

Regional Distribution of Epifascial Swelling and Epifascial Lymph Drainage Rate Constants in Breast Cancer-Related Lymphedema

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ABSTRACT

Background: The view that breast cancer-related lymphedema (BCRL) is a simple, direct mechanical result of axillary lymphatic obstruction ('stopcock' mechanism) appears incomplete, because parts of the swollen limb (e.g., hand) can remain nonswollen. The lymph drainage rate constant (k) falls in the swollen forearm but not in the spared hand, indicating regional differences in lymphatic function. Here the generality of the hypothesis that regional epifascial lymphatic failure underlies regional swelling was tested. To do so, the regional distribution of epifascial swelling along the forearm was compared with that of epifascial (subcutis) k .

Methods and Results: Epifascial k (local lymph flow per unit distribution volume) was measured by quantitative lymphoscintigraphy of subcutaneous radiolabeled human immunoglobulin IgG in regions of maximal and minimal % swelling in the ipsilateral swollen forearm, and at matching sites in the contralateral nonswollen arm, in 11 women with BCRL. Swelling was maximal distally in 5 patients and proximally in 6. Proximal k , $-0.085 \pm 0.025\% \text{ min}^{-1}$ (mean \pm SD), was 27% bigger than distal k , $-0.067 \pm 0.021\% \text{ min}^{-1}$, irrespective of swelling ($p = 0.02$, two-way repeated measures ANOVA). k fell by 11% from $-0.080 \pm 0.028\% \text{ min}^{-1}$ in the nonswollen arm to $-0.072 \pm 0.021\% \text{ min}^{-1}$ in the swollen arm ($p = 0.17$, t test). Local epifascial k was not significantly lower, however, at sites of maximal swelling than minimal swelling, and k correlated positively with arm circumference.

Conclusions: A systematic difference in lymph drainage along the axis of the forearm was demonstrated for the first time. Local differences in epifascial k did not, however, explain the regionality of swelling, in keeping with previous evidence that epifascial k does not correlate with differences in swelling between arms, whereas subfascial k does. The results lead to the rejection of the hypothesis that epifascial (*cf.* subfascial) lymph drainage rate constants govern epifascial swelling in human forearm.

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INTRODUCTION

Breast cancer-related lymphedema (BCRL), also known as postmastectomy edema, is a chronic swelling of the arm caused by surgery and radiotherapy treatment for breast cancer. The swelling can be controlled with elastic compression hosiery and other measures,¹ but deterioration tends to occur with time and the arm may become grossly deformed, leading to functional and psychological morbidity.^{2,3} BCRL was first described by Halsted in 1921⁴ as a side-effect of mastectomy operations. Although there has been a trend towards more conservative surgery, including the introduction of sentinel lymph node biopsy, chronic arm edema remains a common iatrogenic problem with a commonly quoted prevalence of approximately 25% among breast cancer patients.^{5,6,7}

The swelling is often remarkable for its uneven distribution along the length of the arm. It may be predominantly localized in the proximal forearm and distal arm, or vice versa, and may or may not involve the hand. This is referred to as a regional distribution of swelling. Although removal of axillary lymph nodes is clearly the initiating cause, the mechanisms leading to the development of lymphedema are poorly understood. The conventional view is that damage to axillary drainage routes impairs lymph drainage globally from the whole arm (the 'stopcock' mechanism). The adequacy of this simple view has recently been challenged,^{8,9} partly because of the observation that some parts of the limb may be spared from swelling⁸ and partly because of other puzzling features such as the fall in interstitial plasma protein concentration.¹⁰

The regional distribution of swelling indicates that local factors influence the local severity of the edema. The edema is epifascial, that is, outside the fascia bounding the arm musculature, mainly in the subcutis,¹¹ and the degree of swelling correlates with the increase in thickness of both subcutis and skin.¹² Quantitative lymphoscintigraphy (QL) has been used to explore the drainage of the epifascial and the subfascial compartment because the QL rate constant for radioprotein removal is a measure of local lymph flow per unit volume of distribution of radiotracer. The rate constant is reduced

in the subcutis of the edematous forearm⁸ but the size of the reduction does not correlate significantly with the degree of swelling.^{8,9} In the spared, nonedematous hand of the otherwise swollen limb, however, lymph drainage is at least as high as in the contralateral hand.⁸ Gamma camera imaging following injection into the webspace of the nonswollen hand of the ipsilateral swollen arm shows dermal backflow into the distal forearm but this is not evident in the contralateral arm. This raises the possibility that hand lymph is being re-routed through skin collaterals.

The subfascial soft tissue comprises mainly muscle. Its extensive capillary network is potentially a much more abundant source of edema fluid than the subcutis and skin, but the subfascial compartment is not overtly swollen in BCRL, probably due to its low compliance (created by the tight enveloping fascia). The subfascial lymph drainage rate constant is reduced by on average 31% in the ipsilateral swollen arm in BCRL.⁹ Moreover, the decrease in subfascial removal rate, unlike that in the epifascial compartment, correlates with the increase in arm volume, even though most of the swelling is epifascial.⁹ This finding indicates that the epifascial swelling is to some degree a consequence of subfascial lymphatic impairment, possibly via impaired epifascial to subfascial lymph drainage. An alternative possibility is that subfascial fluid is diverted into the subcutis, though there is no evidence of dermal reflux from subfascial injections to support this. It thus seems possible that variations in the epifascial—subfascial interaction may contribute to the variable swelling along the length of the arm (*cf.*, the hypothesis of variation in epifascial drainage rate *per se*).

Local deterioration of lymph drainage may be due to impaired contractility in the lymphatic collectors, which have many similarities to the cardiac pump. By analogy with cardiac failure secondary to hypertensive afterload, it is possible that chronically increased lymphatic collector afterload (due to the increased axillary outlet resistance) causes a selective regional lymphatic pump failure. If the weakest pumps failed first, the regions they normally drain would experience maximal swelling. Chronic afterload-induced failure could also provide a rationale for the long, variable delay

in onset of BCRL, the delay being the time needed for chronic failure to develop.

Other proposals that have been put forward to account for the sparing of local regions in lymphedema include local lymphatico-venous communications^{13,14} and reverse net transport of plasma protein across the blood capillary endothelium.¹⁵⁻¹⁷ Lymphatico-venous studies using ipsilateral blood sampling show substantial local vascular access of interstitial injected radioprotein in the arms of both healthy and BCRL subjects.¹⁸ Movement of injected labeled protein across the capillary endothelium in a direction opposite to the net physiological direction has been shown experimentally¹⁵⁻¹⁷ but it is difficult to see how this could operate effectively with native proteins.

The hypothesis investigated in the present study is that the regionality of epifascial swelling in the ipsilateral BCRL arm is due to a selective impairment of local epifascial lymph drainage, with relatively good preservation of local lymph drainage in nearby minimally swollen regions. This is an extension of a similar hypothesis to explain the existence of nonswollen hands in swollen BCRL arms, which was supported by a difference in QL removal rate constants between the two sites.⁸ It could be argued, however, that the hand is anatomically different in terms of its lymph drainage, and that inferences drawn from comparison of hand versus forearm are not necessarily applicable to comparisons within the forearm. One indication that the hand may be a special case is that dermal backflow follows subcutaneous administration of radiotracer in the web-space of the nonswollen hand in the BCRL arm but the equivalent phenomenon is not evident following forearm administration.⁸ Physiological control of blood flow in the hand also differs markedly from that in the forearm.¹⁹ Therefore, to test the generality of the hypothesis of regional lymph drainage failure, we compared the removal rate constant k for a subcutaneously injected protein in a maximally swollen region with that in a minimally swollen region of the same forearm. If epifascial swelling is due primarily to epifascial lymph drainage impairment, a correlation is predicted; but this will not be so if epifascial swelling is primarily due to subfascial lymph drainage impairment.

MATERIALS AND METHODS

Subjects

Eleven women aged 59 ± 8 years (mean \pm SD) were recruited from the Lymphoedema Clinics at the Royal Marsden Hospital, Surrey, and St. George's Hospital, London, and via the Lymphoedema Support Network of the United Kingdom. All had been treated for unilateral breast cancer and had subsequently developed BCRL (details of breast cancer treatment and BCRL are shown in Table 1). Chronic swelling of the ipsilateral arm began 8 ± 11 months (range, 0-36 months) after the cancer surgery and had been present at the time of the study for 11 ± 9 years (2-24 years). Patients with recurrence of breast cancer, cardiovascular disease, or other serious illness were excluded. Nine patients routinely wore a compression sleeve but on the day of the study this was not worn. Patients were classified into two cohorts (Fig. 1). Patients 1-5 had percentage swelling of the distal forearm greater than that of the proximal forearm (Dist_{MAX} group); patients 6-11 had percentage swelling of the proximal forearm greater than that of the distal forearm (Prox_{MAX} group). The study was approved of by Wandsworth Local Research Ethics Committee, by the Ethics Committee of the Royal Marsden Hospital, and by the Administration of Radioactive Substances Advisory Committee of the United Kingdom (ARSAC). The study was performed in accordance with the Declaration of Helsinki and all patients gave informed, written consent.

Measurement of arm volume and selection of injection sites

To calculate total percentage increase in ipsilateral arm volume, an opto-electronic limb volumeter (Perometer 300 S, Pero-System Messgeräte GmbH, Wuppertal, Germany)²⁰ was used. Arm volume was measured between the ulnar styloid process of the wrist and mid-upper arm; the proximal limit was set by the geometry of the Perometer. Sites of minimal and maximal swelling on the ipsilateral swollen forearm were selected for subcutaneous (s.c.) injection. Matching sites were also studied in the contralateral nonswollen arm. To determine the sites, arm circumference (taken from the Per-

TABLE 1. DETAILS OF PATIENTS WITH BCRL

Patient No.	Age (yr)	Breast Surgery*	Axillary Surgery	RT	CT	Tamoxifen	BCRL			
							Onset (mo) [†]	Duration (yr)	Side	Hand Swelling
1	71	WLE	Y	Y	Y	Y	0.5	5	R	Y
2	48	WLE	Y	Y	Y	N	12	4	L	Y
3	58	WLE	Y	Y	Y	Y	36	3	L	Y
4	46	Mast	Y	Y	Y	N	3	2	R	N
5	66	Mast	Y	Y	N	Y	12	21	L	Y
6	60	Mast	Y	N	N	Y	6	3	L	N
7	61	WLE	Y	Y	N	Y	0	9	R	N
8	57	Mast	Y	Y	Y	Y	5	7.5	R	N
9	66	WLE	Y	Y	N	N	2	24	R	N
10	49	WLE	Y	Y	N	Y	0	16	R	N
11	64	WLE	Y	Y	N	N	9	24	L	N

*Mast, Mastectomy; WLE, Wide local excision; Y, Yes; N, No; RT, Radiotherapy; CT, Chemotherapy; L, Left; R, Right. [†]Time between completion of breast cancer treatment and onset of swelling (months). Patient 6 was left-handed. All others were right-handed.

ometer readings) at 2 cm intervals, was used to calculate the local percentage swelling. Selected sites were at least 16 cm apart to accommodate the scintillation probes. The skin was marked at these sites and at the equivalent sites on the contralateral arm.

Injection and acquisition protocol

Patients acclimatized to their surroundings for 45 min before the study. Each patient sat with both arms resting at heart level on a table, lightly gripping a vertical handle in each hand (Fig. 2). The radiopharmaceutical agent ^{99m}Tc-HIG (polyclonal human immunoglobulin G labeled with technetium-99m, TechneScan HIG, Mallinckrodt Medical B.V., Petten, Netherlands) was prepared by the addition of 25–35 MBq ^{99m}Tc-sodium pertechnetate to sodium chloride (0.9% w/v) followed by dilution to a radioactive concentration of 2.5 MBq/mL. The pertechnetate was used within 2 h of elution from a generator that had been itself eluted within 24 h. Activities of 0.5 MBq ($\pm 10\%$) in 0.2 mL of ^{99m}Tc-HIG were drawn into four 1 mL syringes ready for injection. Using thin-layer chromatography, radiochemical purity was $99.1 \pm 1.0\%$ ($n = 11$) (i.e., $<1\%$ of the total radioactivity was present as nonprotein bound impurities).

0.2 mL ^{99m}Tc-HIG in saline containing 0.02–0.04 mg immunoglobulin G, activity 0.56 ± 0.13 MBq, was injected s.c. through a 25-gauge needle at the selected sites (distal followed by

proximal) in the ipsilateral swollen forearm and, immediately afterwards, in the contralateral forearm. The distal injection was into the lateral aspect of the forearm and the proximal injection was into the lateral or ventrolateral aspect depending on arm shape.

Acquisitions were performed using two 2" \times 2" NaI scintillation detectors (ORTEC Scintipack 296, Ametek, Wokingham, U.K.) mounted in cylindrical lead collimators (32.0 cm high, 10.9 cm outer diameter, 6.5 cm inner diameter). The detector was supported on a shelf 20 cm above the collimator opening. The detector-collimator units, or 'probes', were mounted on a trolley-based gantry system (Rotary Engineering, Sheffield, U.K.). The detectors were connected via an interface card (ORTEC μ ace, Ametek, Wokingham, U.K.) to a computer. ScintiVision-32 software displayed γ -ray spectra as a histogram of the number of detected events or pulses against the pulse size, resulting in a pulse height spectrum of detected events.

The probes (Figure 2) were lowered to ~ 1 mm above the skin (equivalent to a detector-to-source distance of just over 20 cm), although in some cases the distance was greater because of the shape of the arm. A long source-to-detector distance minimized the effect of subject movement. Disintegrations of the injected radiotracer were recorded from each site every 20 min for 3 h. The individual acquisitions lasted 100 s. The probes were carefully repositioned for repeated acquisitions at each site to keep the source-to-

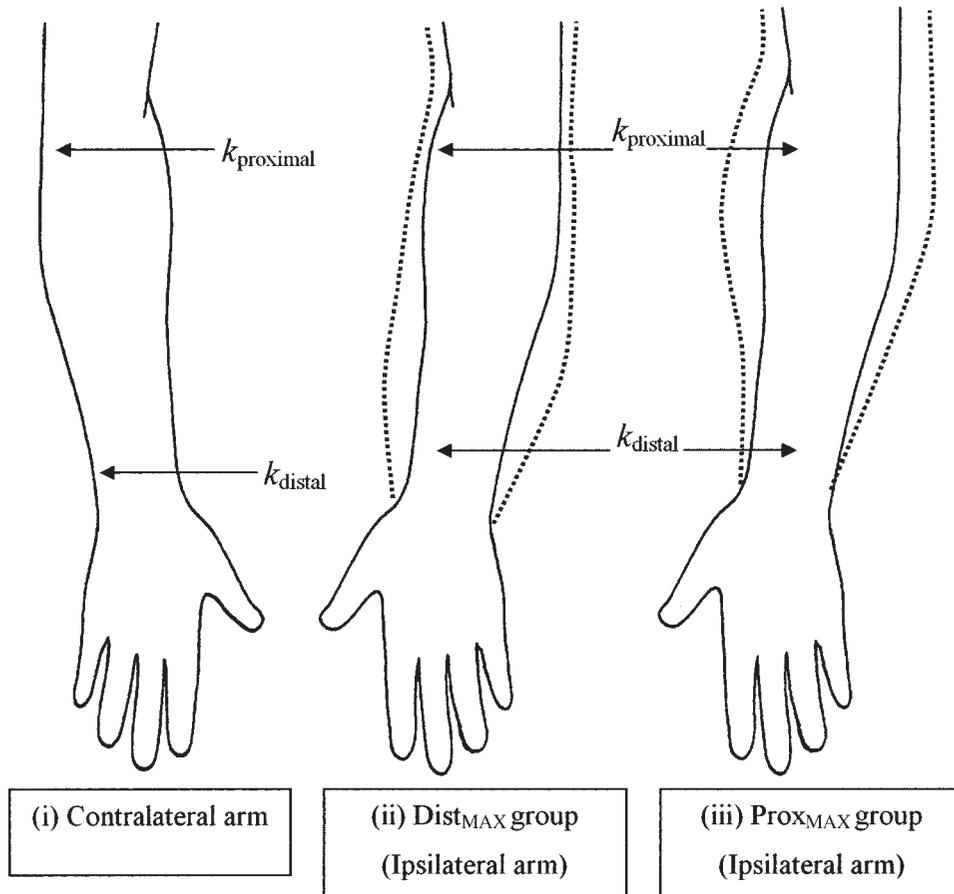


FIG. 1. Regional distribution of swelling in BCRL. (i) Nonswollen contralateral arm; (ii) Dist_{MAX} group (distal swelling > proximal swelling); (iii) Prox_{MAX} group (proximal swelling > distal swelling).

detector distance as constant as possible. Ambient temperature was $23.8 \pm 1.1^\circ\text{C}$.

Determination of local removal rate constant, k

Lymph drainage was quantified by measuring the rate of removal of interstitially injected ^{99m}Tc -HIG. Its large size (150 kDa) prevented significant microvascular clearance from the depot. The count rate was corrected for background and physical decay of the radionuclide [according to the formula $N = N_0e^{-\gamma t}$, where N = corrected counts, N_0 = uncorrected counts, γ = decay constant ($0.001923 \text{ min}^{-1}$) and t = time since injection (min)] and then expressed as a fraction of the initial count rate. The decline in count rate appeared to be mono-exponential and was fitted as such by least squares regression. The slope of the semilog plot gave k (units: $\% \text{ min}^{-1}$), representing J_L/V_D , where J_L is local lymph flow and V_D is volume of distribution of tracer.²¹ The terms $k_{proximal}$ and k_{dis-

tal refer to the proximal and distal injection sites, respectively (Fig. 1). In the event of an initial plateau or rise in the plot, measurement of the slope was started from the highest point.

Control study

^{99m}Tc -HIG draining from the distal depot might pass under proximal probe, influencing the proximal counts. To assess this, two BCRL patients received the distal injection in the ipsilateral and contralateral arms 100 min before the proximal injection followed by count monitoring at all four sites. One further BCRL patient received the distal injection in the ipsilateral and contralateral arms but no proximal injections.

Statistical analysis

Results are presented as the mean \pm SD. To compare k at regions of minimal and maximal swelling in the Dist_{MAX} and Prox_{MAX} groups,

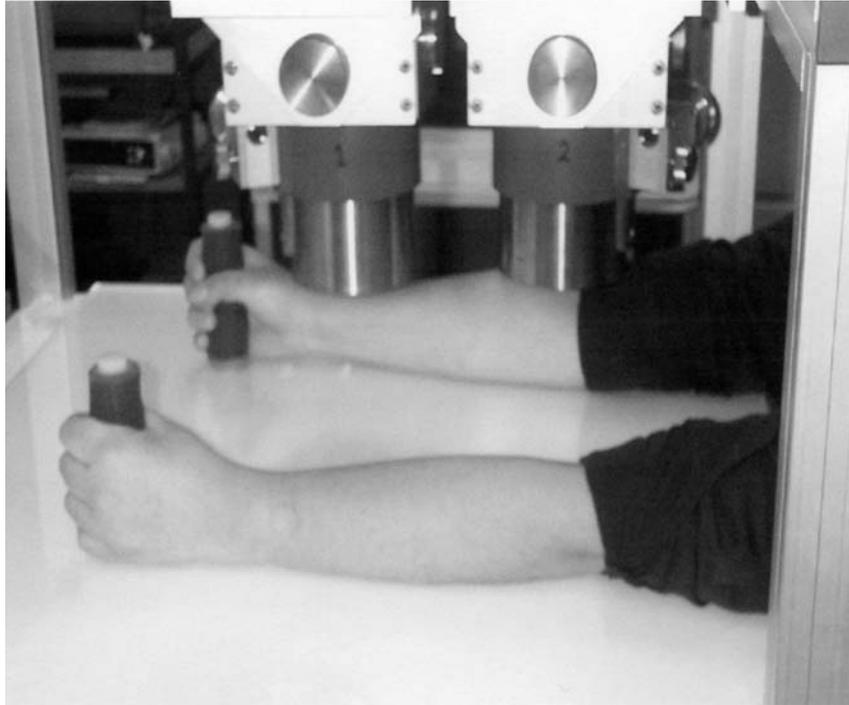


FIG. 2. Position of arms and probes. NaI scintillation detectors mounted inside lead collimators over the sites of minimum and maximum swelling in the forearm. ^{99m}Tc -HIG (0.2 mL, s.c) is injected into distal and proximal forearm sites. Disintegrations emitted by the injected source at each site are detected by the probes. The subject does not have BCRL.

and also to compare the same site in different arms, Student's paired t test was used. To analyze the differences in k between distal and proximal injection sites in ipsilateral and contralateral arms, two-way repeated measures ANOVA was used. Linear regression was used to determine the slope of plots. Calculation of the correlation coefficient, r , using linear regression, was used to assess the relationship between local lymph drainage and the degree of swelling. Unpaired t tests were used to compare differences in k between previous studies and this study. Differences were considered significant when $p \leq 0.05$.

RESULTS

Arm volume and circumferences

The ipsilateral swollen arm volume was $28.9 \pm 18.0\%$ greater than the contralateral arm volume ($p = 0.001$, paired t test, $n = 11$). For pa-

tients with distal swelling $>$ proximal swelling (Dist_{MAX} group), the increase in ipsilateral swollen arm volume was $36.4 \pm 20.3\%$ ($p = 0.02$, paired t test, $n = 5$). For patients with proximal swelling $>$ distal swelling (Prox_{MAX} group, $n = 6$), the increase was $22.7 \pm 14.8\%$ ($p = 0.03$, paired t test, $n = 6$).

The distribution of swelling in Dist_{MAX} and Prox_{MAX} patients along the long axis of the arm is shown in Figure 3. In the Dist_{MAX} group, the circumference at the distal ipsilateral injection site was $23.7 \pm 10.4\%$ greater than at the distal contralateral injection site, whereas the circumference at the proximal ipsilateral injection site was $11.7 \pm 5.9\%$ greater than at the proximal contralateral injection site. In the Prox_{MAX} group, the increase in circumference at the distal ipsilateral site was $2.4 \pm 4.6\%$, whereas at the proximal ipsilateral site it was $17.1 \pm 8.1\%$. The difference in % swelling between distal and proximal sites was significant in both groups ($p = 0.02$, paired t test).

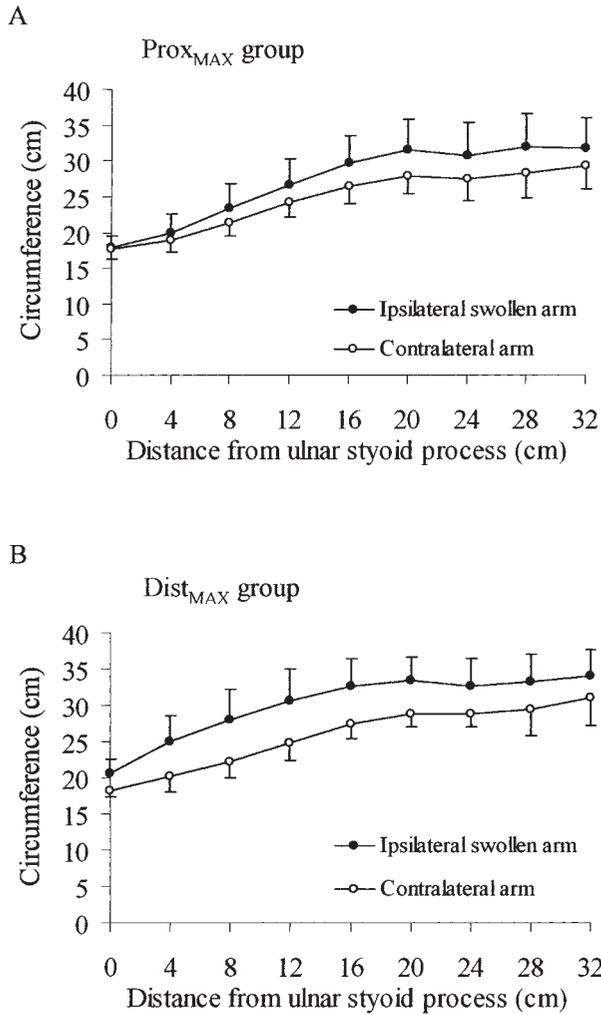


FIG. 3. Mean circumferences (\pm SD) of ipsilateral and contralateral arms plotted at 4 cm intervals, starting distally. (A) Patients with proximal swelling > distal swelling ($n = 6$). (B) Patients with distal swelling > proximal swelling ($n = 5$).

Control studies: effect of ^{99m}Tc-HIG drainage from distal depot on proximal counts

Initial Distal Injection, Delayed Proximal Injection. Proximal counts were recorded at 20 min intervals from 0 to 60 min in both arms of two control patients. After subtraction of background levels the proximal counts were very low, namely 0.016–0.027% of the counts recorded at the same time-points following proximal injections. Subtraction of these distally-derived counts from the proximal counts of the Dist_{MAX} and Prox_{MAX} patients increased their $k_{proximal}$ values by a factor of 1.0025 (i.e., by $0.25 \pm 2.37\%$). Thus, proximal counts are not materi-

ally affected by label that has tracked up the arm from the distal site.

Distal Injection Only. Counts recorded from the proximal sites were 0.033–0.050% of the counts recorded at the proximal sites of the Dist_{MAX} and Prox_{MAX} patients. Subtraction of these proximal counts from the proximal counts of the Dist_{MAX} and Prox_{MAX} patients increased $k_{proximal}$ negligibly, by a factor of 1.0041 (i.e., by $0.41 \pm 0.39\%$). We conclude, therefore, that distal forearm injection of ^{99m}Tc-HIG does not cause any significant increase in the counts recorded at the proximal site and thus does not significantly affect the value of $k_{proximal}$.

Removal of ^{99m}Tc-HIG from sites with differing degrees of swelling

After the initial injection the counts increased slightly before beginning to fall in 8 patients (2 from the Dist_{MAX} group, 5 from the Prox_{MAX} group, and a control patient who received distal injections only). This was not associated with any specific pathology; it occurred at sites of minimal and maximal swelling, distally and proximally, and in the ipsilateral and contralateral arms. Removal rate constants were always measured from the highest count that was followed by progressively falling counts. Table 2 shows these removal rate constants for all swollen sites, for combined maximally and minimally swollen sites, and for the Dist_{MAX} and Prox_{MAX} patient groups.

When all swollen (ipsilateral) sites were compared with all nonswollen (contralateral) sites, the average k was numerically lower (by 11%) in the swollen arms but the difference was not statistically significant ($n = 22, p = 0.17$, paired t test). A reduction would be in keeping with previous findings of a ~25% reduction in swollen arm k measured by a gamma camera.^{8,22} When the removal rate constant k at the site of either minimal or maximal swelling, irrespective of distal-proximal location, was compared with contralateral k ($n = 11$) the difference was again not statistically significant ($p = 0.40$ at the maximally swollen site; $p = 0.31$ at the minimally swollen site; paired t tests). Moreover, the difference in k between maximally and minimally swollen sites on the

TABLE 2. REMOVAL RATE CONSTANTS (k , MEANS \pm SD) FOR $^{99m}\text{Tc-HIG}$ IN IPSILATERAL SWOLLEN AND CONTRALATERAL ARMS

	<i>Ipsilateral Arm k (% min⁻¹)</i>		<i>Contralateral Arm k (% min⁻¹)</i>	
(i) All sites ($n = 22$)	-0.072 ± 0.021		-0.080 ± 0.028	
	<i>Site of max. swelling</i>	<i>Site of min. swelling</i>	<i>Matching site of max. swelling</i>	<i>Matching site of min. swelling</i>
(ii) Sites of swelling ($n = 11$)	-0.073 ± 0.024	-0.071 ± 0.08	-0.079 ± 0.027	-0.080 ± 0.031
(iii) Dist _{max} group ($n = 6$)	-0.065 ± 0.024	-0.084 ± 0.011	-0.070 ± 0.019	-0.089 ± 0.033
Prox _{max} group ($n = 5$)	-0.079 ± 0.024	-0.060 ± 0.016	-0.088 ± 0.031	-0.073 ± 0.030

(i) All ipsilateral swollen sites and all matching contralateral sites ($n = 22$); (ii) All maximally and minimally swollen sites (and matching contralateral arm sites) ($n = 11$); (iii) Groups where the swelling was either predominantly distal (Dist_{max} group, $n = 5$) or predominantly proximal (Prox_{max} group, $n = 6$).

ipsilateral arm was not significant ($n = 11$, $p = 0.85$, paired t test), contrary to the hypothesis under investigation. We therefore analyzed the two subgroups separately, as follows.

Figure 4 shows k for sites of minimal and maximal swelling in the Dist_{MAX} patient group (i.e., those with distal swelling $>$ proximal swelling) and the k for matching sites on the contralateral arm. The equivalent is shown for Prox_{MAX} patients. The difference in k between maximally and minimally swollen sites in the ipsilateral arm in the Dist_{MAX} patient group was again not significant ($n = 5$, $p = 0.19$, paired t test) nor were reductions of k in the swollen arm compared with the contralateral arm ($p = 0.35$ for maximally swollen site; $p = 0.76$ for minimally swollen site; paired t tests).

Similar conclusions apply to the Prox_{MAX} group. The difference in k between maximally and minimally swollen sites did not reach conventional significance ($n = 6$, $p = 0.07$, paired t test) nor did reduction of k in the swollen arm compared with the nonswollen arm ($p = 0.57$ for maximally swollen site; $p = 0.25$ for minimally swollen site; paired t tests).

Removal of $^{99m}\text{Tc-HIG}$ from distal versus proximal arm, irrespective of swelling

Inspection of the results led us to suspect that k showed a systematic change with axial location along the arm. To test this, we compared all distal k values with all proximal k values in both the control and swollen arms, irrespective of

whether the sites were maximally or minimally swollen. Proximal k was greater than the distal k in both arms (Fig. 5). Mean k in the proximal forearm (ipsilateral $-0.081 \pm 0.019\%$ min⁻¹, contralateral $-0.089 \pm 0.030\%$ min⁻¹) was 23.9–26.6% greater than k in the distal forearm (ipsilateral $-0.063 \pm 0.019\%$ min⁻¹, contralateral $-0.071 \pm 0.025\%$ min⁻¹). The effect of axial location was statistically significant ($p = 0.02$, two-way repeated measures ANOVA) whereas the effect of swelling was not.

Relation between degree of swelling and drainage rate constant

There was a positive correlation close to statistical significance between arm circumference and $k_{\text{ipsilateral}}$ ($n = 22$, $r = 0.39$, $p = 0.07$). A positive correlation is the opposite of the trend predicted under the local epifascial drainage failure hypothesis, so we assessed the possibility that it was related to the proximal-distal dependence of k identified in the previous section. There proved to be a significant positive correlation between arm circumference and $k_{\text{contralateral}}$ ($n = 22$, $r = 0.42$, $p = 0.05$) and a significant correlation between arm circumference and all k values ($n = 44$, $r = 0.32$, $p = 0.03$; Fig. 6). These findings reinforce the conclusion that k_{proximal} is greater than k_{distal} , irrespective of whether the arm is swollen or not.

There was no significant correlation between local arm circumference and $k_{\text{ipsilateral}}$ at the site of maximum swelling ($n = 11$, $r = 0.10$, $p = 0.85$), even if patients were subdivi-

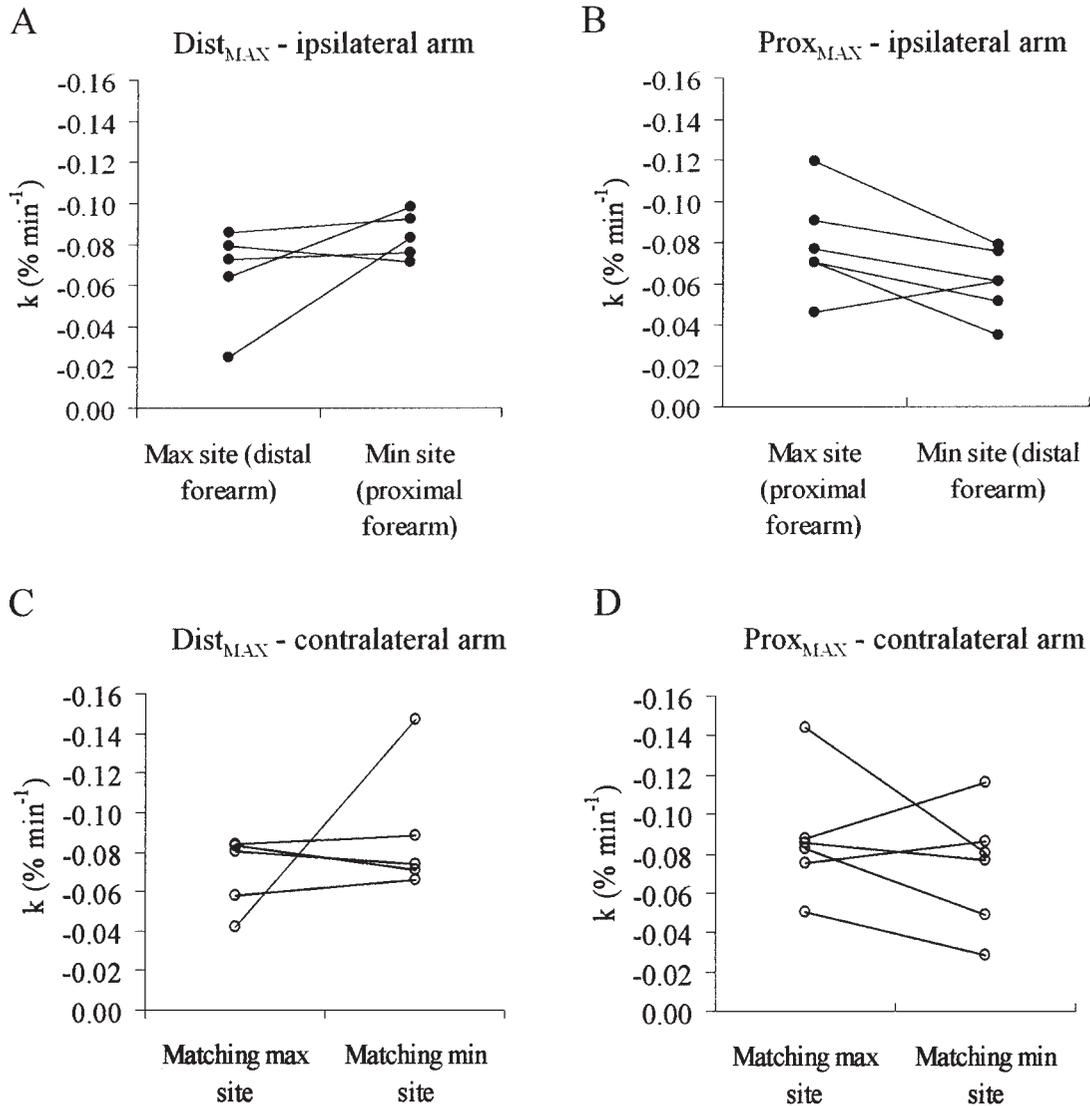


FIG. 4. Removal rate constants (k) at sites of maximal and minimal swelling in the ipsilateral arm and at matching 'max' and 'min' sites in the contralateral arm. (A) Ipsilateral arm of patients who had maximal swelling distally (Dist_{MAX} , $n = 5$); (B) Ipsilateral arm of patients who had maximal swelling proximally (Prox_{MAX} , $n = 6$); (C) Contralateral arm of Dist_{MAX} group; (D) Contralateral arm of Prox_{MAX} group.

vided according to the axial location of their swelling (Dist_{MAX} group: $n = 5$, $r = 0.01$, $p = 0.1$; Prox_{MAX} group: $n = 6$, $r = 0.01$, $p = 0.1$).

CONCLUSIONS

Previous studies have shown that lymphedema is associated with a reduction in the epifascial drainage rate constant. Stanton et al. reported a 25% reduction in k with 28% swelling ($n = 9$, $p = 0.012$, paired t test) and Gothard et al. reported a 24% reduction of k with 54% swelling ($n = 21$, $p = 0.05$).^{8,22} In keeping with this, the average removal rate constant for ^{99m}Tc-HIG in the

swollen arms in this study was numerically lower than in the control arm, by 11%, but there was a 1 in 6 probability that the difference arose by chance ($p = 0.17$, paired t test). A reduction in the rate constant k would indicate a reduction in local lymphatic clearance and hence in local lymph flow,²¹ as might be expected in lymphedema arising from axillary trauma.

Lack of support for hypothesis that local differences in epifascial lymphatic clearance cause local differences in swelling

The concept of local lymphatic pump failure arose from the finding that k for the swollen

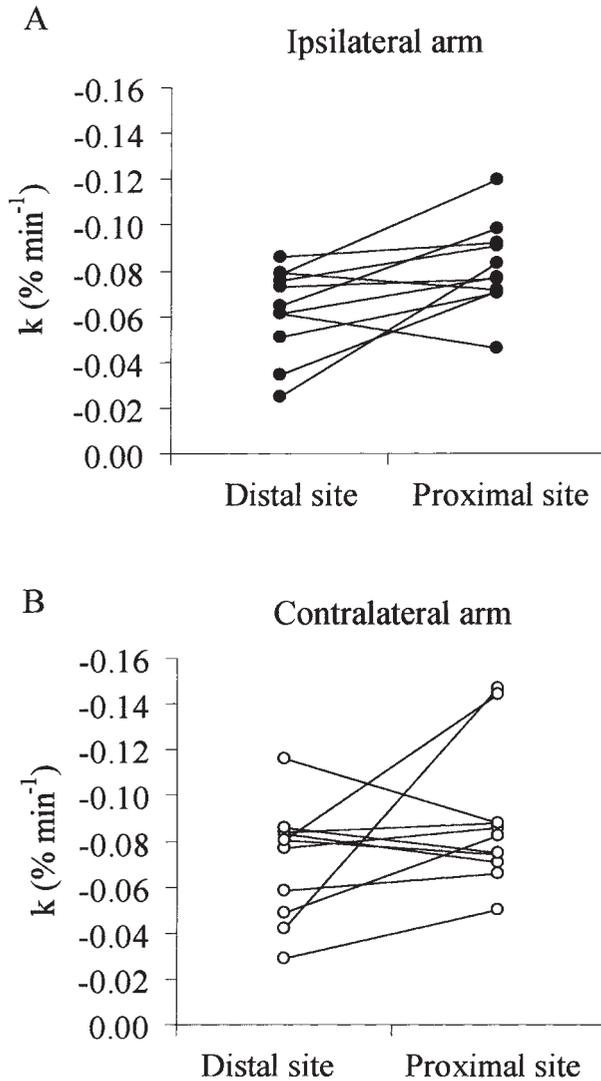


FIG. 5. Removal rate constants (k) for distal and proximal injection sites of all patients ($n = 11$). (A) Ipsilateral arms; (B) Contralateral arms. The rate constant differed significantly with location along the longitudinal axis of both arms and was significantly higher proximally compared with distally ($p = 0.02$, two-way repeated measures ANOVA).

forearm is significantly reduced when compared with k for the nonswollen hand of the same, swollen arm (forearm $k_{ipsilateral} = -0.070\% \text{ min}^{-1}$ compared with hand $k_{ipsilateral} = -0.110\% \text{ min}^{-1}$; forearm $k_{contralateral} = -0.093\% \text{ min}^{-1}$ and hand $k_{contralateral} = -0.095\% \text{ min}^{-1}$).⁸ Although the primary insult is axillary, and should in principle affect the drainage from the entire arm (traditional stopcock theory), k only fell in swollen regions. Here we tested whether the local pump failure hypothesis could be extended to explain regional differences in the severity of forearm swelling. If the

hypothesis is valid for epifascial lymphatic vessels, k should be lowest at sites of maximal swelling. The results did not support this. Only in Dist_{MAX} patients was k at sites of maximal swelling (distal) numerically 23% lower than at sites of minimal swelling (proximal). By contrast, in Prox_{MAX} patients, k was numerically 32% bigger at the site of maximal swelling (proximal) than at the site of minimal swelling (distal). Moreover, local $k_{ipsilateral}$ correlated positively, not negatively, with degree of swelling. These findings led to the discovery of a systematic difference in k between proximal and distal sites.

Differences in lymphatic drainage rate constant along axis of arm

The proximal forearm k is significantly greater than distal k by on average 27% (Fig. 5). Moreover, k correlated positively with arm circumference (Fig. 6). The results thus reveal, for the first time, regional differences in epifascial lymph drainage rate along the axis of the forearm, irrespective of the presence or absence of edema. The existence of this axial gradient of k

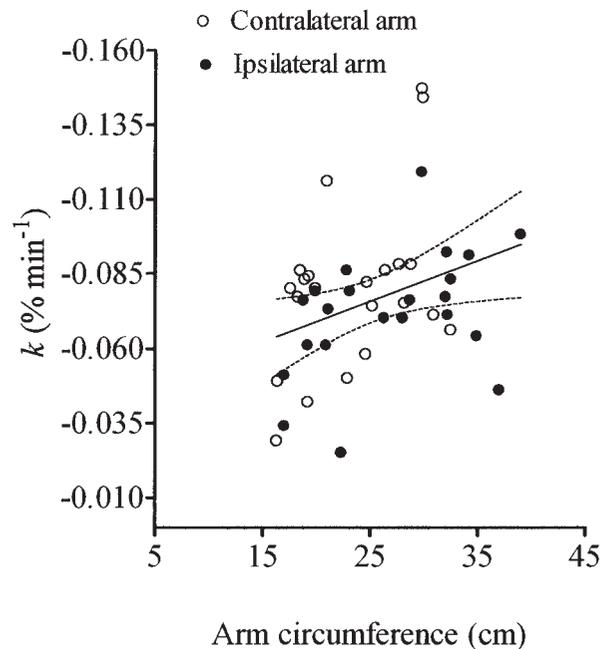


FIG. 6. Scatter diagram of arm circumference plotted against removal rate constant (k). There was a positive correlation between the two variables ($n = 44$, $r = 0.34$, $p = 0.02$). Filled circles: the ipsilateral arm; open circles: the contralateral arm. The linear trendline and 95% confidence intervals are also shown.

clearly increases the difficulty of demonstrating a relation between local swelling and local k when swelling is distal in some patients and proximal in others. The cause of these differences in local lymph drainage along the forearm is unclear, but it could perhaps have an anatomical basis. There is a greater amount of muscle in the proximal forearm and lymph drainage rates here could relate to the finding that subfascial k is approximately twice as fast as epifascial k .²³

Relation of epifascial swelling to subfascial rather than epifascial rate constant

In an earlier study of BCRL our group found no correlation between epifascial k and severity of swelling ($n = 14$, $r = 0.2$, $p = 0.5$).^{8,9} By contrast, there is an excellent correlation between reduction of subfascial k (i.e., lymph drainage from the muscle compartment of the forearm) and the severity of swelling ($n = 9$, $r = -0.88$, $p = 0.002$).⁹ The subfascial removal rate constant was on average 31% lower in the ipsilateral than contralateral forearm (ipsilateral swollen arm: $-0.096 \pm 0.041\% \text{ min}^{-1}$; contralateral arm: $-0.138 \pm 0.037\% \text{ min}^{-1}$, mean \pm SD, $p = 0.037$, paired t test). This has interesting implications for pathogenesis, since the swelling is almost exclusively epifascial and mainly in the subcutis.¹¹ It appears that subfascial k is more closely coupled to epifascial swelling than is epifascial k .⁹ The reason may be that a greater volume of capillary filtrate per unit time is formed by the large, highly vascularized mass of muscle than by subcutis and skin. As a result, it is changes in subfascial lymphatic clearance that govern the degree of arm swelling. The anatomical location of the swelling is determined not by where the undrained fluid forms but by where it subsequently accumulates; and the latter is where interstitial compliance is high (subcutis) rather than low (subfascial muscle).²⁴

The above explanation assumes that there are connections between the two systems to allow subfascial edema fluid to spill over into the more compliant epifascial space. Such evidence has been reported. An injection of radio-opaque contrast medium into the ipsilateral arm of a breast cancer patient 8 months after treatment (in the absence of clinical edema) re-

vealed connections from the deep to the superficial lymphatic system.²⁵ Connections between the epifascial and subfascial systems have also been described in normal arms at the wrist and at the elbow,^{26,27} but the direction of flow is unknown. In view of this hypothesis, it would be of great interest to examine the relation between local subfascial k and local epifascial swelling. This was not, however, considered practical or ethical, because the smaller thickness of muscle distally makes intramuscular injection too difficult.

Technical issues: scintillation counters versus gamma camera

Since the k values in the swollen and non-swollen arms were less clearly differentiated than in our previous experience, we considered methodological differences. Stanton et al.⁸ and Gothard et al.²² used a gamma camera whereas scintillation detectors were used here because of camera access restrictions and because scintillation detectors are ~ 40 -fold more sensitive than gamma cameras, reducing radiation dose. A disadvantage, however, is that count detection is sensitive to distance between the source (depot) and the detector. Despite this, the coefficient of variation for each method was similar, being 32–38% for the gamma camera and 29–36% for the scintillation detectors. The substantial coefficient of variation may help explain the difficulty in detecting the 11% difference in k values with a conventional significance level.

Despite the technological differences, mean k in the swollen arms of our 11 patients, namely $-0.072 \pm 0.021\% \text{ min}^{-1}$, was not significantly different from that in a previous series using the gamma camera, namely $-0.070 \pm 0.026\% \text{ min}^{-1}$ ($p = 0.72$, unpaired t test).⁸ The same is also true for the contralateral arms.

The 54% swelling in the study by Gothard et al.²² was greater than the 28% in the study by Stanton et al.⁸ but the latter was similar to the group studied here (29%). The duration of swelling at the time of study in the present series, 11 ± 9 years, was greater than that in the Stanton et al. series, namely 5 ± 3 years. The sites of study along the forearm also differed. In the present study the proximal depot was on the lateral rather than the ventral aspect of

the arm and there was partial pronation of the arm during acquisitions, unlike the two earlier studies. The combination of a substantial coefficient of variation, differences in detector system, differences in disease duration, differences in limb positioning occasioned by the object of the present study, and differences in k with anatomical location along the arm axis may together account for the difficulty in demonstrating statistically significant differences between k in the swollen and non-swollen arm.

An early plateau phase, or phase of only gradually diminishing counts, similar to that observed with the probes before the onset of obvious clearance, has also been observed using a gamma camera under otherwise similar circumstances.⁸ The plateau was considered to represent the time required for tracer to access the initial lymphatic vessels, or even transient failure of the transport process, perhaps due to injection trauma. An *increase* in counts seems explicable only by a migration of counts towards the detector (i.e., transport of the ^{99m}Tc-HIG into the superficial subcutis).

Is the contralateral arm 'normal' in BCRL patients?

The contralateral 'control' arm of patients with BCRL may differ in some way from that of normal subjects or breast cancer patients without BCRL. The indications are as follows. [i] Mortimer et al.⁵ found that the prevalence of BCRL in patients treated bilaterally is, surprisingly, no higher than in those treated on one side only. [ii] Mellor et al.²⁸ found that skin lymphatic vessels in the *contralateral* forearm of BCRL patients are abnormally wide relative to non-BCRL patients. [iii] In BCRL patients with a swollen ipsilateral hand, the removal rate constant in the contralateral nonswollen hand was unusually high ($-0.162 \pm 0.044\% \text{ min}^{-1}$, $n = 7$)²⁹ compared with contralateral hand k in other women ($-0.095 \pm 0.028\% \text{ min}^{-1}$, $n = 10$).⁸

These puzzling differences seem to indicate that the contralateral limb in BCRL patients is not entirely normal, and they may possibly point to a constitutional predisposition in certain patients. If so, changes in $k_{\text{contralateral}}$, the 'control' for $k_{\text{ipsilateral}}$ in this study, may obscure changes in $k_{\text{ipsilateral}}$. A further factor confusing

the comparison is the significant difference in k between distal and proximal forearm regions discovered in this study.

SUMMARY

The present study tested the hypothesis that local failure of epifascial (subcutis) lymphatic clearance accounts for local variations in the severity of swelling along the BCRL arm. The hypothesis stemmed from the finding that subcutis k in the swollen forearm is lower than in the nonswollen hand of the swollen arm. The ^{99m}TcHIG removal rate constant in the subcutis did not, however, differ significantly between regions of maximal and minimal regional swelling of the forearm, and thus provided no support for the hypothesis. This is in line with previous evidence that epifascial k does not correlate with the severity of swelling in BCRL patients, whereas subfascial k does. It appears that epifascial k may be less important than subfascial k in determining the severity of epifascial forearm swelling. The present study also revealed a hitherto unsuspected variation in drainage rate constant along the axis of the forearm that is unrelated to the presence or absence of oedema, with a greater removal rate constant proximally than distally. This needs to be taken into account in future studies of limb edema.

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