A quantitative lymphoscintigraphic evaluation of lymphatic function in the swollen hands of women with lymphoedema following breast cancer treatment

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ABSTRACT

In BCRL (breast cancer-related lymphoedema), arm swelling is unevenly distributed and some regions are partly or entirely spared. In particular, the hand may or not be swollen, but when involved functional impairment can be substantial. We have found previously that, when the ipsilateral hand is spared of swelling (in a limb with swelling proximal to the hand), the local lymph drainage rate constant (k) is at least as high as in the contralateral hand, contrary to the traditional ‘stopcock’ concept of reduced lymph drainage from the whole limb. In the light of this finding, we have investigated lymph drainage in the hands of eight women with BCRL and moderate-to-severe hand swelling, using γ-camera quantitative lymphoscintigraphy. Images showed pronounced superficial activity in the ipsilateral swollen arms of most patients, indicating dermal backflow. k for 99mTc-labelled hIgG (human IgG) measured over 5 h in the subcutis of the ipsilateral swollen hand was 34 ±24 % less than in the contralateral hand (P = 0.013). Activity measured in the ipsilateral swollen forearm increased progressively, but there was very little increase in the contralateral forearm, indicating retention of 99mTc-labelled hIgG in the swollen forearm. It is concluded that lymphatic function in the swollen hand is impaired, and that there appears to be two populations of women with BCRL, i.e. spared-hand and swollen-hand, irrespective of the cancer treatment received.

INTRODUCTION

Lymphoedema of the arm is a common sequel to the treatment for breast cancer, with a commonly quoted incidence of approx. 25 % of all cases [1–3]. SLNB (sentinel lymph node biopsy) alone still results in BCRL (breast cancer-related lymphoedema) in 6 % of cases [4]. Arm swelling at up to 12 months post-surgery is less, however, in patients receiving SLNB (plus level 2 axillary dissection if node positive) than in patients receiving axillary

Key words: arm swelling, breast cancer, IgG, lymph flow, lymphoedema, quantitative lymphoscintigraphy.

Abbreviations: ANCOVA, analysis of covariance; BCRL, breast cancer-related lymphoedema; hIgG, human IgG; k, drainage rate constant; QL, quantitative lymphoscintigraphy; ROI, region of interest; s.c., subcutaneous; SLNB, sentinel lymph node biopsy; VD, volume of distribution.

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dissection [5]. BCRL is a disfiguring and disabling condition that can often be controlled but not cured. The hand may be spared, but when it is involved functional impairment is substantial and treatment can be difficult (Figures 1a and 2a) [6]. The uneven distribution of the swelling along the length of the arm and the sparing or involvement of the hand has attracted attention and has led to the assumption of globally impaired lymph drainage ('stopcock theory') being challenged [7–10].

In BCRL, lymph drainage can be estimated by measuring the drainage rate constant ($k$) for a radiotracer bound to a plasma protein injected into the subcutis (epifascial compartment) or muscle (subfascial compartment), using a $\gamma$-camera QL (quantitative lymphoscintigraphy). It is found that $k$ is decreased in the oedematous subcutis of the proximal ipsilateral forearm when compared with the contralateral forearm [7,11]. Likewise in the muscle (subfascial compartment) of the ipsilateral arm $k$ is also decreased. In the subfascial compartment the decrease in $k$ correlates with the degree of swelling of the arm. No such correlation exists between $k$ in the subcutis and degree of swelling [8], even though most of the swelling in BCRL is confined to the epifascial compartment [12,13]. Measurement of epifascial $k$ at the site of maximal and minimal swelling within the same forearm did not support the hypothesis that regional variations in epifascial (subcutis) lymphatic clearance account for regional variations in the distribution of forearm swelling, but showed that lymph flow per unit of subcutis tissue volume has an axial gradient along the forearm (proximal > distal). This gradient confounds examination of the proposed relationship between local $k$ and local swelling along the axis of the arm [10].

When QL was performed by injecting radiotracer in the second web-space of ipsilateral hands spared of swelling, $k$ was found to be no lower (in fact 18 % higher) than in the contralateral hand. Images of the ipsilateral arm following web-space injection in the spared ipsilateral hand showed dermal collateralization of activity ('dermal backflow'). This phenomenon was not evident following injection in the swollen ipsilateral forearm. It was concluded that there was a collateral route of enhanced drainage from the spared hand along the skin and subcutis, possibly accounting for the preserved or increased hand drainage [7]. Few other studies have
addressed hand lymph drainage. Pain et al. [9] performed QL using a scintillation detector and a dual-isotope technique on women with spared hands who performed exercise and found that lymph drainage in the ipsilateral hand, although numerically less than in the contralateral hand, did not differ significantly from drainage in the contralateral hand, consistent with the findings of Stanton et al. [7].

The unexpected finding that lymph drainage from the spared hand of the otherwise swollen arm is preserved led us to examine a group of women with swollen hands. The aim was to test the hypothesis that local lymph drainage is impaired in the oedematous subcutis of the ipsilateral hand when compared with the contralateral hand, consistent with the findings of Stanton et al. [7].

METHODS

Patients

Eight women aged 58 ± 8 years (mean ± S.D.) were recruited from the Lymphoedema Clinics of St George’s Hospital, London, the Royal Marsden Hospital, Surrey, and Ealing Hospital, Southall, Middlesex. All had been treated for unilateral breast cancer as shown in Table 1. Chronic swelling of the ipsilateral arm (i.e. the arm on the same side as the cancer surgery) began 28 ± 38 months after axillary surgery. The swelling was first noticed in the hand or wrist in seven patients and in the forearm in one (patient 3; numbers of patients referred to in the text are as given in Table 1). In patient 3 (Figure 2a) a constricting gutter was present around the wrist (it was not evident in any other patient). At the time of the study, the swelling had been present for 4.8 ± 6.9 years. All patients normally wore a compression sleeve and glove in the daytime but, on the day of the study, this was not worn. The study was approved by the Local Research Ethics Committees of the above hospitals plus that of the Hammersmith Hospital, and by the Administration of Radioactive Substances Advisory Committee of the U.K. (ARSAC). The study was carried out in accordance with the Declaration of Helsinki. The volunteers gave informed written consent.

Measurement of arm volume, hand volume and temperatures

Serial circumferences were measured at 4 cm intervals along the axis of the arm using a flexible tape measure, starting from the styloid process of the ulna and ending at the anterior axillary fold (11 or 12 measurements), and arm volume was calculated using the formula for a truncated cone [16]. Hand circumference was measured with a tape measure around the metacarpal heads. Hand volume was measured by water displacement, the proximal limit of the measurement being the styloid process of the ulna. The average of three measurements was used [17]. Hand skin temperature (Tsk) and ambient temperature (Ta) were recorded (YSI Telethermometer).

γ-Camera, injection and imaging

Injection and imaging was as described previously [7]. Briefly, patients acclimatized to their surroundings for 45 min before resting both arms at heart level and with palms facing downwards on the upward-facing γ-camera for ventral imaging (Integrated Siemens Nuclear Medicine System with Diacam large-field-of-view γ-camera and low-energy high-resolution collimator). Matrix size was 256 × 256 pixels and one pixel represented 0.057 cm². A 1 ml syringe and a 25-gauge needle (16 mm) were used to inject subcutaneously approx. 35 MBq of 99mTc-labelled hIgG (human IgG) in 0.2 ml of saline (67–80 µg of hIgG per injection; DRN 4369 TechneScan® HIG;
Mallinkrodt Medical) in the second web-space of each hand. Imaging began immediately after injection. No exercise was performed.

Hands and forearms were imaged for 30 min (dynamic acquisition) followed by static acquisitions lasting 1 min at intervals of approx. 30–90 min for a total period of approx. 300 min. To assist analysis of ROIs (regions of interest) from the images, an outline of the forearms and upper arms (i.e. above the elbow) was obtained by tracing the edges with a $^{57}$Co pencil. The patient sat reading in the waiting room between acquisitions. Near the end of the total period of hand/forearm acquisitions, a single acquisition of the upper arms and axillae was obtained (3 min). For patient 8, no dynamic imaging was performed and only the counts from the depot were available.

**Measurement of counts and $k$ values**

Counts from the depots were determined within a rectangular ROI of area 55 cm$^2$. Counts from the forearms and upper arms were determined in ROIs outlining the limb segment, whereas counts from the axillary lymph nodes were determined within an elliptical ROI. Decay correction was performed according to the formula $N = N_0 \cdot e^{-\lambda t}$, where $N$ is the corrected count, $N_0$ is the uncorrected count, $\lambda$ is the decay constant (0.001923 min$^{-1}$) and $t$ is the time since injection (min). For the depot, the count at each time point was divided by the count obtained immediately following injection. The natural logarithm of this fraction against time gave a monoeXponential plot. The slope, determined by regression analysis, gave $k$ (%/min) for $^{99m}$Tc-labelled hIgG.

**Estimation of distribution of radiotracer**

For a solute cleared exclusively by lymph, $k$ depends on lymph flow per unit volume of distribution ($V_D$) of the injected tracer [18]. $V_D$ could not be measured, but distribution was estimated from the two-dimensional images of the depots. A plot of the transverse profile of radioactivity was obtained across each depot. Profiles took the form of bell-shaped curves whose widths were measured in cm at 10% of the peak. This measurement was unavailable from patient 8.

**Statistical analysis**

Results are presented as means ± S.D. or (in the Figures) means ± S.E.M. Linear regression was used to determine the slopes (and hence $k$) of the semi-log plots of depot counts. Further analysis was performed using paired Student’s $t$ test, one- and two-way ANOVA, the Newman–Keuls post-test and ANCOVA (analysis of covariance). The correlation coefficient ($r$) was calculated to test for relationships between $k$ and limb volume. Differences were considered significant if $P < 0.05$. Statistical analysis was performed using Prism version 4.03.

**RESULTS**

**Arm, hand, and temperature measurements**

Ipsilateral swollen arm volume (3899 ± 922 ml) was 50 ± 49% greater than contralateral arm volume (2650 ± 361 ml; $P = 0.012$, as determined by paired Student’s $t$ test). Ipsilateral swollen hand circumference (22.2 ± 2.8 cm) was 13 ± 16% greater than contralateral hand circumference (19.7 ± 0.5 cm; $P = 0.050$). Ipsilateral swollen hand volume (489 ± 159 ml) was 50 ± 57% greater than contralateral hand volume (332 ± 33 ml; $P = 0.051$). $T_s$ was 24.5 ± 0.6°C, ipsilateral $T_{ik}$ was 31.4 ± 1.5°C and contralateral $T_{ik}$ was 31.3 ± 1.1°C.

**Appearance of images**

In the contralateral arm, tracks of activity representing subcutaneous lymphatic collector vessels were imaged in either the forearm or upper arm or both in all patients, but were often only faint. In the ipsilateral swollen arm a lymphatic vessel was imaged in one patient only. In most cases any such vessels would have been obscured by the superficial activity (see below). Lymph nodes were clearly imaged in all eight contralateral axillae and faintly in five out of the eight ipsilateral axillae.

Diffuse superficial activity (Figure 1b), indicating dermal backflow, was evident in the ipsilateral arm images of seven patients. It was absent in patient 2. Dermal backflow extended from the wrist to the anterior axillary fold in patient 1 and from the wrist to the mid-upper arm in patient 5. In patient 4, backflow was present in the hand and extended to the anterior axillary fold. In patient 3, dermal backflow was imaged throughout the hand, but was sharply demarcated at the wrist (glove distribution) and did not pass this point (Figure 2b). In patients 6, 7 and 8, dermal backflow was present in the hand and extended to the elbow.

**$k$ values for the hands**

During an early phase lasting approx. 30 min, counts recorded from the hand depots rose slightly, a phenomenon noted previously [10]. After this counts fell progressively in each hand (Figure 3). $k$ was measured from the end of the early phase. In the ipsilateral swollen hand $k$ was $-0.101 ± 0.035$%/min ($n = 8$) and in the contralateral hand was $-0.157 ± 0.043$%/min ($n = 8$), i.e. $k$ was 34 ± 24% less in the ipsilateral swollen hand ($P = 0.013$, as determined by paired Student’s $t$ test). $k_{\text{ipsilateral}}$ was numerically lower than $k_{\text{contralateral}}$ in seven patients. Intra-individual comparison of the regression slopes of the plots from the ipsilateral and contralateral hands by ANCOVA indicated that in six patients $k_{\text{ipsilateral}}$ was significantly lower than $k_{\text{contralateral}}$ ($P < 0.02$) and that in two patients (patients 4 and 8) $k_{\text{ipsilateral}}$ and $k_{\text{contralateral}}$ did not differ significantly ($P = 0.13$ and 0.43; Figure 4). There were no
Figure 3: Fraction of counts remaining at the depot in each hand plotted over 300 min
Values are log\(_n\) fraction of the counts recorded immediately after injection compared with time (means ± S.E.M., n = 8). Counts rose slightly before falling progressively from 30 min. Counts in the swollen hand fell less steeply than counts in the contralateral hand and \(k_{\text{ipsilateral}}\) was less than \(k_{\text{contralateral}}\). The regression lines shown give \(k\) values obtained from the mean fractional counts (± S.E. of \(k\)): \(k_{\text{ipsilateral}}\), \(-0.096 ± 0.006\%/\text{min}\); and \(k_{\text{contralateral}}\), \(-0.157 ± 0.010\%/\text{min}\).

Figure 4: Individual and mean (± S.D.) \(k\) values for the contralateral and ipsilateral hands
Patient numbers are shown adjacent to respective plots (see Table 1).

Distribution of radiotracer
The width of the depot increased steadily and similarly in each hand with time (Figure 5). By the end of the acquisition period the profile width of the ipsilateral depot had increased by 47 ± 22%, from 1.41 ± 0.10 cm to 2.18 ± 0.31 cm, and the profile width of the contralateral depot had increased by 51 ± 19%, from 1.41 cm to 2.20 cm (\(n = 7\); \(P < 0.0001\) for both hands). There was no difference in widths between the ipsilateral swollen hand and the contralateral hand (\(n = 7\); \(P = 0.3\), as determined by two-way repeated measures ANOVA).

Forearm activity
Activity in the ipsilateral swollen forearm rose dramatically after 33 min and was still rising at the last acquisition (298 min), whereas activity in the contralateral forearm remained low throughout in comparison (Figure 6). This was in keeping with the qualitative appearance of superficial activity (dermal backflow) imaged in the ipsilateral forearms of most patients. The increase in activity in the ipsilateral swollen forearm with time and the difference between the arms were significant (\(n = 7\); \(P = 0.0004\) and \(P < 0.0001\) respectively, as determined by two-way repeated measures ANOVA). In other words, there was statistically significant correlations between \(k_{\text{ipsilateral}}\) and the percentage increase in hand or arm volume (\(r \leq 0.2, P \geq 0.6\)).
retention of labelled protein in the ipsilateral swollen forearm.

**Upper arm and axillary counts**
The counts recorded in the upper arm (as a fraction of the initial depot counts) 262 min after injection were 0.020 ± 0.08 on the ipsilateral swollen side and 0.008 ± 0.002 on the contralateral side. These values did not differ significantly (n = 7; P = 0.16, as determined by paired Student’s t test). In the axillary region, ipsilateral counts (0.006 ± 0.003) were 58 ± 15 % lower than contralateral counts (0.015 ± 0.003; n = 7; P = 0.0003).

**DISCUSSION**
The principal findings of the present study were that (i) k measured using a γ-camera was decreased by 34 % in the non-exercised ipsilateral swollen hand when compared with the contralateral hand; and (ii) dermal backflow and retention of counts in the forearm occurred on the ipsilateral swollen side, but not on the contralateral side. In conjunction with earlier findings, considered in detail below, there appears to be two distinct populations of patients with BCRL, those with and without hand involvement.

**Images and dermal backflow**
Lymphatic vessels in the contralateral arm are not well delineated following s.c. (subcutaneous) injection of 99mTc-labelled hIgG. It is well-established that the intra-dermal route gives better anatomical delineation [19], but the s.c. route (acknowledged as being better for testing microlymphatic uptake and local lymphatic clearance) was used in the present study because most of the swelling is in the subcutis and the aim was to quantify clearance of the excess interstitial fluid. 99mTc-Labelled hIgG delineated clearly axillary lymph nodes in the contralateral axilla, and axillary surgery explains the absence or faintness of lymph node images ipsilaterally.

The present findings showed dermal backflow in most cases. In women with spared hands, s.c. injection in the second web-space also resulted in dermal backflow in the ipsilateral arm; it did not occur following s.c. injection in the swollen forearm [7]. Dermal backflow, therefore, occurs whether or not the hand is swollen and whether or not the lymph k is reduced in that hand. Indeed, dermal backflow was present when k was numerically increased, namely in patient 4 in whom backflow was imaged along the full length of the arm. Patient 2 had no discernible backflow, but had the second greatest reduction in k. Dermal backflow is therefore not a specific indicator of reduced local lymph drainage in the hand or of local oedema.

Dermal backflow has been proposed to represent a low-resistance lymph drainage pathway along the dermis [7]. If so, it was insufficient to prevent swelling, but could have ameliorated it. Dermal re-routing or dermal forwardflow might be more precise terms for this phenomenon (the superficial activity is probably moving proximally along the limb, clearly so from the images of some patients). The most distal (or only) site of access to dermal lymphatic routes appears to be either in the hand or at the wrist. The constricting gutter at the wrist in patient 3 prevented drainage of superficial activity into the forearm, and this may have contributed to the severity of the swelling.

**Forearm and upper arm counts**
Counts in the ipsilateral forearm increased throughout the acquisition period, consistent with the dermal backflow. Backflow did not extend to all upper arms by the end of the acquisition period and activity in this segment was not significantly greater than in the contralateral upper arm. Activities in these limb segments represent the balance of inflow and outflow of radioprotein. Lymph flows from the swollen hand into the swollen forearm, but is then held up there. Counts in the contralateral forearm show no increase after approx. 1 h (Figure 6), so lymph drains out of the contralateral forearm as fast as it enters.

**Lymph drainage from the hand**
The close similarity between depot widths at any given time in the ipsilateral swollen hand and the contralateral hand indicates that V_D is unlikely to differ significantly between sides. Thus the decrease in the ipsilateral k (local lymph flow/V_D) implies that local lymph flow itself is decreased.

The only previous quantification of local lymph drainage from swollen hands in BCRL is by Pain et al. [9], who used a different technique. They employed a scintillation detector, 99mTc-labelled hIgG plus 111In-labelled hIgG and a protocol of exercise (fistclenchings). They found that k in the swollen hand was significantly lower than k in the contralateral hand (k ipsilateral = −0.073 %/min, and k contralateral = −0.17 %/min; n = 7, P < 0.05); k ipsilateral was less than in the present study. The label used in each hand was not stated. 99mTc-Labelled hIgG and 111In-labelled hIgG are reported to behave similarly when injected in the hands of healthy volunteers [9,20], but comparison in arms of women with BCRL has not been performed. Possible differences arising from the use of a scintillation detector rather than a γ-camera have been considered elsewhere [10]. Exercise would be expected to increase clearance. In healthy female subjects of mean age 29 years performing handgrip exercise, clearance of 99mTc-antimony colloid from ‘subdermal’ depots in hands (first and fourth web-spaces) (k = −0.18 ± 0.03 %/min) was numerically faster than clearance from the opposite non-exercised hand (k = −0.14 ± 0.05 %/min; n = 6; P = 0.09) [21]. If lymph drainage from the ipsilateral swollen hand is already close to its maximum, exercise...
Comparison of mean \((\pm \text{S.E.M.})\) \(k\) values in the ipsilateral swollen hand and contralateral hand from the present study with the values for the ipsilateral spared hand and contralateral hand from Stanton et al. [7]

The mean ± S.D. (n) is stated above each column. \(k\) for the contralateral hand in the swollen-hand patients was significantly higher than \(k\) for the other three groups of hands \((P = 0.0009)\), \(P < 0.01\) for all three comparisons, as determined using the Newman–Keuls post-test.

The two ipsilateral hand groups did not differ significantly from each other \((P > 0.05, \text{as determined by Newman–Keuls post-test})\), \(k\) for the swollen hand being only 8 % lower than \(k\) for the spared hand from the earlier series [4]. The patients in the present study were of similar age and received similar treatment to those in the earlier study [7], and QL was performed by the same operator using the same \(\gamma\)-camera system. The principal difference between the two groups, apart from hand involvement, was the increased volume of the rest of the arm, namely 27 % \((\text{range}, 4–47\%)\) in the earlier study and 50 % \((\text{range}, 18–167\%)\) in the present study.

It was reported that \(k\) for ipsilateral spared hands \((0.15 \% / \text{min})\) did not differ significantly from \(k\) for contralateral hands \((0.17 \% / \text{min}, n = 11)\) \((k_{\text{contralateral}}\) was derived from combined swollen- and spared-hand groups) [9]. ANOVA was not performed in this series. The BCRL of these subjects was relatively mild: mean forearm swelling was 17 % \((\text{range}, –5 \text{ to } 95\%)\), including four subjects with a smaller ipsilateral arm than a contralateral arm, and only one-third of the group had at least 10 % swelling (the negative ‘swelling’ was presumably due to fibrosis or arose from natural differences in arm size due to hand dominance in subjects with no oedema at the time of study) [9,24]. Hand size was not stated. Collection of blood samples from each arm indicated a lower blood gain rate of the radiotracer injected in the contralateral hand in the swollen-hand group compared with the contralateral blood gain rate in the spared-hand group. The differences between spared- and swollen-hand subgroups led the authors [24] to conclude that differences in lymphatic function were present preoperatively.

Is the contralateral arm normal in BCRL?

The swollen ipsilateral hand had a lower \(k\) value than the contralateral non-swollen hand. This indicates local lymphatic dysfunction in the swollen hand. When we also considered those women with spared hands on the swollen arm, as in Figure 7, the difference between the swollen and spared hands is relatively small; what is much more striking is that the lymph drainage in the contralateral hands of women with swollen hands is unexpectedly high. The reason is unclear, but could indicate a constitutive difference in lymphatic and microvascular function between those who develop severe lymphoedema including the hand (hyperdynamic fluid exchange) and those who develop milder lymphoedema that excludes the hand. There is normally a balance between microvascular filtration and lymph drainage [25], so microvascular filtration may have been raised in the contralateral hands of the women in the present study. The contralateral hands were not oedematous, indicating good contralateral hand lymph drainage. The filtration rate and filtration coefficient are normal in the BCRL forearm, as is control of cutaneous microvascular blood flow.
flow and hence capillary pressure [26,27], but these have not been measured in the hand.

There is also recent structural evidence for a constitutional predisposition to BCRL. The dermal microlymphatic width in the contralateral (non-swollen) forearm of women with BCRL is greater than in the forearms of matched breast cancer patients without BCRL and in the ipsilateral swollen forearm [14]. This raises the question, is the contralateral arm normal in BCRL? Either BCRL exerts a systemic or remote influence on lymphatic vessels or there is a constitutional (genetic) difference in the lymphatics of women prone to lymphoedema. The similar prevalence of BCRL among women treated for bilateral breast cancer as for unilateral breast cancer supports the genetic hypothesis of a predisposition to BCRL [1].

An important group not yet assessed by QL of the hand is a matched group of women treated for breast cancer but without BCRL. This would indicate the presence, if any, of lymphatic dysfunction in the contralateral hand occurring as a result of the cancer treatment and unrelated to BCRL.

Conclusions
It is concluded that, in moderate-to-severe lymphoedema of the hand resulting from breast cancer treatment, local lymph drainage in the subcutis is decreased in comparison with the contralateral hand. Comparison with previous findings from women with spared hands indicates that \( k \) in the contralateral hands of women with swollen hands is apparently increased when compared with contralateral hands of the spared-hand group. On the basis of findings from these relatively small groups of subjects, there appears to be two populations of BCRL patients (irrespective of cancer treatment and age): hand-spared (sustained \( k \)) and hand-swollen (decreased \( k \)). Hand swelling perhaps results from failure of peripheral lymphatics in the forearm or at the wrist, rather than as a result of axillary intervention.

ACKNOWLEDGMENTS
We thank the Wellcome Trust (grant no. 063025) for financial support; Joy Murrell, Lucy Rahman and colleagues (Nuclear Medicine Unit, Hammersmith Hospital) for assistance with lymphoscintigraphies; Dr Salem Sassi, Department of Physics, St George’s Hospital, for assistance with analysis of images; and the patients who participated.

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Received 6 September 2005/12 October 2005; accepted 12 December 2005
Published as Immediate Publication 12 December 2005, doi:10.1042/CS20050277