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Evaluation of transport kinetics in lymphoscintigraphy: Follow-up study in patients with transplanted lymphatic vessels

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Abstract. To quantitate visual findings in lymphoscintigraphy with ^{99m}Tc-labeled stannous sulfur colloids, a numeric index of transport kinetics was designed by combining visual assessment of five criteria: temporal and spatial distribution of the radionuclide, appearance time of lymph nodes, and graded visualization of lymph nodes and vessels. For assessment, scores were used ranging from 0 to 9. Thus, the resulting transport index (TI) ranged from 0 (normal) to 45 (pathological). TI in healthy extremities was less than 10.

Lymphoscintigraphy was performed routinely in healthy lower extremities to ensure normal drainage before transplantation. In 122 investigations of upper and lower extremities, TI was found to be very sensitive (97.4%). Specificity was 90.3%. An interobserver study in 179 investigations revealed a high correlation ($r = 0.96$). A total of 23 patients underwent autologous lymphatic transplantation. The average decrease of TI was 5.9: 31.1 before and 25.2 after transplantation. This decrease of TI was correlated with a marked decrease of the volumes of the extremities (from 3423 ml to 2580 ml). Changes in TI and volume were significant ($p < 0.05$).

This method of evaluation has proved to be very sensitive, reproducible, and able to measure the transport capacity of only two or three transplanted lymph collectors.

Key words: Lymphoscintigraphy – Lymph vessel transplantation – Lymphatic transport kinetics

The development of lymphatic transplantation techniques in the surgical department of our hospital [1, 2, 3] required a simple method to determine and quantitate the success rate. Although volume measurement of the affected limb seems to be adequate, it depends on physiological parameters such as heart and kidney function and, therefore, may be influenced by drug therapy of cardiac and renal diseases. In addition, bandages and lack of mobilization of the extremity diminish the value of volume measurements in follow-up studies.

Radiocontrast lymphography requires technical expertise and, particularly in patients with lymphedema, is extremely difficult to perform. Thus, it is not suitable for follow-up studies [7]. Lymphoscintigraphy is a versatile, simple technique [6, 8, 10] which may be suited well to assess lymphatic function even in patients not accessible to radiocontrast lymphography. Lymph passage through vessel grafts is visualized by lymphoscintigraphy. However, verbal description of lymphoscintigraphic findings fails to assess the effects of surgical intervention on lymphatic flow. The goal of this study was the evaluation of surgical intervention on lymph drainage by quantifying lymphoscintigraphic criteria.

Materials and methods

A total of 81 patients (61 women and 20 men) with lymphedema or suspected lymphedema gave informed consent for lymphoscintigraphy of the affected limb. When transplantation was planned, the healthy lower extremity was investigated in addition to ensure normal lymph drainage before removal of lymph vessels. In the beginning of this study lymphoscintigraphy of the healthy contralateral side was also done.

Of the patients 32% suffered from malignoma, particularly from breast carcinoma (19%). The mean age was 45.5 years; 23 patients underwent lymphatic transplantation.

Stannous sulfur precolloids (Lymphoscint, Nuclear GmbH, D-7889 Grenzach-Wyhlen) were labeled with 75 MBq (2 mCi, upper extremity) or 110 MBq (3 mCi, lower extremity) ^{99m}Tc-pertechnetate and boiled for 4 min. Particle size ranged from 20 to 60 nm [4]. Up to 0.5 ml of the solution was injected SC into the web space of the first and second fingers or toes, avoiding intravascular injection [5]. Discomfort was minor and momentary.

Mobilization of the extremity was done by handgripping for 3 min or by ergometric stress (25 W for 3 min). Then a series of up to four scintigraphic images with a large field of view gamma camera was started, imaging the whole limb and the corresponding thoracic, pelvic, and abdominal regions. Registration was limited by 100000 counts or 10 min. Mobilization and acquisition were repeated until lymph nodes and vessels appeared. The procedure was terminated after a maximum period of 4 h. After 60 min, the time increment between the images was increased to 1 h. Then only the interesting part of the affected extremity was imaged.

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Table 1. Evaluation of lymphoscintigrams

K: Lymphatic transport kinetics			
0	No delay	5	Extreme delay
3	Low-grade delay	9	Missing transport
D: Distribution pattern			
0	Normal distribution, i.e. nearly no background	5	Diffuse distribution
3	Partial diffuse (e.g. only in the surroundings of a knee)	9	Transport stop
T: Time to appearance of lymph nodes			
n	Time in minutes to the first appearance of regional lymph nodes	9	No appearance
N: Assessment of lymph nodes			
0	Clearly demonstrated	5	Hardly recognizable
3	Faint visualization	9	No visualization
V: Assessment of lymph vessels			
0	Clearly demonstrated	5	Hardly recognizable
3	Faint visualization	9	No visualization

Volume measurements were performed by the method described by Kuhnke [9]. Several circumferences of the affected limb were measured before and after surgery. The volume was calculated by a microcomputer program, using a conical model.

Transplantation of several lymph collectors is a microsurgical procedure [1–3]. Two or three collectors are removed from the superficial medial bundle of the thigh in a length of 25–30 cm. In patients with postmastectomy edema the transplants are interposed between collectors of the upper arm and collectors of the neck. In this way a restoration of a certain amount of the lymphatic transport capacity is achieved. The anastomoses are mostly end-to-end anastomoses performed by a tension free anastomosing technique [1]. In patients with unilateral edema of the lower extremity due to a local blockade at the groin, the collectors of the contralateral thigh are transposed via the symphysis and anastomosed with ascending collectors of the affected leg. Therefore, the lymph may flow from the swollen extremity to the controlateral inguinal nodes.

Evaluation of lymphoscintigrams

Visually, five criteria were assessed according to the scores shown in Table 1.

Table 2. Evaluation of normal lymphoscintigram

$K=0$	Lymphatic transport kinetics	No delay
$D=0$	Distribution pattern	Not diffuse
$T=1$	Appearance time of lymph nodes	30 min
$N=0$	Assessment of lymph nodes	Clearly demonstrated
$V=1$	Assessment of lymph vessels	Clearly demonstrated
TI = 2	Transport index	Normal

Table 3. Evaluation of abnormal lymphoscintigram

$K=3$	Lymphatic transport kinetics	Low-grade delay
$D=4$	Distribution pattern	Partial diffuse
$T=2$	Appearance time of lymph nodes	57 min
$N=3$	Assessment of lymph nodes	Faint visualization
$V=2$	Assessment of lymph vessels	Clearly demonstrated
TI = 14	Transport index	Pathological

Transport index was calculated by the formula:

$$\mathrm{TI}=K+D+0.04\,T+N+V.$$

The rational for this formula is that all criteria are considered as equivalent. Score values range from 0 to 9 including all integer numbers. Thus, TI values range between 0 (normal) and 45 (pathological).

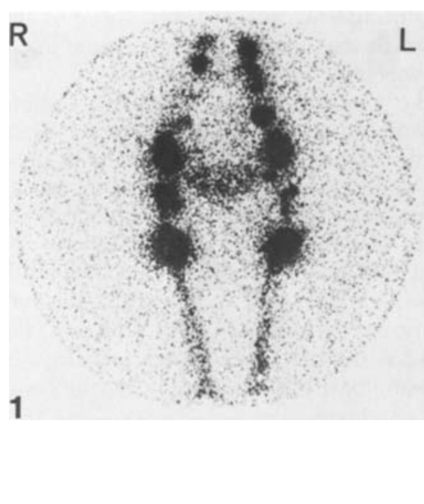
Normalization of T (min) is performed by the factor 0.04, i.e., 200 min (maximal delay of lymph node appearance) yields the score value 8. No appearance is evaluated by 9.

Figure 1 shows a normal lymphoscan of a 41-year-old man with an injury of the right lower thigh. The pelvic region, scanned 30 min after injection, revealed distinct imaging of the inguinal and iliac lymph node chains. Score values were assessed as shown in Table 2.

Figure 2 shows lymphedema in the left upper thigh in a 31-year-old woman suffering from cancer of the bladder. Distal to the left knee, marked by the medial and lateral incisure, several lymph vessels can be distinguished. Lymphedema in the left upper thigh is characterized by diffuse distribution of radioactivity. These findings were assessed by the scores shown in Table 3.

Results

An interobserver study was performed in 179 investigations. A second observer reassessed 179 limbs without knowledge



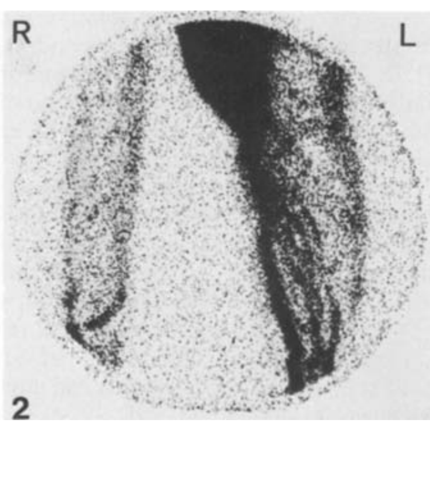


Fig. 1. Normal visualization of inguinal and iliac lymph nodes in a 41-year-old man with injury of the right lower thigh

Fig. 2. Lymphedema of the left upper thigh in a 31-year-old woman with cancer of the bladder. Note diffuse distribution of radioactivity

Table 4. Interobserver study (TI = Transport index, K = kinetics, D = distribution, T = time to appearance of lymph nodes, N = lymph nodes, V = lymph vessels)

$n = 179$	TI	K	D	T	N	V
Observer 1	11.43	1.98	2.00	47.8	2.04	2.54
Observer 2	11.94	1.69	2.06	45.0	2.63	2.76
Mean difference	2.61	0.54	0.67	7.1	0.89	0.78
Correlation	0.96	0.92	0.88	0.78	0.91	0.93

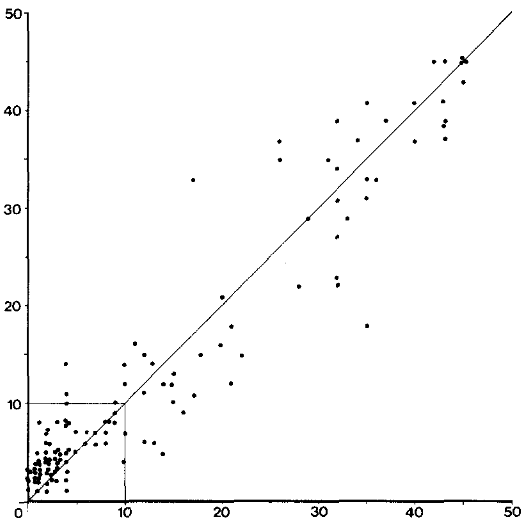


Fig. 3. Transport index in 179 investigations as evaluated by two independent observers

of the results of the first observer. Table 4 shows mean values, differences, and correlations of this study. In Fig. 3, each point of the scattergram depicts the TI as evaluated by the first observer (abscissa) and the second observer (ordinate). Borderlines between normal transport and disorder of drainage (TI = 10) are marked.

For TI, the mean difference between the two observers was rather small (2.61). The five score values showed somewhat higher deviations. Calculation of TI with these score differences yields 3.14. Obviously, differences in one criterion are compensated partially by other criteria. Only eight investigations (4.5%) were classified as normal (TI < 10) by one observer and pathological (TI > 10) by the other one.

Table 5 represents the results of 122 investigations.

Table 5. Transport index TI in 122 investigations (TI < 10: negative, TI > 10: positive)

	n	TI		
No lymphedema	83	3.99	True negative 75	False positive 8
Lymphedema	39	30.95	True positive 38	False negative 1

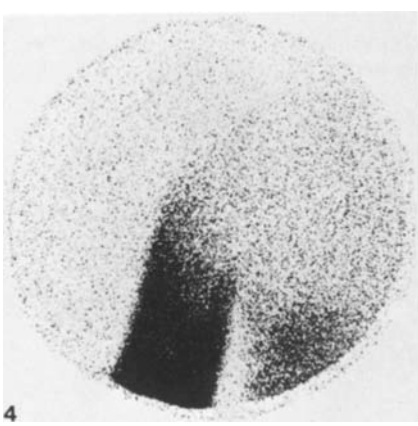
Limbs without edema were investigated before a planned transplantation to ensure normal lymph drainage. The mean value of TI in healthy limbs (3.9) differed significantly from TI in limbs with manifest lymphedema (30.9).

Using TI = 10 to discriminate between normal and pathological lymph drainage, we found 38 true-positive, 75 true-negative, 8 false-positive, and only 1 false-negative results. Thus, sensitivity was 97.4% and specificity 90.3%.

In Figs. 4–7 two examples of successful transplantation are shown. Typical postmastectomy edema (Fig. 4) is characterized by diffuse distribution of radioactivity distal to the blockade of lymph drainage near the right axilla. Seven years after mastectomy, dissection, and radiation of the axilla, a marked swelling of the right arm of the 42-year-old patient occurred. Three lymph collectors were transplanted. At the upper arm, one end-to-end anastomosis with a deep collector and two end-to-end anastomoses with a superficial collector were performed. Lymphoscintigraphy 1 year after transplantation shows restoration of lymph drainage. Both lymphatic pathways and nodes are visualized markedly.

Figures 6 and 7 demonstrate the case of a 31-yearl-old woman who underwent partial resection of the urinary bladder, lymph node dissection, and radiation. Following surgery elephantiasis of the left leg occurred. Three collectors were transposed from the affected left leg via the symphysis to the healthy right side and were anastomosed with ascending lymphatic vessels. Both volume and TI decreased significantly: volume from 3423 ml to 2580 ml, TI from 16 to 4.

In 23 patients with lymphatic vessel grafts the first nuclear medical control was done at the end of hospitalization, i.e., 7–14 days after transplantation. The average decrease of TI was 5.9: 31.1 before and 25.2 after transplantation. The corresponding volumes decreased from 3435 ml to 2547 ml. Changes in TI and volume were significant ($p < 0.05$). By comparison, mean volume in the healthy contralateral side was 1854 ml.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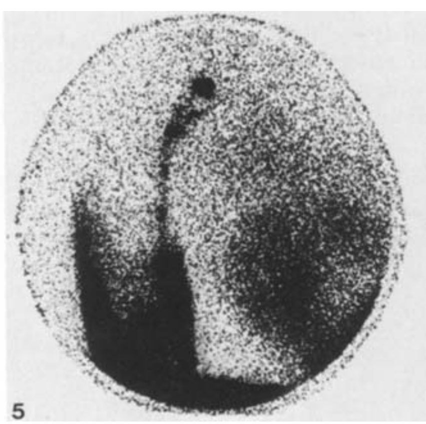
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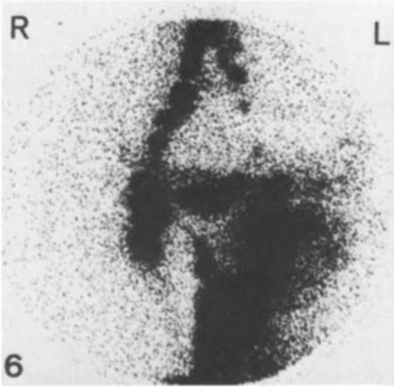
Fig. 4. Typical postmastectomy edema of the right arm in a 42-year-old woman before transplantation. Note diffuse distribution and blockade of lymph drainage near the axilla

Fig. 5. Visualization of vessel grafts and axillary lymph nodes after transplantation.



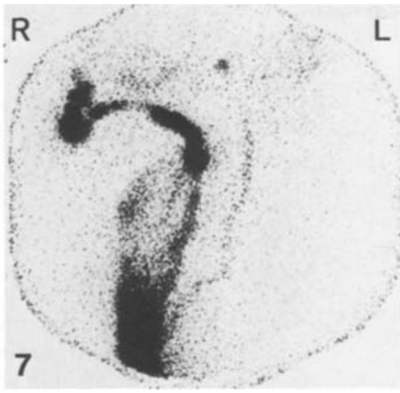


Fig. 6. Elephantiasis of the left leg in a 31-year-old woman following partial resection of the urinary bladder, lymph node dissection, and radiation

Fig. 7. Visualization of anastomoses from the affected left leg via the symphysis to the healthy right side

Discussion

In order to improve the results of autologous lymphatic transplantation success should be determined very carefully. Volume measurements may estimate the results of surgical intervention, but they depend on physiological parameters. One major problem is the natural decrease of volume due to the supine position of the operated limb during the postoperative phase. We suppose that this fact causes somewhat better results in terms of volume measurements than in terms of lymphoscintigraphic transport kinetics. In three patients, lymphoscintigraphy was repeated after 6 months. In all these patients, an additional improvement of lymph drainage was found.

In this study, lymphoscintigraphy was performed routinely in healthy extremities. Thus, true-negative and false-positive findings could be detected, yielding a good specificity (90.3%). In 39 limbs with lymphedema there was only one false-negative result by lymphoscintigraphy (sensitivity = 97.4%). This negative finding is supposed to be caused by intravascular injection of a small fraction of the radiopharmaceutical. Since the first image was registered several minutes after injection (following ergometric exercise), intravascular residuals might be misinterpreted as lymph vessels. In addition, iliac lymph nodes appeared by retrograde filling from the contralateral side which was investigated simultaneously. Occasionally, retrograde filling of iliac lymph nodes can be seen in patients with lymphedema in the corresponding lower extremity.

False-positive findings may result by injection of the radiopharmaceutical into indurated [11] or cutaneous tissue.

Although evaluation of lymphatic transport kinetics depends on the experience of the investigator, a good reproducibility was demonstrated in the present study ($r = 0.96$). Therefore, we believe that quantification of scintigraphic findings is superior to verbal description in order to evaluate lymphatic drainage disorder. Particularly in follow-up studies, this method has proved to be useful to determine surgical success rate, because volume measurements frequently overestimate effects of vessel grafts on lymph flow.

For a period of 3 years, transplantation of lymphatic vessels and lymphoscintigraphy have been performed in our hospital. The positive results of both methods encourage us to continue.

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