Differences in lymph drainage between swollen and non-swollen regions in arms with breast-cancer-related lymphoedema


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ABSTRACT

Recent research indicates that the pathophysiology of breast-cancer-related lymphoedema (BCRL) is more complex than simple axillary lymphatic obstruction as a result of the cancer treatment. Uneven distribution of swelling (involvement of the mid-arm region is common, but the hand is often spared) is puzzling. Our aim was to test the hypothesis that local differences in lymphatic drainage contribute to the regionality of the oedema. Using lymphoscintigraphy, we measured the removal rate constant, $k$, (representing local lymph flow per unit distribution volume, $V_D$), for $^{99m}$Tc-labelled human immunoglobulin G in the oedematous proximal forearm, and in the hand (finger web) in women in whom the hand was unaffected. Tracer was injected subcutaneously, and the depot plus the rest of the arm was monitored with a $\gamma$-radiation camera for up to 6 h. $V_D$ was assessed from image width. Contralateral arms served as controls. $k$ was 25% lower in oedematous forearm tissue than in the control arm (BCRL, $f_i = 0.070 \pm 0.026\%$ min$^{-1}$; control, $f_i = 0.093 \pm 0.028\%$ min$^{-1}$; mean $\pm$ S.D.; $P = 0.012$) and $V_D$ was greater. In the non-oedematous hand of the BCRL arm, $k$ was 18% higher than in the control hand (BCRL, $f_i = 0.110 \pm 0.027\%$ min$^{-1}$; control, $f_i = 0.095 \pm 0.028\%$ min$^{-1}$; $P = 0.057$) and 59% higher than forearm $k$ on the BCRL side ($P = 0.0014$). $V_D$ did not differ between the hands. Images of the BCRL arm following hand injection showed diffuse activity in the superficial tissues, sometimes extending almost to the shoulder. A possible interpretation is that the hand is spared in some patients because local lymph flow is increased and diverted along collateral dermal routes. The results support the hypothesis that regional differences in surviving lymphatic function contribute to the distribution of swelling.

INTRODUCTION

Breast-cancer-related lymphoedema (BCRL) is a common and distressing complication of breast cancer treatment [1–3]. The swelling, which may be controlled by compression hosiery, exercise and manual lymph drainage [4], tends to be non-uniform along the limb; the proximal forearm and distal upper arm are commonly affected, but the hand is frequently spared, or may swell only if certain physical tasks are performed. In occasional

Key words: breast cancer, forearm, hand, immunoglobulin G, lymphatic vessel, lymph flow, lymphoedema, lymphoscintigraphy, subcutis.

Abbreviations: BCRL, breast-cancer-related lymphoedema; hIgG, human IgG; $k$, removal rate constant; $T_{sk}$, skin temperature; $V_D$, distribution volume.

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patients the entire upper limb and upper outer quadrant of the trunk are involved [5].

The conventional view is that global impairment of lymph drainage from the whole limb occurs as a result of damage by the surgery and/or radiotherapy to axillary drainage channels. This obstruction is assumed to reduce lymph flow and to result in the accumulation of water and interstitial plasma proteins. Delineation of lymphatic vessels using radiocontrast lymphangiography (performed via a hand or wrist vessel) demonstrates tortuous lymphatic trunks, failure of medium to reach or pass the axillary scar, and dermal backflow in the forearm [6]. In a similar study [7], dilated and tortuous lymphatic channels were demonstrated in the forearm and upper arm, together with dermal backflow in the upper arm, fine dermal strands crossing the axilla in two patients, evidence of leakage of contrast medium from the dermal vessels, and ‘lymphatic lakes’ in the axilla. These observations are interpreted to support the view of simple axillary lymphatic obstruction, with global impairment of drainage from the entire limb. However, no information on lymph flow itself within the abnormal vessels can be safely inferred from these anatomical studies. Measurement of lymph flow is not possible in BCRL.

Many studies have attempted a semiquantitative evaluation of lymphatic function in lymphoedema by examining regional lymph node uptake of tracer [8]. Most patients have at least some axillary nodes removed during their cancer treatment, limiting this approach.

Recent research indicates that the pathophysiology of BCRL is more complicated than a simple obstructive or ‘stopcock’ event at the axilla. Several studies have examined the interstitial and microvascular factors governing the accumulation of interstitial fluid in BCRL [9–11]. A notable finding is a lower concentration of interstitial fluid protein in the swollen forearm, and hence a lower interstitial colloid osmotic pressure, when compared with the opposite normal forearm of the same patient [9]. On the basis of a simple obstructive process, protein would be expected to accumulate in the interstitial fluid protein in the swollen forearm, and hence a lower interstitial colloid osmotic pressure, when compared with the opposite normal forearm of the same patient [9].

The removal rate constant ($k$) represents the local lymph flow ($J_L$) per unit volume of distribution ($V_{io}$) of the flow marker, i.e. $k = J_L / V_{io}$. We also estimated $V_{io}$ at each site of injection.

Swelling affects the arm to different degrees at different sites, and the preponderance of swelling at the mid-arm region with frequent sparing of the hand lacks a satisfactory explanation. The second aim of the study, therefore, was to compare local lymphatic function at swollen and non-swollen sites within BCRL arms. The sites studied were the subcutis of an oedematous region of the proximal forearm, and the subcutis of the non-oedematous finger web of the hand in patients with more proximal oedema only. A subsidiary aim was to examine the effect of muscular exercise (of the type normally carried out by patients with BCRL) on $k$ in the proximal forearm, to see if this promoted lymph drainage. To achieve these aims, $k$ was measured at matching sites in the control arm and the BCRL arm.

**METHODS**

**Patients**

A total of 24 women (age 62±7 years, mean ±S.D.) were recruited from the lymphoedema clinics of the Royal Marsden, St George’s, Charing Cross and Ealing Hospitals. All had been treated for unilateral breast cancer as follows: lumpectomy (12), simple mastectomy (9) or radical mastectomy (3); removal of axillary lymph nodes (22); radiotherapy (20); chemotherapy (5); tamoxifen (19). Patients with recurrence of breast cancer were excluded, together with those suffering from cardiovascular or other serious illness. Chronic swelling of the ipsilateral arm began 27±28 months (range 1–96 months) after the cancer treatment, and had been present at the time of the study for 65±38 months (3–120 months). All patients normally wore a compression sleeve in the daytime. On the day of the study, this was not worn.
Approval to perform the study was given by the Ethics Committees of the above hospitals plus that of the Hammersmith Hospital. The volunteers gave informed written consent. The study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Measurement of arm and hand circumferences
Arm measurement was performed by the same operator, as described previously [15]. Briefly, serial circumferences of each arm were measured at 4-cm intervals along the axis of the limb using a tape measure, starting from the styloid process of the ulna and ending at the anterior axillary fold (11–12 measurements). Volume was calculated using the formula for a truncated cone. Hand size was determined from a single circumference measurement at its widest point across the metacarpal heads (with the hand flat and fingers adducted and extended). The appearance of the hand, in particular the veins on the dorsum, was examined to check for mild degrees of oedema. The circumference of the forearm at the level of the injection site was measured in groups A and B (see below).

Protocols
Patients were assigned to one of three groups: (A) non-exercised forearm, (B) exercised forearm, or (C) hand. Patients were assigned arbitrarily to group A or B, while group C comprised those with no hand swelling. In group A the dominant arm was affected in four patients and the non-dominant arm in five; in group B the dominant arm was affected in three patients and the non-dominant arm in two; in group C the dominant arm was affected in three patients and the non-dominant arm in seven. All had forearm and upper arm involvement.

Patients acclimatized to their surroundings for at least 45 min before beginning the study. The protocols for each group were as follows.

Group A: non-exercised forearm (nine patients)
The patient sat with both arms resting at heart level on a table with palms facing up, and the camera was positioned above the arms for anterior viewing. The patient sat with both arms resting at heart level on a table with palms facing up, and the camera was positioned above the arms for anterior viewing. The patient sat with both arms resting at heart level on a table with palms facing up, and the camera was positioned above the arms for anterior viewing.

Group B: exercised forearm (five patients)
The protocol was the same as for the non-exercised group, except that intermittent exercise was performed throughout the protocol. Exercise sessions lasted 5 min, and were followed by 25–35 min of rest (no compression sleeve was worn). The exercise consisted of squeezing a ball in both hands simultaneously, together with flexion at the elbow and pronation of the forearm, followed by relaxation; this was performed at a frequency of 20 cycles·min⁻¹ in time to the pulse of a quartz metronome (Yamaha QT-1). Exercise always immediately preceded imaging of the injection site. Imaging of the upper arms/axillae could not be performed in one patient from this group.

Group C: hand (10 patients)
The arms were viewed anteriorly. Both arms, with palms facing down, were supported at heart level on the upward-facing camera. ⁹⁹ᵐTc-labelled hIgG (0.2 ml; ~35 MBq) was injected subcutaneously into the second finger web. No exercise was performed. Imaging of the upper arms/axillae was performed as in groups A and B in eight of these patients.

Imaging
Imaging was performed using an Integrated Siemens Nuclear Medicine System including a Diacam large-field-of-view γ-radiation camera with a low-energy, high-resolution collimator. Images (256 × 256 pixels) were viewed and analysed on an Icon computer. Syringe counts were obtained before and after the injection, and the injected radioactivity was calculated from the difference. The control and BCRL arms (forearm plus hand) were imaged together for 30 min immediately after injection (dynamic imaging). This was followed by 1-min static acquisitions every 30–60 min over a total period of 5–6 h. Images of the upper arms and axillae were obtained at three different time points (anterior and posterior views; 3-min acquisitions). Images of the outline of the forearm and upper arm segments were obtained by tracing edges of each segment with a ⁵⁷Co pencil.
Calculation of counts and \( k \)
Each count from the injection site was determined within a rectangular region of interest. Counts from the entire forearm and upper arm were determined from a region of interest that outlined the actual limb segment. Counts were corrected for decay according to the formula \( N = N_0e^{-kt} \), where \( N = \) corrected counts, \( N_0 = \) uncorrected counts, \( k = \) decay constant (0.001925) and \( t = \) time since injection (min), and background counts were subtracted. The count at each time point was divided by the count at the injection site recorded immediately after injection. The natural logarithm of this fraction was plotted against time (log-linear plot). Regression analysis of the plot was performed by the method of least-squares fitting to determine the regression coefficient, or \( k \), for \( ^{99m} \text{Tc}-\text{hLgG} \) for each site (units of \( \% \, \text{min}^{-1} \), i.e. rate constant \( \times 100 \)).

Estimation of \( V_D \)
The value of \( k \) depends on lymph flow per unit \( V_D \) of the injected tracer (for discussion, see [16]). In order to compare \( V_D \), in the control and BCRL arms, the transverse profile of radioactivity across the subcutaneous depot in each forearm/hand (measured between two horizontal cursors positioned distal and proximal to the images on the computer screen) was determined. The profile took the form of two bell-shaped curves whose widths were measured. A comparison of the depot sizes in each arm in pixels was thus possible; 1 pixel represents 0.238 cm \( \times 0.238 \) cm (0.057 cm\(^2\)).

Statistical analysis
The following analyses were employed: Student’s paired and unpaired \( t \) tests; one- and two-way ANOVA; Newman–Keuls multiple-comparison post-test; Wilcoxon matched pairs test for results that were not normally distributed; and regression analysis. The paired nature of the comparisons (e.g. control compared with BCRL arm; early-phase \( k \) compared with late-phase \( k \)) necessitated the use of several paired analyses rather than ANOVA. Results are presented as means \( \pm \) S.D. unless stated otherwise. Differences were considered significant when \( P < 0.05 \).

RESULTS

Arm size and temperatures
Table 1 gives the volume, forearm circumference at the level of the injection site and hand circumference for the BCRL arm and the control arm for each group. BCRL arm volume was \( 30 \pm 16 \% \) greater than control arm volume in group A, \( 25 \pm 16 \% \) greater in group B, and \( 27 \pm 18 \% \) greater in group C. Forearm circumference at the level of the injection site in the BCRL arm was \( 20 \pm 13 \% \) greater than in the control arm in group A, and \( 14 \pm 7 \% \) greater in group B. Very mild hand swelling (2%) was present in patients in groups A and B. In group C, no swelling was present at the level of the metacarpal heads or distally. The veins on the dorsum of the hand on the side of arm swelling were slightly less obvious than those on the control hand in two group C patients, the skin presumably being more opaque at this site. Forearm \( T_{90} \) was \( 31.7 \pm 1.1 \degree \text{C} \) (control) and \( 31.5 \pm 1.2 \degree \text{C} \) (BCRL); hand \( T_{90} \) was \( 30.3 \pm 1.4 \degree \text{C} \) (control) and \( 30.1 \pm 1.5 \degree \text{C} \) (BCRL). The ambient temperature was \( 24.1 \pm 1.0 \degree \text{C} \).

Groups A and B: non-exercised and exercised forearms

General appearance of images
The appearance of the depot changed little with time, and the control and BCRL arms were similar. There was no evidence of diffuse activity (‘dermal backflow’) as seen in group C (see below). Discrete foci of activity, representing lymph nodes, were imaged in the axillary area, and were clearer on the anterior view than the posterior view. These were detected in nine out of 11 patients on the control side, but in none on the BCRL side (groups A and B combined; in three patients the upper arms and axillae were not imaged). The number of nodes could not be determined because of the lack of resolution of images, but one or two foci were seen. Longitudinal lines or tracks of activity, presumably representing lymph vessels, were evident in only three out of 11 control arms (upper arm to axilla in two, and from the depot, along the forearm to the upper arm and axilla in one) and no BCRL arms.

Removal of hLgG from the injection site
A plot from one patient in group A is shown in Figure 1. After the first 30–60 min following injection, activity at the injection site diminished gradually in both arms of subjects in groups A and B. Prior to this ‘late phase’ of removal of hLgG, there was an ‘early phase’ of slow or absent removal. The difference between the early- and late-phase decay rates was most evident in the non-exercised forearm group (group A), as shown in Table 2.

Group A: non-exercised forearm. Late-phase constants are compared in Figure 2. For the late phase, \( k_{\text{BCRL}} \) was 25% lower than \( k_{\text{control}} \) (\( P = 0.012 \); paired \( t \) test). The half-life (\( t_1/2 \)) corresponding to \( k_{\text{BCRL}} \) (0.693/\( k_{\text{BCRL}} \times 60) \) was 19.46 \pm 9.14 h; for the control arm, \( t_1/2 = 13.36 \pm 3.85 \) h. Early-phase \( k \) did not differ between the control and BCRL arms (\( P = 0.74 \)). On comparing the early- and late-phase removal of hLgG in each arm, the late phase was significantly faster both in the control arm (\( P = 0.050 \)) and in the BCRL arm (\( P = 0.004 \)).

Group B: exercised forearm. For the late phase, \( k_{\text{BCRL}} \) was 24% lower than \( k_{\text{control}} \) (Table 2, Figure 2) (\( P = 0.009 \); paired \( t \) test). The corresponding \( t_1/2 \) values were
Table 1  Arm volumes and circumferences
Values are means ± S.D. for the BCRL arm and the control arm of patients injected in the proximal forearm (group A, non-exercised forearm; group B, exercised forearm) and in the second finger web of the hand (group C). Significance of differences for BCRL compared with control: *P < 0.05. All measurements were made by the same operator using a tape measure. Arm volume was measured from the styloid process of the ulna to just below the anterior axillary fold. Hand circumference was measured around the widest part of the hand (metacarpal heads). Circumference at the injection site was measured only in patients injected in the forearm.

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>BCRL</th>
<th>Control</th>
<th>BCRL</th>
<th>Control</th>
<th>BCRL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 9)</td>
<td>2329 ± 445</td>
<td>2975 ± 494*</td>
<td>23.01 ± 2.88</td>
<td>27.27 ± 2.94*</td>
<td>20.29 ± 0.92</td>
<td>20.71 ± 1.49</td>
</tr>
<tr>
<td>B (n = 5)</td>
<td>2065 ± 628</td>
<td>2601 ± 925*</td>
<td>26.18 ± 3.85</td>
<td>29.79 ± 4.27*</td>
<td>20.42 ± 1.24</td>
<td>20.78 ± 1.13</td>
</tr>
<tr>
<td>C (n = 10)</td>
<td>1900 ± 347</td>
<td>2456 ± 468*</td>
<td>20.29 ± 1.49</td>
<td>20.71 ± 1.35</td>
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</tr>
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</table>

Figure 1  Loge-linear plot of the fraction of counts remaining at the injection site in a patient from group A (non-exercised oedematous forearm)
During the late phase at 60–326 min post-injection (onset determined by eye), a slower decay of counts is evident in the BCRL forearm compared with the control forearm. Regression lines are shown, with the slopes giving the values of k. For this patient, kcontrol = 0.083% min⁻¹ and kBCRL = 0.055% min⁻¹.

21.39 ± 13.43 h for the BCRL arm and 15.79 ± 8.63 h for the control arm. During the early phase, removal of hIgG was again similar in the two arms (P = 0.35). In the control arm, late-phase removal was again significantly faster than early-phase removal (P = 0.052), but a similar trend in the BCRL arm did not achieve significance (P =

Table 2  Removal rate constants (k) for 99mTc-labelled hIgG following subcutaneous injection
Values are means ± S.D. for the early and late phases of decay of activity at the site of injection in the proximal forearm (group A, non-exercised forearm; group B, exercised forearm) and in the second finger web of the hand (group C). Values are given for the control and BCRL arms. The hand of the BCRL arm in group C was unaffected by swelling. The paired t test was used for comparisons between control and BCRL arms (P values).

<table>
<thead>
<tr>
<th>Group</th>
<th>Early k (% min⁻¹)</th>
<th>Late k (% min⁻¹)</th>
<th>Early k (% min⁻¹)</th>
<th>Late k (% min⁻¹)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 9)</td>
<td>0.034 ± 0.020</td>
<td>0.093 ± 0.028</td>
<td>0.036 ± 0.024</td>
<td>0.070 ± 0.026</td>
<td>0.74</td>
</tr>
<tr>
<td>B (n = 5)</td>
<td>0.042 ± 0.030</td>
<td>0.088 ± 0.068</td>
<td>0.054 ± 0.009</td>
<td>0.068 ± 0.030</td>
<td>0.35</td>
</tr>
<tr>
<td>C (n = 10)</td>
<td>0.048 ± 0.058</td>
<td>0.095 ± 0.028</td>
<td>0.042 ± 0.051</td>
<td>0.110 ± 0.027</td>
<td>0.72</td>
</tr>
</tbody>
</table>

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Values are from groups A and B combined (n = 14), and are means ± S.E.M. The profile width, an index of distribution space, increased with time, especially between 30 min and 60 min when approx. 40% of the total increase occurred in each arm. After the initial measurement, profile width was greater in the oedematous BCRL forearm than in the control forearm (P < 0.0001; two-way ANOVA).

To assess the effect of exercise on the removal of hIgG from the injection site, the $k$ values for group A were compared with those from group B. For the late phase, neither the ratio of $k$ values ($k_{BCRL}/k_{control}$) nor the absolute $k$ value (% min$^{-1}$) in either arm differed between the groups (ratio, $P = 0.89$; $k_{control}$, $P = 0.92$; $k_{BCRL}$, $P = 0.75$; unpaired t test). For early-phase removal there were similarly no significant differences between groups A and B (ratio, $P = 0.11$; $k_{control}$, $P = 0.59$; $k_{BCRL}$, $P = 0.15$).

$V_D$ assessed from activity profiles

The widths of the activity profiles of the depot were similar in groups A and B. In both groups, width increased with time. At 342 min, profile width in group A had increased by $31 ± 19\%$ in the control arm and by $56 ± 38\%$ in the BCRL arm. This increase with time was statistically significant, and the width was greater in the BCRL arm than in the control arm after 5 min ($P < 0.0001$ for each factor; two-way ANOVA). In group B, profile width had increased at 342 min by $45 ± 16\%$ in the control arm and by $62 ± 36\%$ in the BCRL arm ($P < 0.0001$ for each factor). Results from groups A and B combined are shown in Figure 3, with the numbers of pixels converted into cm. For the combined groups, mean profile width of the control depot increased from 1.70 cm to 2.26 cm with time, whereas that of the BCRL depot increased from 1.94 cm to 3.01 cm. The rate of increase in depot width was also greater in the BCRL arm ($0.0022 ± 0.0020$ cm min$^{-1}$) compared with the control arm ($0.0011 ± 0.0007$ cm min$^{-1}$; $P = 0.017$, Wilcoxon test). Initial depot width (at 5 min) did not differ significantly between the arms ($P = 0.24$, paired t test).

Group C: hand

General appearance of images and ‘dermal backflow’

The hands and forearms of a patient injected in the finger web are shown in Figure 4, and the upper arms/axillae of the same patient are shown in Figure 5. On the BCRL side, but not the control side, prominent diffuse activity in superficial tissues (skin and subcutis) was present; this is often called ‘dermal backflow’. Superficial activity was present in the hand in two patients, but started proximal to the wrist in the others. It extended into the upper arm in nine patients, and in one patient the proximal limit extended as far as the anterior axillary fold and the acromion process. Activity in the forearm and upper arm, quantified by determining the total counts in each segment (outlines defined using the cobalt pencil; lymph vessels and nodes excluded), is shown in Figures 6 and 7.

(a) Forearm counts. After an initial lag of ~ 30 min, the fraction of the injected counts in the whole BCRL forearm increased progressively with time, and was 5-10-fold higher than in the control forearm. In the control
Figure 5  Upper arms/axillae of the same group C patient as in Figure 4 (right arm affected)
Shown are anterior (left image) and posterior (right image) views taken at 290 and 295 min after injection. The scale bar represents 10 cm. Elbows are at the bottom of the images and shoulders at the top. The BCRL arm is on the left of the anterior image and on the right of the posterior image. Dermal collateralization on the BCRL side extends almost to the shoulder. Evidence of uptake by axillary lymph nodes is present on the control side only.

Figure 6  Activity in the whole forearm following hand injection
Counts are expressed as a fraction of initial injection site counts, and are means ± s.e.m. The x-axis error bars for the control forearm (not shown) were identical with x-axis error bars for the BCRL forearm. Activity was much higher in the BCRL arm, as seen qualitatively in Figure 4.

Figure 7  Activity in the whole upper arm following hand injection (from the anterior view)
Counts are expressed as a fraction of initial injection site counts, and are means ± s.e.m. Activity was higher in the BCRL arm, as seen qualitatively in Figure 5.

forearm, counts remained relatively stable from 74 min onwards (Figure 6).

(b) Upper arm counts. Upper arm counts were significantly higher in the BCRL arm than in the control arm (n = 8, P < 0.0001, two-way ANOVA) (Figure 7). Anterior and posterior view counts were the same in the BCRL arm (P = 0.83), indicating similar superficial activity on the two aspects of the arm; in the control arm, anterior counts tended to be higher than posterior counts (P = 0.07). In the BCRL arm, upper arm counts had increased significantly by the time of the third acquisition (anterior view: P = 0.022, one-way ANOVA, Newman–Keuls post-test).

Axillary lymph nodes were imaged in all 10 patients on the control side (between two and five foci of activity), plus one focus at the elbow in one patient. On the BCRL side, axillary lymph nodes were present in five patients (one to three foci), and at the elbow in the same patient as before. Lymph vessels (lines/tracks of activity) were evident in nine control arms. Vessels were imaged in four BCRL arms (near the depot and/or upper arm to axilla).

Removal of hIgG from the injection site
A plot of the fractional removal of \(^{99m}\text{Tc}\)-hIgG from the injection site in one patient is shown in Figure 8. As in the forearm, a lag of 30 min or so preceded the main (late) phase. In contrast with the forearm, \(^{99m}\text{Tc}\)-hIgG was removed more quickly (18% faster) from the depot in the BCRL hand compared with the control hand (n = 10, P = 0.057, paired t test). Late-phase constants are compared in Figure 2. \(t_2\) corresponding to late \(k_{BCRL}\) was 11.63 ± 5.18 h; for late \(k_{control}\), \(t_2 = 12.99 ± 3.24\) h. Early-phase \(k\) was similar in each hand (P = 0.72, Table 2), and late-phase removal was sig-
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Figure 8 Log$_e$–linear plot of the fraction of counts remaining at the injection site in a patient from group C (hand injection)

During the late phase, i.e. 62–348 min post-injection (onset determined by eye), a faster decay of counts is evident in the BCRL hand compared with the control hand. Regression lines are shown, with the slopes giving the values of $k$. For this patient, $k_{\text{control}} = 0.071\% \cdot \text{min}^{-1}$ and $k_{\text{BCRL}} = 0.109\% \cdot \text{min}^{-1}$.

Figure 9 Width of the hand depot profile of $^{99m}$Tc-labelled hIgG in group C

Values are means ± S.E.M. Profile width (and hence assumed VD) was the same in the control and BCRL hands.

Removal kinetics

Removal from the depot is attributed to bulk flow, i.e. lymph drainage; diffusion is too slow over distances greater than 1 mm. Uptake by blood microvessels is unlikely to be significant, because the molecular mass of the IgG molecule is 2.25 times that of albumin. Slight removal by blood vessels traumatized by needle insertion is possible, but the low value of the early-phase $k$ argues against this.

The removal of tracer from the depot was clearly biphasic. The reason for the delay in onset of the phase of faster removal is unclear. It could represent the time taken for the labelled protein to access the initial lymphatic vessels, or the time taken to reach the contractile collector vessels, or even an initial ‘stunning’ of the transport process. Lymphatic density is lower and tissue compliance greater in the subcutis (the site of injection here) than in the dermis; removal of $^{99m}$Tc-labelled rhenium sulphide colloid from a subcutaneous depot is slower than from a subepidermal depot in the pig flank [17], and accumulation of activity in the axillary nodes 100 min after subcutaneous injection of $^{99m}$Tc-labelled human serum albumin in the healthy human forearm is one-twentieth of that following intradermal

ANOVA), which was in keeping with the clinical judgement that oedema was essentially absent from the BCRL hands.

DISCUSSION

The main findings were that the rate constant ($k$), i.e. lymph flow per unit volume of tracer distribution, was reduced in the oedematous forearm but, to our surprise, increased in the non-oedematous hand of the BCRL arm. Also, following injection into the hand, prominent diffuse activity was imaged in the BCRL arm that was apparently concentrated in the skin and/or subcutis of the swollen forearm and upper arm (epifascially), and counts at these sites were correspondingly high.

Anatomical findings

Major lymph vessels were not demonstrated by forearm depots in BCRL arms and were shown in only a minority of normal arms, indicating that forearm subcutaneous injection of tracer is unsuitable for vessel imaging. No axillary nodes were imaged on the side of the cancer treatment, but these were generally visible on the opposite side, consistent with the history of lymph node removal. Depots in the finger web were much better at delineating major lymph trunks and nodes. Clearer images of vessels and nodes following finger-web injection of $^{99m}$Tc-labelled hIgG, compared with injection into the dorsum of the distal forearm, have been reported [14].
Association of oedema and reduced local removal of tracer

Late-phase $k$ was 25% lower in the swollen BCRL forearm than in the control forearm. Reduced flow per unit $V_o$ in the affected forearm indicates that local lymphatic removal is impaired following axillary trauma. A possible contributory factor to the forearm lymphatic dysfunction in some patients is the subsequent damage caused by acute inflammatory episodes (cellulitis). $^{131}$I-labelled albumin, injected subcutaneously into the forearm or lower leg, disappeared at a much lower rate from the lymphoedematous limb (mean $t_2 = 101$ h) than from the normal limb ($t_2 = 26$ h) in five BCRL patients treated by radical mastectomy and in the legs of one patient treated by groin dissection [19]. The value for the normal limb compared with the 13–16 h obtained using $^{99m}$Tc-labelled hlgG presumably reflects the different behaviour of the two tracers (the albumin may have been in micro-aggregated form) when being removed from the interstitium by the lymphatic system. The greater relative kinetic impairment in the swollen limb in the study of Hollander et al. [19] compared with ours, however, may reflect the more aggressive surgery practised 40 years ago and the less effective treatment of the swelling.

We reported recently that the microvascular filtration rate per unit volume of forearm soft tissue (which should match lymph flow in the steady state) is 47% lower than in the normal arm at a physiological venous pressure [11]. Similarly [9], the net pressure opposing capillary blood pressure is raised in BCRL. These various observations, taken with the reduced $k$ values reported here, support the view that local fluid turnover per unit volume of tissue (i.e. microvascular filtration and lymph drainage) is reduced in the oedematous forearm.

Distribution space of tracer

In the present study, the width of the activity profile, and hence presumably $V_o$, increased with time in each forearm, especially at the time when the removal rate increased rapidly. The latter observation may indicate that access to the lymphatic pump requires local spread. depot width was greater in the BCRL forearm than in the control arm, in keeping with the oedematous state of the former. Spread of the depot is attributed to local flow (since the injectate raises local tissue fluid pressure), and to diffusion. The greater water content of the subcutaneous tissues in the swollen arm would lead to greater mobility of the interstitial fluid on that side, and hence to the observed greater spread of the depot. With subcutaneous injection of $^{131}$I-albumin in lymphoedema [19], ‘some diffusion of the injected albumin….not appreciably different in the two limbs’ was reported, an observation based on measurement of depot image area. It is unlikely that the difference in $V_o$ between the control and BCRL forearms in the present study could confound the data interpretation, especially as $k$ represents lymph flow per unit $V_o$.

Effect of exercise on removal of tracer

Exercise of the type routinely performed by BCRL patients did not enhance local lymph drainage ($k$). This supports the general belief that exercise is effective only when the arm is compressed by wearing a sleeve [20]. The latter raises the interstitial fluid pressure in the oedematous subcutis [21,22].

Removal of tracer from the non-swollen region of the BCRL limb

The most unexpected finding was that late-phase $k$ was not reduced (and in fact was increased by 18%) in a non-oedematous region (the second finger web) on the side with BCRL. Absence of oedema at this site was based on inspection, on circumference measurements and on $V_o$, which were the same on both sides. Since $V_o$ was unchanged and $k$ increased marginally, this implies that local lymph flow itself is increased marginally at this site. Since the hands of these patients were in the steady state (not changing in volume), this further implies that the capillary filtration rate is increased in the hand. A lack of lymph drainage failure in the hand in BCRL (i.e. no significant difference in the percentage of tracer removed at 6 h from the finger webs compared with the control hand, and a significant increase in removal from the BCRL hand at 1 h) has been reported elsewhere [23], but the authors did not state if swelling extended to the hand. The novel finding of preserved or even increased local lymph flow from the hand argues against the common interpretation of a global impairment of lymph drainage from the limb following axillary surgery and radiotherapy. The route of the increased lymph drainage is considered next.

Another notable finding was the presence of diffuse activity in the superficial tissues of the forearm and upper arm on the BCRL side, but not the control side, following finger web, but not forearm, injections. This superficial activity had the appearance of ‘dermal backflow’, a commonly reported feature in lymphoedema [7,24]. The considerably higher counts in the BCRL forearm and upper arm compared with the normal arm was a consequence of the superficial activity, and indicated substantial redistribution and re-routing of drainage within the limb. The diffuse activity appears to indicate a collateral route of enhanced drainage along the skin/subcutis, which could account for the increase in $k$ in the finger web and lack of hand swelling in these patients. We therefore propose that lymph flow from the hand is preserved, or even increased, in BCRL patients in whom this region is spared, and that this drainage occurs via the
dermis of the forearm and upper arm. The appearance of
dermal ‘backflow’ in this case is more appropriately
termed dermal ‘collateralization of flow’. This is
supported by fluorescence microlymphography studies
[25] showing that the dermis of the BCRL forearm has a
far higher density of initial lymphatic vessels and hori-
zontal spread of injected dye than in the normal forearm.
It is likely that lymphangiogenesis contributed to the
increase in vessel density. This enables re-routing of
lymph along a dermal pathway of low resistance and
increased capacity.

Conclusion
A concept of regional lymph drainage failure at sites of
swelling emerges from the present study, contrary to the
traditional, simpler view of a ‘stopcock’ link between
axillary damage following breast cancer treatment and
the subsequent lymphoedema. A working hypothesis,
compatible with the new findings, is as follows. The
actively contractile lymphatic collectors of the arm have
to work against increased resistance following the axillary
radiotherapy and surgery. The distribution of swelling
within a limb ultimately depends on the fatigue and
eventual pump failure of the constitutionally weakest
vessels, which may be those draining the mid-arm region.
In regions where local collectors have not yet undergone
failure, no oedema appears. Further studies are required
to test this hypothesis, in particular the examination of
swollen hands, and forearm regions that are spared.

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