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Original article

A constitutional predisposition to breast cancer-related lymphoedema and effect of axillary lymph node surgery on forearm muscle lymph flow

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ABSTRACT

Aim: The aims of this prospective study were (a) to examine the relationship between pre-operative muscle lymph flow and the predisposition to BCRL in women treated by axillary nodal surgery for breast cancer; and (b) to test the 'stopcock' hypothesis that axillary lymph node surgery impairs forearm lymph flow in the short term.

Methods: ^{99m}Tc-nanocoll was injected intramuscularly into both forearms of women undergoing surgery for breast cancer. Lymphatic clearance rate constant, *k*, representing lymph flow per unit interstitial fluid volume, was measured as the fractional disappearance rate of radioactivity from the depot site by gamma camera imaging. Axillary lymph node activity was calculated as percentage injected activity. BCRL was assessed by clinical examination and upper limb perometry.

Results: Of 38 pre-operative women, 33 attended at 8 ± 6 weeks post-operatively and 31 at 58 ± 9 weeks post-operatively. Seven patients (18%) developed BCRL. Prior to surgery the BCRL-destined patients had a higher mean *k* (0.0962 ± 0.034%/min) than non-BCRL patients (0.0830 ± 0.019%/min) ($p = 0.10$, unpaired *t* test). Post-operative *k* values were not significantly different from pre-operative, in either the ipsilateral (operated) or contralateral limb. Also, post-operative *k* values did not differ significantly between both upper limbs. Furthermore, there was no significant difference between pre- and post-operative axillary activity.

Conclusion: Patients who develop BCRL have high lymph flow pre-surgery, which may predispose them to lymphatic overload and failure. Axillary lymph node surgery has no early, measurable effect on forearm muscle lymph flow despite surgical disruption of routes of lymph drainage.

Introduction

Breast cancer is the most common cancer in the UK, with approximately 50,000 new cases diagnosed each year (www.cancerresearchuk.org [1]). Breast cancer-related lymphoedema (BCRL) develops after axillary lymph node surgery or radiotherapy, and commonly presents months to years after intervention [2,3]. The estimated risk of BCRL is 8–28% in patients undergoing axillary node clearance (ANC) but as low as 4–6% in patients undergoing sentinel lymph node biopsy (SLNB) [4–9]. Despite a trend towards more conservative breast cancer surgical treatment, BCRL remains a common problem with associated significant physical, functional, psychological and social morbidity [10,11].

The traditional view of the pathophysiology of BCRL is that removal of the axillary nodes obstructs lymph drainage from the upper limb, resulting in the accumulation of a protein-rich fluid in the interstitium (the 'stopcock' hypothesis) [12]. This theory,

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however, does not account for several factors. Firstly, some patients do not develop BCRL despite undergoing ANC, whereas others develop BCRL following the removal of a few nodes. Secondly, the latency period is variable. Thirdly, the swelling is often non-uniform. Finally, the interstitial fluid protein concentration is lower in the ipsilateral BCRL upper limb than in the contralateral upper limb, and is inversely proportional to the degree of swelling [13]. These observations indicate that the pathophysiology of BCRL is more complex than a simple 'stopcock' mechanism.

Local lymph flow can be assessed indirectly by the well-established method of quantitative lymphoscintigraphy (QL) [14]. A radiolabelled macromolecule is injected interstitially and its rate of removal, assumed to be predominantly via lymphatics, is monitored to determine the local removal rate constant (k). In breast cancer patients, with and without BCRL, k has been measured in the forearm epifascial compartment (subcutis or skin), forearm subfascial compartment (skeletal muscle) and hand (subcutis) [15–18].

Previous work by our group has led to the 'high filterers' hypothesis, namely that some women have a constitutively high rate of capillary fluid filtration and hence high fluid loading of the lymphatic system, which predisposes them to secondary lymphoedema, independent of the number of axillary nodes removed [18]. These studies however, did not address the question of whether the high fluid load was constitutive, i.e. existed prior to surgery, or was the response of a subset of patients (those who later developed BCRL) to axillary lymph node surgery.

The aims of this prospective study were therefore (a) to examine the relationship between pre-operative muscle lymph flow and the predisposition to BCRL in women treated by axillary nodal surgery for breast cancer; and (b) to test the 'stopcock' hypothesis that axillary lymph node surgery impairs forearm lymph flow in the short term.

Patients and methods

Thirty-eight patients diagnosed with invasive breast cancer and due to undergo axillary lymph node surgery were recruited from Guy's Hospital, London and the Royal Sussex County Hospital, Brighton. The following assessments were performed before and 8 weeks (mean) after axillary lymph node surgery [1]: clinical assessment for BCRL [2]; upper limb volume measurement using a Perometer [3]; measurement of forearm muscle lymph drainage ('k') by QL; and [4] axillary lymph node gamma camera imaging. Patients underwent mastectomy (Mx) or wide local excision (WLE), and axillary lymph node clearance surgery (ANC) or axillary node sampling (ANS) as recommended by the multidisciplinary team (Table 1). Patients were followed up for three years or until BCRL developed. On follow-up visits the upper limbs were assessed for BCRL and limb volume measurement was performed. Follow-up

Table 1
Clinical, surgical and pathology details of patients.

Patient ID	Age (yrs)	Breast surgery	Axillary surgery	Number of lymph nodes removed (+)		Histology			
						Grade	Type	Size (mm)	ER status
001B	56	WLE	ANS	4	(0)	3	IDC	40	+
002B	67	WLE	ANC	17	(13)	2	IDC	18	+
003B[a]	75	WLE	ANS	8	(0)	2	IDC	18	+
004B	66	WLE	ANC	11	(3)	2	IDC	54	+
005B	61	WLE	ANS	7	(0)	2	IDC	21	+
006B	59	WLE	ANS	5	(0)	2	IDC	12	+
007B	76	WLE	ANS	4	(0)	1	IDC	8	+
008B	55	Mx	ANS	5	(2)	2	IDC	15,18	+
009B	51	WLE	ANS	7	(0)	1	IDC	15	+
010B	47	Mx	ANC	9	(9)	2	ILC	50	+
011B	51	WLE	ANS	9	(2)	2	IDC	6	+
012B	52	WLE	ANS	7	(0)	2	ILC	95	+
013B	69	WLE	ANS	6	(0)	2	IDC	29	+
014B	51	WLE	ANS	6	(0)	2	IDC& ILC	20,6	+
015B	49	WLE	ANS	2	(0)	3	IDC	11	+
016B	65	WLE	ANS	5	(0)	2	IDC	22	+
017B	66	WLE	ANS	4	(0)	2	IDC	20	+
018B	50	WLE	ANS	10	(0)	1	IDC	12,6,2	+
019B	60	WLE	ANS	8	(0)	2	ILC	20	+
020B	56	WLE	ANS	5	(0)	2	IDC	11	+
021B	45	WLE	ANS	4	(0)	1	IDC	15	+
022B	57	WLE	ANS	6	(0)	2	IDC	15	+
023B	64	WLE	ANS	4	(0)	3	IDC	16	–
007G	46	Mx	ANC	13	(1)	3	IDC	30	+
008G[a]	56	Mx	ANC	5	(0)	2	ILC	17,11	+
009G	51	Mx	ANC	8	(1)	2	IDC	28	+
010G	71	Mx	ANC	13	(2)	2	IDC	44	–
011G	66	Mx	ANC	20	(11)	3	IDC	30	–
012G[a]	49	WLE	ANC	9	(1)	3	IDC	10	+
013G[a]	67	WLE	ANC	5	(0)	3	IDC	0	–
014G	52	WLE	ANC	7	(1)	2	IDC	12	+
015G[a]	62	WLE	ANC	8	(3)	2	ILC	31	+
016G	44	Mx	ANC	29	(28)	2	ILC	28	+
017G[a]	52	Mx	ANC	4	(3)	2	IDC	120	+
018G[a]	53	WLE	ANC	15	(2)	2	IDC	29	+
019G	57	WLE	ANC	14	(1)	2	IDC & ILC	17	+
020G	33	WLE	ANC	19	(1)	2	IDC	14	+
024G	49	Mx	ANC	15	(7)	3	IDC	17	–

[a] Patients who developed BCRL; ANS, axillary node sampling; ANC, axillary clearance surgery; ER, oestrogen receptor; WLE, wide local excision; Mx, mastectomy; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.