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ANALYSIS OF LYMPHATIC DRAINAGE IN VARIOUS FORMS OF LEG EDEMA USING TWO COMPARTMENT LYMPHOSCINTIGRAPHY

P. Bräutigam, E. Földi, I. Schaiper, T. Krause, W. Vanscheidt, E. Moser

Abteilung Nuklearmedizin, Radiol. University Klinik Freiburg (PB,TK,EM), Földiklinik, Fachklinik für lymphologische Erkrankungen, Hinterzarten (EF), Zentrum für Nuklearmedizin, Paracelsus-Klinik Osnabrück (IS), and Universitäts-Hautklinik, Freiburg (WV), Germany

ABSTRACT

The anatomical and functional status of the epifascial and subfascial lymphatic compartments was analyzed using two compartment lymphoscintigraphy in five groups of patients (total 55) with various forms of edema of the lower extremities. Digital whole body scintigraphy enabled semiquantitative estimation of radiotracer transport with comparison of lymphatic drainage between those individuals without (normal) and those with leg edema by calculating the uptake of the radiopharmaceutical transported to regional lymph nodes. A visual assessment of the lymphatic drainage pathways of the legs was also performed.

In patients with cyclic idiopathic edema, an accelerated rate of lymphatic transport was detected (high lymph volume overload or dynamic insufficiency). In those with venous (phlebo)edemas, high volume lymphatic overload (dynamic insufficiency) of the epifascial compartment was scintigraphically detected by increased tracer uptake in regional nodes. In patients with deep femoral venous occlusion (post-thrombotic syndrome), subfascial lymphatic transport was uniformly markedly reduced (safety valve lymphatic insufficiency). On the other hand, in the epifascial compartment, lymph transport was accelerated. In those patients with recurrent or extensive skin ulceration, lymph transport was reduced. Patients with lipedema (obesity) scintigraphically showed no alteration in lymphatic transport.

This study demonstrates that lymphatic drainage is notably affected (except in obesity termed lipedema) in various edemas of the leg. Lymphatic drainage varied depending on the specific compartment and the pathophysiologic mechanism accounting for the edema. Two compartment lymphoscintigraphy is a valuable diagnostic tool for accurate assessment of leg edema of known and unknown origin.

The lymphatic system is deranged in various forms of leg edema of both lymphatic and non-lymphatic origin including venous-lymphedema, cyclic idiopathic edema, and lipedema (obesity) (1,2). As no discrete differences exist on clinical grounds among the various edema syndromes, differential diagnosis and identification of the main pathophysiologic factors may be difficult or impossible (1).

Cyclic idiopathic edema of women entails much more than manifestations of the premenstrual syndrome. Because of increased permeability of the blood capillaries, both plasma proteins and great quantities of fluid (6-8 liters) may accumulate in the interstitium within a few days. As a result, the lymphatic system is overloaded (high volume insufficiency) with anasarca and in rare instances, even pulmonary edema (2).

In phleboedema, the venous and capillary hydrostatic pressure are increased and the demand for lymphatic drainage increases (2). Over time, the lymphatic system becomes functionally insufficient, the lymph transport capacity decreases, and edema ensues (termed safety valve lymphatic insufficiency) (2). In more chronic venous insufficiency, lymph flow is also impaired (lymphedema). In lipedema or obesity, the pathophysiology of lymphatic drainage is less clear. Stallworth et al (3) claims that the lymphatics, arteries, and veins are unaltered. Herpertz (4), on the other hand, suggests a slight mechanical drainage blockage to lymph capillaries, precollectors, and collectors secondary to increased pressure of the excess fatty tissue. Földi et al (2) emphasizes a combination of contributions to leg enlargement including lipedema + lymphedema and lipedema + cyclic idiopathic edema. In the clinical presentation of patients with lipedema (pressure sensitive edema and a supramalleolar fat collar), both edema of the top of the foot and a positive Stemmer's thickened skin fold sign (signs of lymphedema) are present as well.

Two compartment lymphoscintigraphy is a useful method to quantify lymphatic drainage in the epifascial and subfascial compartment of the legs (5-7). This study analyzed the lymphatic drainage in the previously mentioned forms of leg edema as well as in deep venous occlusion (post-thrombotic syndrome) using two compartment lymphoscintigraphy. Of special interest was the contribution of this scintiscan technique in the differential diagnosis in leg edema of uncertain origin.

MATERIAL AND METHODS

Patients

Between 1990 and 1996, 55 patients clinically separated into five groups were subjected to two compartment lymphoscintigraphy.

Group 1: Eighteen patients (10 female, 8 male; age 19-48 years) had localized malignant melanoma of the skin proximal to the umbilicus. Accordingly, involvement of the lymphatic drainage of the lower extremity was deemed unlikely. Two compartment lymphoscintigraphy was carried out and the results were used to define normal values.

Group 2: Ten women (age 21-41 years) had cyclic idiopathic edema likely from increased microvascular permeability (8). Fluid retention consisted of swelling of the face, breast, abdomen, and legs which worsened as the day advanced. A diurnal weight variation of more than 1.4 kg daily was considered abnormal. A modified Streeten test (9) was also used and was considered positive if the renal excretion of an oral fluid load (20 ml/kg body weight) was less than 60% after 4 hours of orthostasis.

Group 3: Seven patients (4 male, 3 female; age 36-64 years) with primary venous varicosities of the greater saphenous vein (phleboedema) (stage IV according to Hach) (10) underwent lymphoscintigraphy to exclude occult lymphedema before excision and ligation of varicose veins. Functionally and morphologically, the femoral (deep) venous system was intact according to Doppler sonography and phlebography.

Group 4: Eleven patients (6 male, 5 female; age 45-68 years) had deep vein thrombosis (from 1-19 years) (post-thrombotic syndrome) before lymphoscintigraphy. Clinical complications included dermatoliposclerosis and recurrent skin ulcerations.

Group 5: Five of 9 women (age 23-37 years) showed considerable fat changes of the upper and lower legs (lipedema). In the other four patients, "edema" was seen only in the upper leg. Stemmer's skin fold sign was absent in all patients and lipedema had been present for over 5 years.

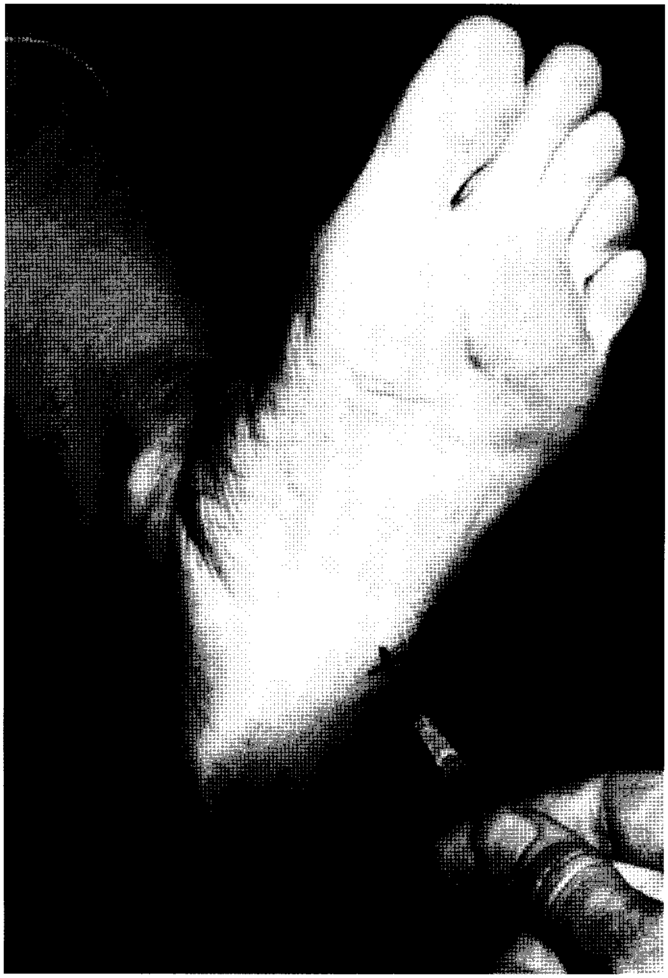


Fig. 1. Injection of the radiotracer into the lateral aspect of the side of the foot at a depth of 1.5 cm ensures drainage by the subfascial lymphatics.

Lymphoscintigraphy

Subfascial compartment: 4x20 MBq 99m Tc of labeled human albumin nanocolloid was injected into the dorsolateral muscles of the sole of the foot *(Fig. 1)*. Standardized stimulation of lymph flow followed using bicycle ergometry at a low level of intensity (25 Watt) in 2 phases. After 20 minutes the first whole body scintigram was performed using a single head gamma camera (Diacam®, Siemens Company). After another 30 minutes of bicycle ergometry and a recovery phase, a second scintigram was obtained at 2 hours.

To examine the epifascial compartment, a second study using identical lymphatic stimulation and acquisition was performed after disappearance of residual tracer activity (at least 2 days later) but the radiopharmaceutical was injected subcutaneously between the first and third toes.

Lymphatic function was assessed by analyzing the uptake of the radiopharmaceutical into the lymph nodes. For this purpose, regions of interest (ROI) were drawn, one over the inguinal and parailiac lymph nodes (ROI_1), and a second over the injection site and the lymph vessels (ROI_2).

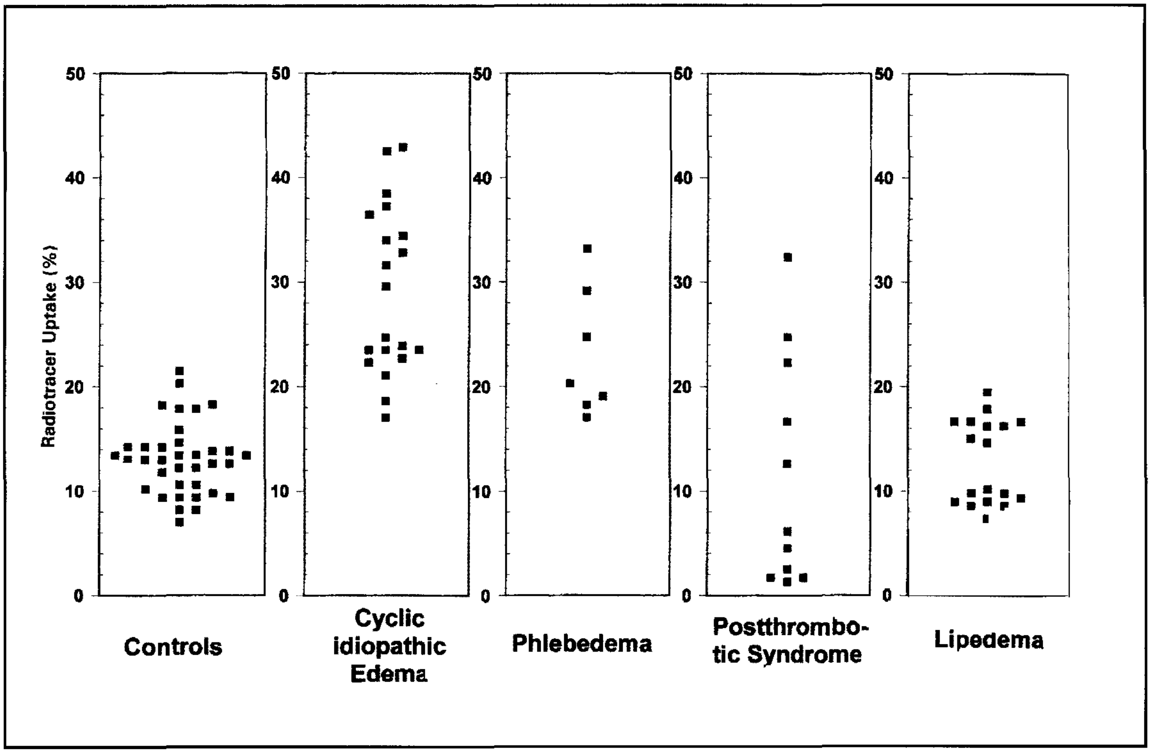


Fig. 2. Lymph node radiotracer uptake (%) for each patient in the epifascial compartment.

Percent uptake was calculated as $(ROI_1)/(ROI_1 + ROI_2) \times 100$.

Lymphatic transport was also visually evaluated. Reduced or absent radiotracer activity in regional lymph nodes represented impaired lymphatic drainage. The appearance of 99m Tc nanocolloid in the proximal portion of the thoracic duct was interpreted as physiologic lymph pooling before entry into the venous system and thought to represent accelerated lymphatic transport (high lymph volume overload or dynamic insufficiency).

The median, the 5th and the 95th percentiles were determined for each set of data. The data were also analyzed with one way ANOVA followed by multivariant analysis (Dunn's test). A significant difference was accepted at a p value of <0.05.

RESULTS

The radiotracer uptake values for each patient are shown in *Fig. 2* (epifascial compartment) and *Fig. 3* (subfascial compartment). In cyclic idiopathic edema and lipedema, the uptake values are shown for both legs. In phleboedema and deep venous occlusion (post-thrombotic syndrome), only the uptake values for the affected (edematous) side are shown. The median, the 5th and the 95th percentiles of each patient subgroup are shown in *Table 1.* A comparison of these results with those of patients with lymphedema (11) are shown in *Table 2.*

Control Group

Quantitative evaluation: The radiotracer

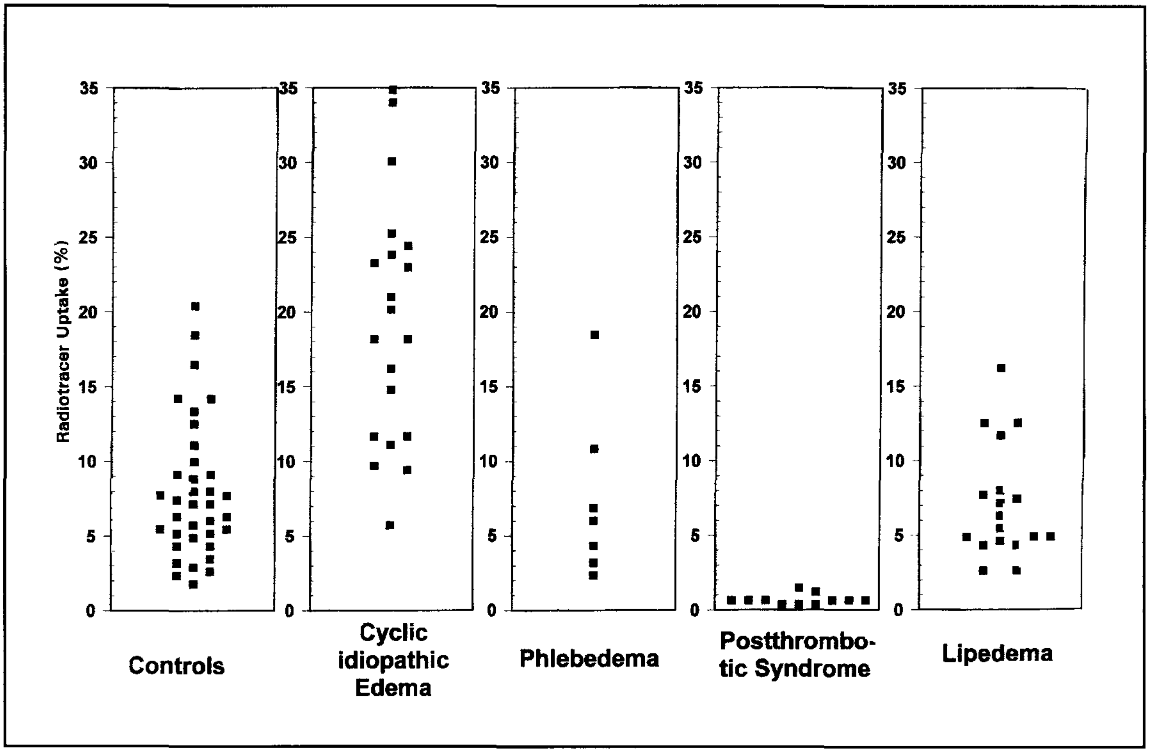


Fig. 3. Lymph nodal radiotracer uptake (%) for each patient in the subfascial compartment.

uptake in the lymph nodes of patients with intact lymphatic systems varied widely with the range of uptake values in the subfascial compartment greater than those of the epifascial compartment *(see Table 1, Figs. 2,3).*

Visual assessment: Each of 18 patients showed both epifascially and subfascially a substantial enhancement of the inguinal and parailiac lymph nodes *(Fig. 4).* The paraaortic lymph nodes were visualized in 6/18 patients. The popliteal lymph nodes were visible after subfascial injection in 16/18 patients and in 2 patients also after epifascial injection. Radioactive "bands" of the draining lymph vessels were observed within 20 min. after tracer injection.

Cyclic Idiopathic Edema

Quantitative evaluation: There was a significantly higher epifascial uptake in both legs when compared with the control subjects. In one patient, tracer uptake of 43% was approximately 3 times higher than that of the average uptake of control patients. None showed a reduced uptake. Subfascially, the uptake was also significantly increased compared with the controls as well as those with phleboedema *(Table 1). Fig. 5* shows a characteristic pattern of a patient with cyclic idiopathic edema.

Visual assessment: Lymphoscintigraphy typically showed unusually intense activity of regional lymph nodes involved in lymph drainage of the legs in the epifascial compartment. In 4 of 10 patients, the labeled nanocolloid was detectable at the origin of the thoracic duct. Liver and spleen activity was also seen. Of interest, highly intense activity bands were seen in draining lymph vessels 2 hours after injection in 5 of 10 patients suggestive of ongoing (increased) lymphatic

TABLE 1
Median, 5th and 95th Percentile of the Radiotracer Uptake Values of Each Patient in Each Subgroup for Both the Epifascial and Subfascial Compartment. A Significant Statistical Difference Between a Given Group and Control Subjects is Marked with ★, and with Cyclic Idiopathic Edema with ▲, and Phleboedema with ■.

	Epifascial			Subfascial		
Patients	median	5th percentile	95th percentile	median	5th percentile	95th percentile
Controls	13.0% ■ ▲	11.8%	13.5%	7.0% ▲	5.6%	9.0%
Cyclic idiopathic edema	27.2% ★	23.0%	34.5%	19.2% ★	11.9% ■	23.9%
Phleboedema	20.4% ★	17.5%	33.5%	6.1% ▲	2.1%	18.5%
Post-thrombotic syndrome	6.3% ▲ ■	1.8%	24.5%	0.4% ▲	0.2% ★	0.7%
Lipedema (obesity)	12.7% ▲ ■	9.3%	16.8%	5.9% ▲	4.7%	8.1%

TABLE 2
Comparison of the Scintigraphic Results with the Functional State in Different Forms of Leg Edema. The Lymph Transport Rates, as Quantified by Two Compartment Lymphoscintigraphy.

Leg Edema	Lymph Transport		Pathophysiological comments	
	subfascial	epifascial	subfascial	epifascial
Lymphedema*	–	N –	low volume (lymph) insufficiency	low volume (lymph) overload; in the first four months transport rates often are normal*
Lipedema (obesity)	N	N	unchanged but lymphatics may be involved with both low and high volume insufficiency	
Cyclic idiopathic edema	+	+	high volume (lymph) insufficiency	high volume (lymph) overload
Varicosities with patient deep veins	N	+ N	no changes in lymph transport	high volume (lymph) overload
Post-thrombotic syndrome (deep varicosities)	–	+ N	safety valve (lymphatic) insufficiency	high volume (lymph) overload early; safety lymphatic valve insufficiency, superimposed late

N = Normal + = Increased, – = Decreased.
*The data for lymphedema were taken from a previous report (25).

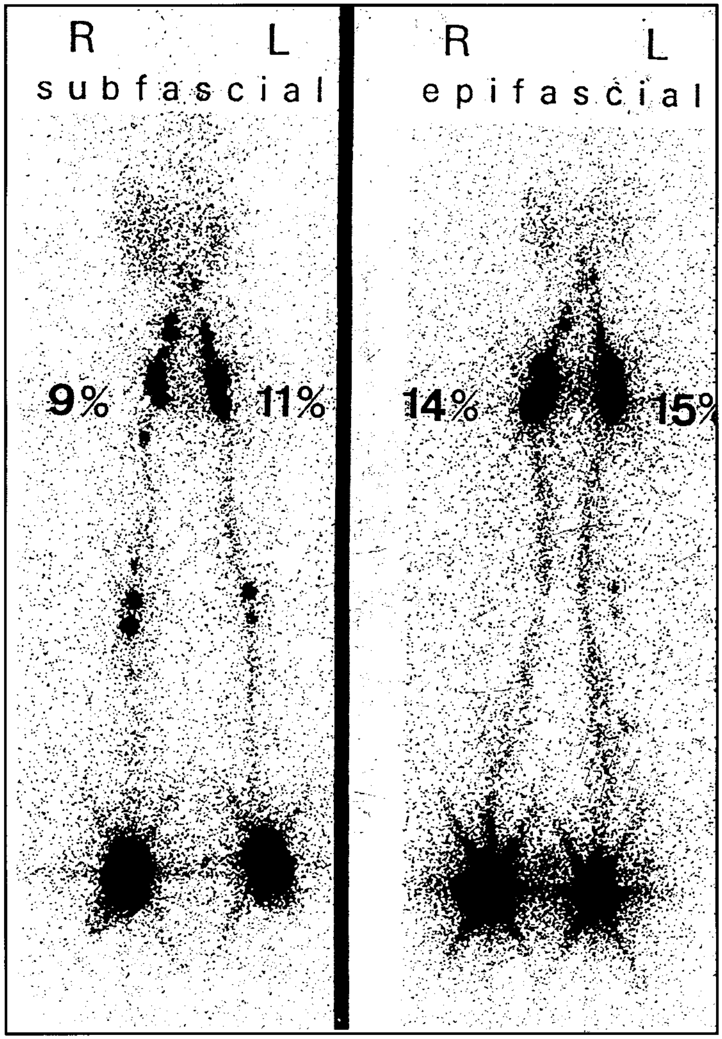


Fig. 4. Normal scintigraphic findings (control). Epifascially, the inguinal and parailiac lymph nodes are well visualized with intact lymphatic drainage. Subfascially, the popliteal lymph nodes are also visible in most patients. The tracer uptake values are shown (% of injected dose).

transport of the radiopharmaceutical. Subfascially, patients uniformly showed bilaterally good enhancement of the regional lymph nodes.

Phleboedema

Quantitative evaluation: Epifascially, uptake was significantly increased compared with the control groups suggesting accelerated lymph transport. Subfascially, the uptake was similar to those of the control group *(Table 1).*

Visual assessment: Epifascially, normal storage activity was seen in 4 patients. In the remaining 3, the storage was intense on the affected side. In one patient, the radiopharmaceutical was found at the origin of the thoracic duct suggestive of accelerated lymph transport. Two patients showed supramalleolar activity at a site with lipodermatosclerotic changes. Subfascially, all 7 patients showed well demarcated inguinal and parailiac lymph nodes.

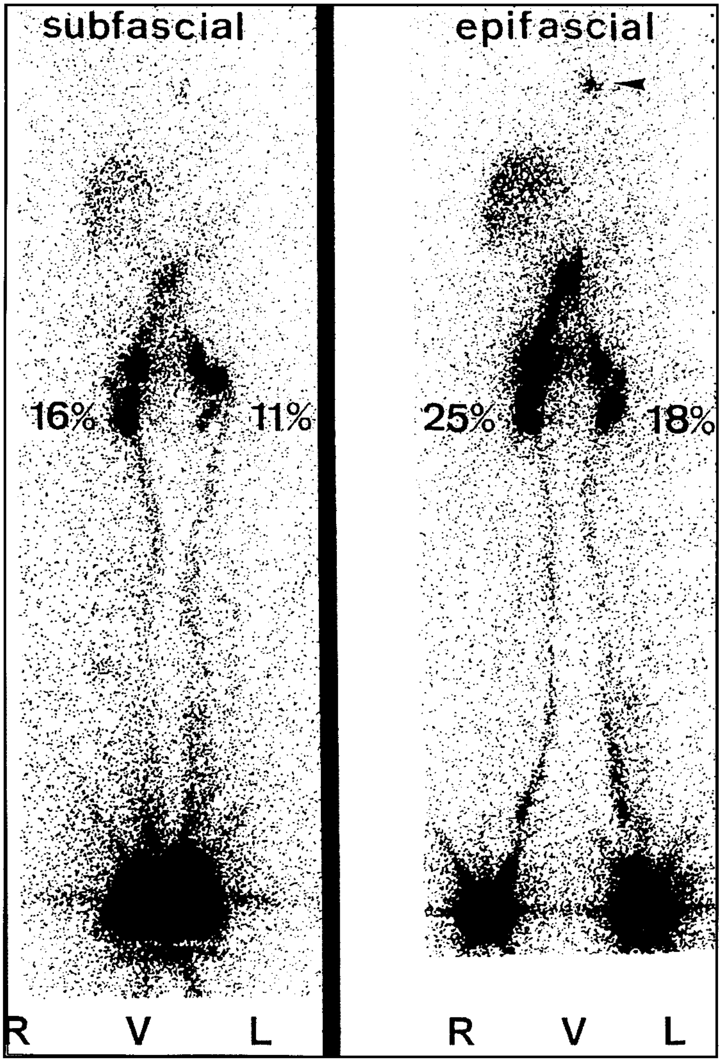


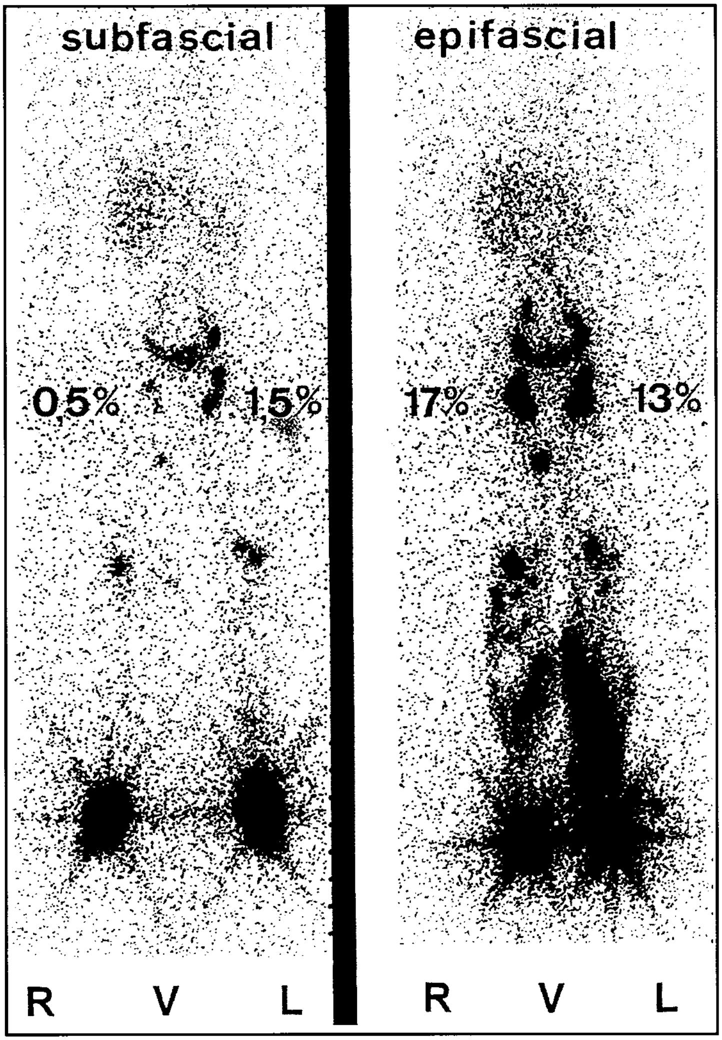
Fig. 5. Two compartment lymphoscintigraphy in a 33-year old woman with cyclic idiopathic edema. The scintigram shows a symmetrical, "supernormal" enhanced uptake in lymph nodes draining the legs suggestive of accelerated lymph transport. Increased lymphatic drainage is also suggested by activity in the distal thoracic duct (arrowhead), likely representing physiologic "pooling" before entry into the bloodstream. As the scintigrams display, radiotracer uptake values are increased bilaterally as lymph transport is accelerated with high lymph volume overload (dynamic insufficiency).

Deep Venous Occlusion (Post-Thrombotic Syndrome)

Quantitative evaluation: Subfascially, uptake was sharply reduced (<1.5%) in each of 11 patients *(Fig. 2)*. In contrast, radiotracer uptake was within the normal range or higher epifascially in 5 patients who had developed deep vein thrombosis within the last few years. In the other 6 patients with advanced lipodermatosclerotic and ulcerated skin changes, the epifascial uptake was reduced *(Fig. 3)*.

Visual assessment: In the 11 patients with post-thrombotic syndrome, the inguinal lymph nodes were either not or just faintly seen. Epifascially, on the other hand, the uptake in the inguinal lymph nodes was well depicted in most of the patients *(Fig. 6)*. Only in 3 patients with longstanding skin ulceration were the regional lymph nodes not visualized. In 5 of 9 patients after epifascial injection, lymphatic drainage was impaired only above the malleolus at a site where lymph vessels were likely obliterated by ulceration.

Fig. 6. A 49-year old patient with deep femoral venous occlusion (post-thrombotic syndrome) in the right leg for 6 years and on the left for 5 years. The scintigram shows good epifascial lymph drainage on both sides although prominent supramalleolar dermal backflow is demonstrable. This local disturbance of lymph drainage corresponds to ulceration of the skin. In contrast, subfascially the inguinal lymph nodes are poorly seen suggesting damage to the subfascial lymphatic system.



Obesity (Lipedema)

Quantitative evaluation: The uptake of these 9 patients was similar to that of the control group *(Table 1, Figs. 2,3).*

Visual assessment: Each patient displayed a normal and usually symmetrical lymph transport in both compartments with normal activity of the draining lymph nodes. A regional lymph transport disturbance was not observed.

DISCUSSION

Proper assessment of peripheral edema requires entertaining a variety of causative factors. Among these are chronic superficial venous insufficiency, deep vein thrombosis (post-thrombotic syndrome), lymphedema, lipedema or obesity, and cyclic idiopathic edema (2). There are often several indeterminant forms of edema, in which the individual etiologic components can not be easily distinguished. If not properly recognized, undue consequences may arise. For example, where venous or phleboedema is combined with primary lymphedema, venous stripping and ligation may result in severe worsening of the peripheral edema, especially the lymphedema component. Scintigraphic assessment of the lymphatic system is therefore strongly recommended.

Electron microscopy suggests that cyclic idiopathic edema derives from a microangiopathy (2) with increased permeability for plasma protein leakage and subsequent high volume lymphatic overload (dynamic insufficiency). Two compartment lymphoscintigraphy demonstrates this phenomenon in cyclic idiopathic edema. A previous report suggested that normal findings occurred in 2 patients (12), but these findings were based solely on visual and not semiquantitative analysis.

The observed differences between the slight increase in subfascial uptake and the more prominent epifascial increase in uptake may relate to the fact that greater interstitial fluid drainage from the subfascial lymphatic system is less well handled and that in cyclic idiopathic edema, the lymph transport capacity decreases subfascially before that in the epifascial compartment. A similar mechanism may pertain to primary lymphedema, which may lead to a form of subclinical compartment syndrome (5,6,11).

Analysis of lymphatic drainage by two compartment lymphoscintigraphy shows that high lymph volume overload (dynamic insufficiency) in cyclic idiopathic edema is demonstrable by this technique. In contrast to a high volume overload, the lymphoscintigraphic criteria are different in low lymph volume impairment (lymphedema). The differential diagnostic criteria in mixed forms, for example, a combination of lymphedema and cyclic idiopathic edema, are shown in *Table 2* (2,5).

An accelerated lymph transport in the epifascial compartment observed in phleboedema results from increased microvascular hydrostatic pressure, and an increase in the lymphatic load from increased transcapillary filtration. Similar findings have been described after radiotracer studies by Jacobsson and Feldmann (13) and Seki et al (14). These investigators report increased work of lymphatics, which is pathophysiologically similar to the situation in cyclic idiopathic edema.

Radiotracer active retention at the site of local trophic skin disturbances was detected in some patients. These localized lymph transport disturbances, however, did not necessarily reflect global lymphatic dysfunction. Tiedjen et al (15) found localized disturbances of epifascial lymph drainage without impaired lymph transport in nearly every patient with phleboedema.

The functional implications of epifascial high volume insufficiency have a morphological counterpart in the lymphographic investigations of Battezzati (16) and Nitzsche (17) and their coworkers. They described lymphographically dilated and elongated lymph collectors with postvalvular dilatation.

Vitek and Kaspar (18) examined the subfascial compartment by lymphography. They found that in phleboedema, 11 of 12 patients had morphologically normal lymph vessels. In contrast to the epifascial, the subfascial compartment exhibited only minor localized dilatations of lymph collectors (18). These morphological findings correlate well with our scintigraphic studies, which show normal subfascial lymph transport in most of these patients.

In phlebological disorders, our results demonstrate the importance of the lymphatic circulatory system as an important alternative pathway for removal of excess tissue fluid. In deep venous occlusive disease (postthrombotic syndrome), two compartment lymphoscintigraphy demonstrated a marked functional disturbance of lymphatic transport. The pathophysiological disturbance is characterized by an increased lymph load in the presence of reduced lymphatic transport capacity (i.e., termed safety valve insufficiency) (2).

Subfascially, each patient studied showed markedly reduced lymph transport *(Fig. 2)*. Impaired lymph transport secondary to venous thrombosis is lymphoscintigraphically demonstrable shortly after deep vein thrombosis of the leg (19). With deep vein thrombosis, there is acute venous hypertension which apparently damages adjacent lymph vessels by direct mechanical and inflammatory effects (20). Therefore, the lymphatic transport capacity is reduced at the same time the lymph load is increased (15,21).

Epifascially, a uniform lymphoscintigraphic pattern was not observed. There was, however, a relation between the status of the lymphatic transport capacity and the complication rate and duration of the underlying disorder. That the epifascial lymphatic transport may be normal or accelerated in uncomplicated disease has previously been recognized (15,22). The findings in the epifascial compartment are probably explained by venous hypertension secondary to insufficient perforating veins. Venous hypertension leads to a high lymph volume overload or phlebo-lymphodynamic insufficiency from increased blood capillary filtration and increased production of lymph (2). As the disease progresses and complications ensue (e.g., recurring skin ulceration), the epifascial lymphatic transport capacity and subsequently the lymph transport rate decreases. This outcome is likely due to persistent overburdening of and local destruction of lymphatics (dermatoliposclerosis and skin ulceration) (2,19). In this situation, high lymph volume overload (dynamic insufficiency) deteriorates into a functionally less favorable condition termed safety valve insufficiency of the lymph circulation (2).

Deep venous occlusion (post-thrombotic syndrome) shows coexistent functional involvement of the lymphatic system as exemplified by two compartment lymphoscintigraphy. The lymph system is an important component in post-thrombotic syndrome, which at least during the early phase, tends to mitigate the edematogenic effect of deep vein thrombosis by a compensatory increase of lymph transport in the epifascial compartment (23). This phenomenon becomes clinically important when post-traumatic edema is examined. The most common differential diagnosis in this situation consists of edema from deep venous occlusion with or without secondary lymphedema (7). Using two compartment lymphoscintigraphy, this distinction can be readily made *(Table 2).*

All patients with pure lipedema (obesity) showed normal lymph transport rates in both the epifascial and subfascial compartments confirming previous reports (24,25). In contrast, Bilancini et al (26) observed an asymmetrical lymphoscintigraphic appearance of the inguinal lymph nodes and decreased lymph drainage. These results are similar to findings in lymphedema. Nevertheless, such asymmetry, especially by quantification of number of lymph nodes, is not indicative of the function of the lymphatic system and has not been taken into consideration as a proper indicator of lymphedema in lymphoscintigraphy by others (5,6,19,25).

A transition from pure lipedema to lipo-lymphedema and to lymphedema is recognized (2). The sluggish lymph transport in lipedema, as observed by Bilancini et al (26), is probably traceable to a lymphedematous component in patients with lipedema. Tiejen et al also regarded lipedema as a “risk factor” for lymphostatic edema (24). This concept is supported by the lymphatic distribution found after indirect lymphography at the injection site and by remarkably large caliber lymph collectors (20). Again, these morphologic changes are not necessarily indicative of functional abnormalities as no alterations in lymphatic function were seen in pure lipedema.

It is important to recognize that no clear cut difference can be detected on lymphoscintigraphy between a normal functional state and a minor functional alteration in lymph transport. Patients with varicose and epifascial high volume overload (dynamic insufficiency) may have uptake tracer values within the normal range reflecting considerable physiological variability in lymphatic drainage. Olszewski and Engeset (27), for example, found leg lymph flow (stimulated through movements of the foot) that varied from 0.2 to 2.2 ml/h. A similar wide range was seen in the normal distribution of the uptake values in our studies. Thus, epifascially, lymph flow varied from 7.5% to 21.8% uptake. If a normal individual is taken at 8% uptake, then it could double (16%) in the presence of a high volume overload and technically still be within the normal range. Only if the value tripled to 24% would lymph transport rate be seen to be clearly pathological. Accordingly, with respect to quantitative analysis, small changes in the functional state may escape lymphoscintigraphic detection. It is noteworthy that the distribution range of leg lymph flow rates decreases to a similar extent as stimulation of lymph flow increases (27). Lymph flow in a two compartment lymphoscintigraphy, however, can not be indefinitely stimulated within a standardized protocol as the increased lymphatic workload would not be tolerated by every patient.

In conclusion, two compartment lymphoscintigraphy is a powerful method for detecting lymphatic abnormalities in a variety of leg edema syndromes. The functional and anatomical state of each lymphatic compartment can be analyzed. By demonstrating the pathophysiology of leg edema including its effect on lymphatic function on both the epifascial and subfascial compartments, two compartment lymphoscintigraphy allows the pathogenesis of the edema to be better understood.

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Dr. Peter Bräutigam
Leiter des Zentrums für Nuklearmedizin
Paracelsus-Klinik Osnabrück
Am Natruper Holz 69
49076 Osnabrück, GERMANY
Telephone: 49-541-966 3022/3023
Fax: 49-541-966 3024