosis.

Saito et al (2005) also provide evidence that venous haemodynamics in lymphoedematous lower limbs show similarities to that of limbs with chronic venous insufficiency secondary to reflux disease. By measuring deoxygenated haemoglobin with near-infrared spectroscopy during exercise, they calculated an ambulatory venous retention index (AVRI). The mean AVRI of the lymphoedema group was significantly higher than that of healthy legs and similar to that observed in limbs with mild chronic venous insufficiency.

More direct evidence of venous congestion and hypertension comes from Kim et al (1999), who studied 41 patients with lymphoedema using air plethysmography. They showed an increase in ambulatory venous pressure (31.4 *versus* 23.4mmHg), venous volume (94.1 *versus* 77.6ml) and venous filling index (2.1 *versus* 1.3ml/sec) in lymphoedematous limbs. The changes in venous filling index and venous volume correlated with greater leg volume and subcutaneous thickness in the lymphoedematous limbs, suggesting that soft tissue oedema from lymphatic stasis gradually impedes venous return.

Although the evidence analysed leans towards venous outflow obstruction, which has been identified in large veins in secondary lymphoedema (Svensson et al, 1994; Szuba et al, 2002), none of the studies in primary lymphoedema have demonstrated venous obstruction with venography or Doppler ultrasound. It would, therefore, appear that any obstruction is at the level of small veins down to the venules; the mechanism of this obstruction remains unclear. Given the observed association with venous reflux, it is also possible that some cases of lymphoedema may be precipitated by the development of venous reflux resulting from congenital valve abnormalities or post thrombotic damage.

These observed changes in venous haemodynamics and the increase in P_c would, in the author's opinion, most likely result in oedema exacerbation. The degree to which venous hypertension contributes to tissue oedema is unknown, and, although correcting superficial venous reflux may logically help to reduce oedema, the available evidence from Földi and Idiazabal (2000) is to the contrary. Földi and Idiazabal (2000) reported on a series of 68 patients with lower limb lymphoedema who had undergone operation for varicose veins. Leg swelling worsened or was unchanged in more than 90% of patients. Considering the risks of surgery in lymphoedematous limbs, surgery can only be recommended if there is an absolute indication present (for example, ascending phlebitis and/or bleeding). This leaves complete decongestive physiotherapy and support bandaging as the best treatment options for both the lymphoedema and any contribution from venous hypertension.

The observation of venous hypertension and increased arterial inflow is on the face of it paradoxical, since increased P_c as a result of venous hypertension would be expected to reduce arterial inflow. The results of a study by Gamble et al (1998) offer a potential explanation for this paradox.

Strain gauge plethysmography was used to measure lower limb blood flow in 21 participants during small cumulative increases in the pressure of a venous occlusion cuff. At the highest venous congestion pressure of 59.2mmHg, arterial blood flow did not differ significantly from flow at the lowest congestion pressure of 4.8mmHg (2.45 *versus* 2.77ml/min⁻¹/[100ml]⁻¹). This observation is a result of the decrease in precapillary vascular resistance as venous pressure increases, which maintains a constant flow through the capillaries. The signal pathway for this response is likely to lie in the endothelium of the microvasculature. This reaffirms an overall picture of high hydrostatic pressures within the capillary microcirculation that maintain flow and also accentuate fluid loss into the interstitial space.

Calf muscle pump function

The importance of the calf muscle pump in leg oedema is clear from the common observation of foot swelling following long periods of relative immobility, such as long-haul flights. The effects of flying on calf muscle pump function in lymphoedematous limbs have been investigated by a questionnaire-based study (Casley-Smith et al, 1996). The results from this study suggested that reduced muscle pumping may have a role in the initiation or exacerbation of the swelling.

Two of the studies already discussed also assessed calf muscle pump function. Struckmann et al (1986) measured the expelled volume using ambulatory strain gauge plethysmography, and Kim et al (1999) measured ejection fraction using air plethysmography.

Struckmann et al (1986) observed a normal mean ejection volume in lymphoedematous limbs, while limbs associated with previous deep vein thrombosis had reduced ejection volumes resulting from obstruction of the outflow tract of the calf muscle pump. The normal ejection volume in lymphoedema is consistent with the absence of venous obstruction observed in venous outflow studies.

Contrary to these results, Kim et al (1999) observed a significant reduction in ejection fraction in the lymphoedematous legs (63.0% *versus* 68.6%) compared with that of normal limbs. This reduction in ejection fraction correlated with increased volume of the leg and increased subcutaneous thickness. Once again, B-mode ultrasound did not demonstrate any overt venous outflow obstruction in the limbs. An alternative explanation from outflow obstruction is poor functioning of the calf muscle pump due to the restricted movement of a swollen leg. Leg swelling may result in a vicious circle of reduced calf muscle pump function, venous hypertension and exacerbation of tissue oedema. Although it is difficult to predict its effect, maintaining the range of movement in the leg may help limit leg and foot oedema.

Conclusions

There have been few studies of the haemodynamics of lymphoedema. The studies which have been done are small and difficult to compare because of the range of data collected and the varying techniques used. Variation in the aetiology, extent and duration of oedema in the limbs studied also makes comparisons difficult.

There is evidence of changes in arterial and venous haemodynamics associated with lymphoedema. Arterial inflow appears to be increased in lymphoedematous limbs. Although the pathophysiology of this is unclear, it may be because of autonomic nerve damage or a consequence of changes in the microcirculation of the skin and subcutaneous tissues.

There is evidence of venous outflow obstruction, raised venous pressure and also an association with valve incompetence and venous reflux in lymphoedematous limbs. Overt venous obstruction has been identified within large veins in secondary lymphoedema. However, in primary lymphoedema the site of restricted venous outflow is unclear. Maintaining calf muscle pump function may help limit foot oedema, but other interventions in the venous system are only appropriate in very particular cases. JL

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