Thieme

Go with the (Lymph) Flow?

Presentation for the Max Ratschow medal

My inspiration for a career in lymphatics came from two sources: the first was a visit to the Foeldi clinic and the second was a visit to Professor Fredi Bollinger's angiology lab in Zurich. These back to back visits in 1984 gave me insight into the best practice in lymphoedema treatment at the time as well as state of the art research techniques. On my return, I unashamedly introduced the Foeldi principles of lymphoedema treatment to the UK. I also set about setting up Fluorescence microlymphangiography in my new lab. Also present during my visit to Zurich was Hugo Partsch who, as a fellow dermatologist, has been very influential ever since as a role model, mentor and friend.

The idiom 'go with the flow' means go with the prevailing attitude or do what the majority are doing even if you disagree. There is an implication one does not really believe it is necessarily the right thing to do but it is the easiest thing to do. There is a tendency currently with interstitial fluid dynamics to 'go with the flow' despite overwhelming scientific evidence that the accepted direction of flow is actually incorrect. As a result, the lymphatic system has been underestimated in its importance for the understanding and treatment of peripheral oedema.

Starling principle of fluid exchange

Interstitial fluid is formed from plasma ultrafiltration across the capillary wall. The filter is the endocapillary coating known as the glycocalyx. The glycocalyx is a semi-permeable membrane which covers the intercellular cleft of the capillary wall through which the plasma ultrafiltrate flows [1]. The primary force encouraging filtration from blood into the interstitium is the capillary hydrostatic pressure, whereas the dominant force in 'sucking' fluid into the capillary, and so opposing filtration, is the plasma osmotic pressure.

In his classic equation for fluid filtration Starling considered both plasma and interstitial hydrostatic and osmotic pressures [2]. However, the interstitial pressures were considered generally negligible so subsequently largely ignored. Venous capillary pressure (~15 mmHg) is less than plasma osmotic pressure (~25 mmHg) at heart level so if only these two Starling forces are considered then venous reabsorption would occur. This resulted in the traditional view that venous capillaries continuously reabsorb the filtrate generated by arterial capillaries leaving the lymphatic drainage as largely redundant.

The revised Starling Principle indicates no venous reabsorption in peripheral tissues

In recent years it has been possible to measure interstitial hydrostatic and osmotic pressures and they are not negligible. Measurements in human skin, muscle and mesentery indicate that the sum of the forces opposing filtration (essentially the difference between interstitial and plasma osmotic pressures plus interstitial hydrostatic pressure) is ~12.5 mmHg which is lower than venous capillary pressure (~15 mmHg). From all experimental data, without exception, the venous capillary and even venular pressure exceeds the force that would create reabsorption. This indicates that a well perfused capillary is in a state of filtration along its entire length although with dwindling filtration from arterial to venular end [3].

One factor that ensures this process of filtration in the steady state is the glycocalyx within the capillary wall. There is a low protein concentration within the subglycocalyx providing filtration occurs. If filtration declines or ceases, plasma proteins accumulate in the interstitium and raise the interstitial protein concentration. This enables plasma proteins to diffuse into the subglycocalyx space, so reducing the venous reabsorption force and encourage restoration of fluid filtration into the interstitium. The subglycocalyx therefore acts as a regulator or stabilizer for filtration [4].

Transient venous reabsorption

Venous reabsorption can occur but only transiently if the Starling forces change. The default position is always to return to a state of filtration. If a bandage is applied to a leg, then this would raise interstitial fluid pressure and encourage fluid reabsorption but within minutes subglycocalyx plasma protein concentration would rise to restore filtration despite the bandage staying in place.

Interstitial fluid drains via the lymphatic vessels

Traditionalists maintain that 90 % of the plasma ultrafiltrate is reabsorbed with the remaining 10 % drained via the lymphatics. Calculations with the revised Starling pressures and consideration of the subglycocalyx, indicate that If there is no sustained venous reabsorption, then the responsibility for draining interstitial fluid must rest with the lymphatic system. The physiology can then be considered as very simple: capillaries filter to produce interstitial fluid and lymphatics largely drain it.

Capillary filtration equates with lymph flow in the steady state. The rate of lymph formation depends on interstitial fluid pressure and volume. Lymph drainage is therefore the rate limiting step for tissue volume homeostasis. Tissue fluid balance thus depends critically on lymphatic function in all tissues except specialized regions e. g. kidney, intestinal mucosa.

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All chronic oedema is a lymph drainage problem

These fundamental physiological principles relating to capillary fluid dynamics mean that an excess of interstitial fluid (oedema) must indicate a failure of lymph drainage. For interstitial fluid to accumulate sufficiently to produce oedema capillary fluid filtration must exceed lymph drainage for a sufficient period of time. Therefore, all peripheral oedema results either from too much capillary filtration (increased lymph load) or not enough lymph drainage, or a combination of the two. Put another way, either the lymph drainage is impaired and so fails to drain normal amounts of capillary filtrate (this is lymphoedema) or the lymph drainage cannot compensate for the high lymph load e. g. venous oedema.

Venous oedema

The diagnosis of venous oedema is made frequently in clinical practice whether chronic venous disease exists or not. If we analyze the physiology in chronic venous disease, we will still find that it is the capacity of the lymph drainage that mainly determines if oedema occurs or not. When venous hypertension exists then increased capillary pressure will result in increased capillary filtration (increased lymph load). If the lymph drainage is robust and responsive, then lymph drainage should compensate for the higher fluid filtration by increasing lymph flow in which case no oedema will occur. If the lymph drainage is not robust or not sufficiently stimulated through movement and exercise to cope with the level of lymph load, then oedema will occur. Therefore, venous oedema is still mainly determined by the capacity of the lymph drainage.

Varicose veins

Given the ever-changing dynamic balance between capillary filtration and lymph drainage to maintain tissue volume (homeostasis), it can be difficult to determine clinically which is more at fault in the genesis of peripheral oedema; is it the capillary filtration or the lymph drainage?

An example of this is with varicose veins.

Patients with varicose veins may or may not have associated peripheral oedema in that leg. If they do, the varicose veins are not unreasonably blamed. Varicose veins usually indicate venous reflux. This means that in the erect posture venous pressure remains high for longer (venous hypertension) and so capillary filtration increases (higher lymph load). This requires higher lymph drainage to compensate. If the lymph flow cannot keep pace with capillary filtration then oedema occurs. Resolution of the venous reflux through Endovenous Ablation (EVA) should resolve the oedema, but sometimes the oedema does not improve after EVA.

Why?

The answer has to be that the dominant cause of the oedema in the first place was impaired lymph drainage and a reduction in the capillary filtration (lymph load) through treatment by EVA has not reduced lymph load sufficiently to enable the lymph drainage to cope.

As lymph vessels are formed from veins embryologically (see below) it is likely that if veins are constitutionally weak (to produce primary varicose veins) so may be the lymphatic vessels.

Phlebolymphoedema

If high levels of capillary filtration exceed lymph flow over a long period of time in venous disease, then eventually the lymphatic vessels become permanently damaged from this chronic overload. A state of true lymphoedema then supervenes. This is called phlebolymphoedema and can arise with venous hypertension from severe varicose veins and post thrombotic syndrome. Phlebolymphoedema is analogous to high output heart failure from a large A-V fistula where the heart does not recover even if the fistula is closed.

Deep venous obstruction from May-Thurner Syndrome

May-Thurner syndrome (Iliac vein compression syndrome) can present with left leg oedema. There have been very few studies looking at lymph drainage in non-thrombotic May-Thurner Syndrome but from first principles, venous hypertension caused by iliac vein compression would cause oedema if the resulting high capillary (venous) filtration exceeds the lymph drainage. If the non-thrombotic deep venous obstruction was the sole explanation, then release of the iliac vein compression should solve the problem and it often doesn't. Given the fact that a high incidence of iliac vein occlusion can be found in healthy volunteers, perhaps the fault is also with the lymphatics [5].

Venous reflux in inherited forms of primary lymphoedema

There is not only a close relationship between veins and lymphatics physiologically but embryologically as well. It has been established that lymphatic vessels are mainly derived from the cardinal vein [6]. As causal genes for primary lymphoedema have been discovered, and the genotype investigated to establish the full phenotype, so a strong association between venous reflux and primary lymphoedema has been identified. In Milroy disease 90 % of patients with a proven VEGFR3 mutation have superficial venous reflux on venous duplex ultrasound examination, although it may have no physiological impact as the lymphoedema develops at birth before the child is erect [7]. In Lymphoedema-Distichiasis Syndrome due to mutations in the FOXC2 gene 100 % of those affected have superficial venous reflux and approximately a third have deep venous reflux, Mutations in FOXC2 are strongly associated with primary valve failure in veins of the lower limb [8]. Venous reflux should, in theory, increase oedema by increasing lymph load but anecdotal reports indicate that vein ablation in FOXC2 patients does not help with the swelling.

Venous malformations and Klippel-Trenaunay Syndrome

Klippel Trenaunay syndrome (KTS) remains a classically described vascular disorder in which venous abnormalities coexist with port wine stains accompanied by bone overgrowth [9]. Limb swelling related to lymphatic abnormalities is usually present. Identification of causal genes indicates that KTS may not be a specific en-

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tity and may be part of a more heterogenous phenotypic spectrum with somatic mutations in PIK3CA being responsible in at least some cases. The PIK3CA related overgrowth spectrum (PROS) encompasses a range of venous and lymphatic malformations associated with soft tissue overgrowth and KTS falls within that spectrum [10]. Unlike the inherited Milroy and lymphoedema Distichiasis forms of primary lymphoedema where the causal gene is germline and therefore found in the blood, PROS is a somatic mosaic disorder where the gene fault is confined to the tissue affected.

Sporadic vascular and lymphatic malformations can also be caused by somatic mutations in the RAS/MAPK pathway [11]. Mutations in this pathway are well described in cancer as well as in germline RASOpathies such as Noonan syndrome and Neurofibromatosis. Somatic mutations can cause Arterio-venous malformations but also slow flow malformations including lymphatic malformations and lymphoedema.

The identification of causal genes for these somatic mosaic vascular disorders helps understanding of the development of vascular and lymphatic malformations, and once again indicates the close relationship between lymphatics and veins.

Genotyping of affected tissue in vascular malformations should be a key element of management across the diverse medical subspecialties to which affected patients present. Genetic stratification of these disorders may help diagnostically and prognostically but may also serve to guide new therapies given the range of drugs, developed for cancer, which are known to affect these pathways.

Should lymphatic investigations always be performed in cases of peripheral oedema associated with venous disease?

The answer, in an ideal world, is yes. The problem is that lymphoscintigraphy can often appear normal in the presence of venous disease. High capillary filtration causes high 'flush through' of injected tracer to make lymph flow look normal when it may not be. Quantitative lymphoscintigraphy is necessary to investigate venous oedema. If lymph drainage is measured over the period of the scan e. g. 2 hours, by drawing a region of interest over the ilio-inguinal nodes and calculating the accumulation of tracer in the nodes relative to the injection site then a crude estimate of lymph flow can be made. If nodal uptake of tracer remains low e. g. < 3 % of injection dose at 2 hours, then lymph drainage is abnormal irrespective of the degree of venous disease. On the other hand, values of > 15 % ilio-inguinal uptake at 2 hours would suggest high capillary filtration from the veins is the dominant factor in the development of the oedema [12].

Multifactorial lymphoedema from co-morbidities

In modern clinical practice patients often have multiple morbidities and each can contribute to lower limb oedema particularly in the elderly when chronic oedema is very common [13]. The morbidly obese patient can develop lower limb oedema for several reasons: firstly, obesity in itself impairs lymphatic function [14]; secondly, obesity leads to immobility and little stimulation of lymph drainage from movement and exercise; thirdly, long periods spent with the legs dependent results in venous hypertension and increased capillary filtration; fourthly, a large abdominal girth resting on the thighs when sitting (particularly leaning forward to a computer) obstructs venous drainage (and probably lymph drainage as well) [15]. This takes no account of other co-morbidities such as heart failure and sleep apnoea syndrome both of which increase right sided heart pressures and so venous pressures.

Conclusion

The traditional dogma of venous reabsorption being the dominant route by which tissue fluid drains must be abandoned given the overwhelming scientific evidence that the Starling pressures add up to a filtration force. Oedema is always caused by capillary filtration exceeding lymph drainage. Therefore, lymph drainage is the rate limiting step either because the lymph drainage is impaired or, because it is overwhelmed by excessive capillary filtration e. g. venous hypertension (from venous disease, venous obstruction or heart failure) or reduced plasma osmotic pressure (from protein loss-nephrotic syndrome, or malnutrition), or altered vascular permeability e. g. inflammation. In circumstances of sustained capillary filtration, the lymph drainage can be permanently damaged so that reversal of the high filtration does not resolve the oedema (now lymphoedema). This can happen in chronic venous disease (Phelbolymphoedema).

There is an argument for calling all forms of chronic oedema as lymphoedema in order to make clinicians think of the importance of the lymph drainage. Furthermore, oedema is a build-up of interstitial fluid and interstitial fluid is little different in composition from pre-nodal lymph. Also, management is the same for chronic oedema (such as venous oedema) and lymphoedema. The principle is to stimulate lymph drainage through exercise and compression, and to return to normal any excess capillary filtration whatever the cause.

Because of the inescapable close relationship between veins and lymphatics both physiologically and genetically, vascular specialists should always consider the lymph drainage. Don't 'go with the flow' (the prevailing attitude) by thinking most oedema is venous in origin, go with the lymph flow.

Interessenkonflikt

Der Autor gibt an, dass kein Interessenkonflikt besteht.

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