Sports Med 2005; 35 (6): 461-471
0112-1642/05/0006-0461/$34.95/0

Exercise and the Lymphatic System
Implications for Breast-Cancer Survivors

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Abstract

This article summarises the current research on the lymphatic system related to exercise and critically evaluates the implications for exercise performance by breast-cancer survivors. The primary role of the lymphatic system during exercise is to assist in the regulation of tissue volume and pressure by carrying fluid and plasma proteins that have leaked into the interstitial space from tissues back to the cardiovascular system. During steady-state exercise in humans, lymph flow has been shown to increase to levels approximately 2- to 3-fold higher than at rest. Although the lymphatic system does not typically limit exercise performance in the normal population, the function of this system can be impaired in 27–49% of women who have survived breast cancer.

Breast cancer-related lymphoedema (BCRL) is a chronic swelling that can occur in the ipsilateral hand or arm of women treated for breast cancer and results in a number of physical and psychological sequelae. Exercise was once believed to be a factor in the development of BCRL as it was thought that the damage to the axillary lymphatics from breast-cancer treatment resulted in a primary obstruction to lymph flow. However, the exact aetiology and pathophysiology of BCRL appears to be multi-factorial and not as simple as a 'stop-cock' effect. Furthermore, recent studies have shown that participating in vigorous, upper-body exercise is not related to an increase in arm volume, which would indicate the development of BCRL. It is still not known, though, how long-term exercise affects lymphatic system function in breast-cancer survivors with and without BCRL.

The lymphatic system as it relates to exercise is not a physiological system that receives a great deal of attention in the sports medicine literature. It is not often heard that patients are limited by their lymphatic system when performing a job task, recreational activity or sport. However, breast-cancer survivors were once cautioned by healthcare professionals to avoid participating in vigorous, upper-body exercise for fear of causing lymphoedema.[1] Breast cancer-related lymphoedema (BCRL) is a chronic swelling that can occur in the ipsilateral hand or arm of breast-cancer survivors as a result of dissection of the axillary lymph nodes and irradiation.[2] It is essentially an incurable condition, al-

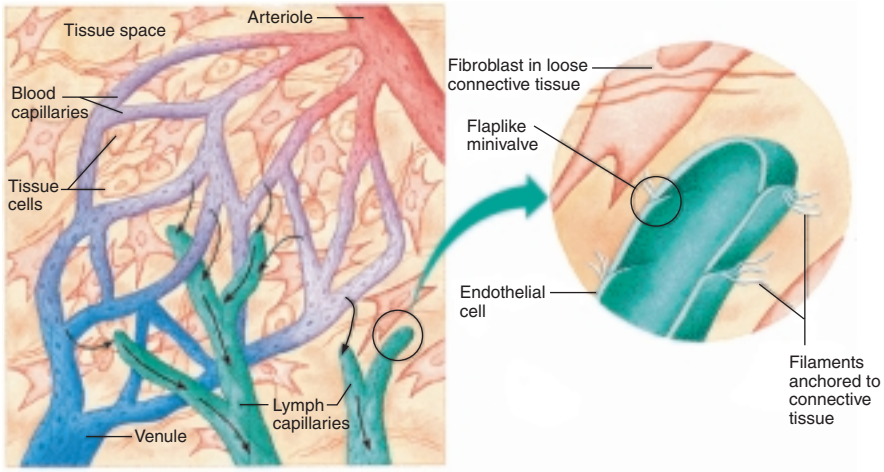

Fig. 1. The distribution and special structural features of lymphatic capillaries (reproduced from Marieb,[10] with permission from Pearson Education Inc.).

though treatments exist to contain swelling. Current research has not supported the notion that there is a relationship between vigorous, upper-body exercise and the occurrence of BCRL.[3,4] In fact, there is the possibility that exercise may be useful in the prevention and treatment of BCRL, but further investigation is required to see what physiological changes may be taking place at the tissue level in the affected arm in response to short- and long-term exercise.

This article summarises the current research on the lymphatic system related to exercise and critically evaluates the implications for exercise performance by survivors of breast cancer. A brief synopsis of the relevant anatomy and physiology of the lymphatic system applicable to the topic of exercise and breast cancer is also included. Aukland and Reed[5] and Schmid-Shönbein[6] provide thorough reviews of the anatomy and physiology of the lymphatic system.

1. Anatomy and Physiology of the Lymphatic System

The lymphatic system is a one-way transport system composed of lymphatic vessels and lymphoid organs. The lymphatic vessels carry fluid and plasma proteins that have leaked into the interstitial space from tissues back to the cardiovascular system, while the lymphoid organs including the bone marrow, thymus, lymph nodes, spleen and tonsils each function to produce, maintain and distribute lymphocytes. Thus, essential functions of the lymphatic system include assisting in the regulation of tissue volume and pressure, and aiding immune system function.[7] For the purposes of this article, only the structures involved in lymph transport and mechanisms involved in lymph return will be discussed.

Two continuous segments of vessels make up the lymphatic system: (i) the initial lymphatics, also known as lymphatic capillaries; and (ii) the contractile lymphatics. Figure 1 illustrates the initial lymphatics, which are blind-ending vessels that originate in tissue parenchyma and found in close proximity to vascular arterioles.[8] They have a single layer of endothelial cells with overlapping regions that form one-way valves.[5] These one-way endothelial valves, also referred to as primary valves,[8] allow interstitial fluid to enter into lymphatic capillaries but prevent lymph from escaping. Evidence for the endothelial valves was provided by Trzewik et al.[9] who injected fluorescent microspheres into the cremaster muscle interstitium of rats. Through a variety of experiments, the researchers demonstrated that the microspheres could pass into the lymphatic lumen but could not be forced out. Other anatomical features of the initial lymphat-

ics include anchoring filaments that attach the vessels to collagen fibres in the extracellular matrix (ECM), an absence of smooth muscle cells, and intralymphatic (or secondary) valves that may or may not be present.[6]

Lymph formation occurs when interstitial substances (i.e. fluid, proteins and colloids) enter lymphatic capillaries through the primary valves. Once lymph enters the initial lymphatics it then travels to the larger, contractile lymphatics which, unlike the lymphatic capillaries, are usually present outside of organ parenchyma and have smooth muscle that undergoes spontaneous, peristaltic contractions. Contractile lymphatics also have intra-lymphatic valves that prevent the backflow of lymph.[8] Contraction of the smooth muscle lining lymphatic vessels is initiated by pacemaker cells[11] but can also respond to sympathetic activation.[5] For example, epinephrine (adrenaline) and norepinephrine (noradrenaline) infusion has been shown to increase the frequency and force of lymphatic pumping in sheep.[12,13] Epinephrine may cause an increase in lymph flow by either acting directly on the lymphatic vessels, reflexively triggering the autonomic nervous system, or increasing blood flow to the region drained by the lymphatic vessels.[12] However, not all vascular beds undergo vasodilation in response to sympathetic activation. While capillary filtration can be reduced in some areas such as the gastrointestinal tract as a result of sympathetic activation, it can be concomitantly increased in other areas such as active skeletal muscle.

Lymph travelling through contractile lymphatic is filtered by clusters of lymph nodes found throughout the body. Lymph nodes relevant to BCRL are found in the axilla and have been classified as levels I–III.[14] If any of the lymph nodes throughout the body detect a foreign substance, then specialised lymphoid cells (T-lymphocytes, B-lymphocytes and macrophages) function to destroy the foreign cells, and if necessary, activate an immune response.[15] Damage to lymph nodes, which can occur as part of breast-cancer treatment (i.e. lymph node excision and/or irradiation), contributes to the development of BCRL.

Lymph re-enters the cardiovascular system by way of the central thoracic ducts that drain into the subclavian veins. There is also the possibility that lymph can enter the venous system by way of lymphaticovenous communications.[14] These communications are thought to exist in normal, healthy individuals but may not be functional unless there is chronic obstruction of lymphatic vessels or nodes.[16] If the lymphatic system is under chronic stress due to obstruction, then the opening of lymphaticovenous communications would allow lymph to bypass the obstructed area. This was demonstrated in early research by Threefoot et al.[17] who used a dog model with the major lymphatic channels obstructed for >5 days to demonstrate the presence of lymphaticovenous communications.

1.1 Mechanisms of Lymph Formation and Transport

Much of what is known about the mechanisms of lymph transport in humans has been derived from animal research. However, caution should be taken when interpreting animal research since there are variations in the length of lymphatic vessels, tissue volumes, gravitational forces and hydrostatic pressures between animals and humans that would affect lymph contractility and flow.

Unlike the cardiovascular system, the lymphatic system lacks an organ to act as a pump and move lymph against gravity from the initial lymphatics to the contractile lymphatics and finally to the cardiovascular system. Consequently, the lymphatic system must rely on both intrinsic and extrinsic forces to drive lymph formation and lymph transport. Extrinsic mechanisms include active and passive limb movements, pressure changes associated with respiration, and the pulse of nearby arteries, while intrinsic mechanisms involve spontaneous, intermittent contraction of the smooth muscle that lines the contractile lymphatic vessels,[5,6] which has been documented in both humans[18] and animals.[19]

Lymph formation and lymph propulsion through the initial lymphatics are both dependent on extrinsic driving forces since the initial lymphatic vessels do not have smooth muscle media. For instance,

skeletal muscle contractions, massage, arterial pressure pulsations and vasomotion of nearby arterioles influence interstitial fluid pressure and strain of the ECM, which in turn affects the rate of lymph formation.[20] As pressure and/or strain of the ECM rises, the anchoring filaments exert radial tension on the lymphatic capillary, thereby increasing the volume of the lumen and pulling open the endothelial microvalves allowing interstitial molecules to enter.[21] This was shown by Mazzoni et al.[22] who investigated lymph formation in the spinotrapezius muscle of rats fixed *in situ* in the stretched and contracted states. Stretched skeletal muscle pulled on connective tissue joined to lymphatic vessels and opened the initial lymphatics permitting interstitial fluid to enter. Contracted skeletal muscle, on the other hand, increased muscle fibre cross-sectional area, which compressed both adjoining connective tissue and the lymphatics resulting in lymph being driven in the proximal direction to collecting vessels.

Lymph propulsion from the initial lymphatics to contractile lymphatics relies on extrinsic mechanisms to expand and compress the initial lymphatics as described in the paragraph above. Also, the presence of both endothelial microvalves and intralymphatic valves ensures that lymph moves proximally to the larger contractile vessels and does not leak out of the initial lymphatic vessel.[8] The compression of an initial lymphatic vessel due to a skeletal muscle contraction, for example, forces open the intralymphatic valve and closes the endothelial microvalves resulting in lymph movement in the proximal direction towards the contractile lymphatics.

Once lymph reaches the contractile lymphatics, then intrinsic forces are believed to be the main factor responsible for lymph flow at rest in humans. Olszewski and Engeset[18] measured lymph pressure, pulse frequency and lymph flow in the legs of healthy males. Pulse frequency increased during free lymph flow conditions when subjects changed from the recumbent to upright position. This increase was thought to be a result of an increase in pressure exerted on the foot tissues, which would compress the initial lymphatics and force lymph to the larger contractile vessels. The increase in pulse frequency occurs because the accumulation of lymph in the contractile lymphatics would stretch the wall of the vessel triggering a reflexive contraction of the smooth muscle endothelium.

Subjects in this study[18] also contracted the foot while in both the recumbent and upright positions. There was no measurable change in flow between pulse waves during foot movement indicating that intrinsic mechanisms were the main factor responsible for propelling lymph through the lymphatic system. Also, neither a significant change in intralymphatic pressures during obstructed flow and free-flow conditions nor a change in pulse amplitude was recorded. Pulse frequency and mean lymph flow, on the other hand, were observed to significantly rise. The increase in mean lymph flow during foot contractions in both the recumbent and upright positions suggests that the increase in lymph formation occurred due to an increase in capillary filtration and/or a rise in total tissue pressure. The increase in lymph formation coupled with repeated foot contractions would also contribute to the higher pulse frequency as described earlier in this section.

2. Measurement of Lymphatic Function

The most direct method of measuring lymph flow is by cannulation of a lymphatic duct and this method has been used in horses, sheep and dogs to investigate the effects of exercise on lymph flow. However, this procedure in humans is less practical as it is invasive; rather, lymph flow is more often measured by lymphoscintigraphy. Lymphoscintigraphy involves injecting a radiopharmaceutical into a subcutaneous depot and imaging the limb using a gamma (γ) camera at various time points from 0 minutes to 6 hours post-injection. The radiopharmaceutical is generally a technetium labelled macromolecule that is of sufficient size (i.e. between 4 and 100nm) to enter the lymphatic capillaries and not blood capillaries.[23,24]

Although lymphoscintigraphy cannot measure true lymph flow because the volume of fluid in the local tissue is not known, it can be used to measure

how well the lymphatics drain a unit volume of tissue.[25] Lymph drainage may be quantified by a number of approaches: measuring the clearance of radiopharmaceutical from the site of injection, determining the time it takes for the tracer to reach the axillary lymph nodes, and/or by calculating the percentage of tracer in the axillary lymph nodes at a fixed timepoint post-injection.[26,27]

Currently, a standardised protocol does not exist for evaluation of lymphatic function in women with BCRL. Most commonly, lymphoscintigraphy is used to investigate the pathophysiology of BCRL, and so, 1-minute acquisitions are taken every 30–60 minutes over a total period of 3–6 hours and either massage at the injection site or light exercise such as fist clenches or squeezing a rubber ball is performed to enhance radioisotope clearance.[24,26,28-33] Despite a standardised protocol, lymphoscintigraphy is being used to evaluate the function of the lymphatic system in response to treatment methods currently prescribed for BCRL.[34,35]

3. Role of the Lymphatic System During Exercise

The general role of the lymphatic system during exercise is to return leaked fluid and plasma proteins to the cardiovascular system. Approximately 2–3L of fluid is returned to the blood in a 24-hour period by the lymphatics.[23] The cardiovascular system could not operate without the lymphatic system since the only means of returning fluids and plasma proteins back to the blood is via the lymphatic vessels.

The effect of exercise on lymph formation and transport has been measured directly in animals using cannulation of a lymphatic duct.[36,37] In response to exercise of short duration (walking eight steps) in an intact lymphatic preparation in sheep, the frequency of lymphatic contractions increased and lymph flow doubled relative to baseline values in the 1–5 minutes after the beginning of movement.[36] Movement was believed to increase lymph formation but not directly affect lymph propulsion since no correlation was found between fluid propulsion and normal walking movements in an isolated preparation.

Exercise of longer duration (2 hours) was measured in the hind limbs of sheep by Coates et al.[37] During the first 15 minutes of steady-state exercise, lymph flow in the hind-limb increased 5-fold from resting values and then gradually decreased to a constant 130% above baseline for the remaining 30 minutes of exercise. The large initial increase in hind-limb lymph flow was thought to be a result of increased pressure in the working muscles and increased sympathetic activation causing increased lymphatic motility. A combination of a greater vascular surface area and a higher hydrostatic pressure likely contributed to the steady-state lymph flow values observed from 90 to 120 minutes of exercise.

Few studies have investigated the role of the lymphatic system during exercise in humans. Havas et al.[38] investigated the effects of dynamic and isometric muscle contractions on lymph clearance using lymphoscintigraphy. Lymph clearance was measured in the legs of four sedentary males and four endurance-trained males (each leg counted as an independent observation; thus, n = 8 per group). The authors did not explain what constituted being endurance trained. The exercises included dynamic knee extensions and two types of isometric contractions (leg flexed at 90° and leg fully extended). In total, 100 submaximal contractions were performed in 10 minutes for each condition and all conditions were performed on the same day with 65 minutes rest between each. The results showed that lymphatic clearance rates were highest in both the dynamic and isometric leg-extended conditions compared with the isometric leg-flexed condition. Moreover, the lymphatic clearance rate during the 65 minutes of rest between exercise conditions was nearly 2-fold higher in the endurance-trained versus sedentary subjects. The higher clearance rates seen in the endurance-trained group was thought to be a result of an increase in capillary density, which is a known adaptation to long-term endurance exercise.[39] A higher capillary density would provide a greater surface area for capillary filtration and endothelial conductance. If the higher capillary density accounts

for the difference in lymphatic clearance rates between subject groups during rest, then it might also be expected that clearance rates should be faster in the endurance-trained subjects during exercise. However, the 10-minute exercise bouts used by Havas et al.[38] may not have been of sufficient duration and/or intensity to sufficiently tax the lymphatic system and cause clearance rates to differ between subject groups during exercise. Furthermore, the first 10–15 minutes of exercise has been shown[37,40] to result in an initial overshoot of lymphatic clearance rates that is approximately 5-fold higher than rest and then declines to a steady-state value for the remainder of the exercise period that is still 2- to 3-fold higher than rest. It is possible that this initial overshoot response to exercise is similar for all healthy subjects and does not depend on training status. If this is the case, then the 10-minute exercise bouts as used by Havas et al.[38] could reflect the initial overshoot of lymphatic clearance rates and any differences between endurance-trained and sedentary subjects would be masked during this time. A longer exercise bout allowing steady-state conditions to be achieved may have shown differences between endurance-trained and sedentary subjects. More research is needed to clarify the effect of endurance training on lymphatic function during rest, exercise and recovery from exercise.

Havas et al.[40] again used lymphoscintigraphy to investigate lymph flow dynamics in the lower limbs of eight males during 2 hours of steady-state exercise at 70% maximum heart rate. Similar to the results found by Coates et al.,[37] the first 15 minutes of exercise showed a clearance rate that was 5-fold higher than at rest and remained ~2- to 3-fold higher for the remainder of the 2-hour exercise bout. A faster lymphatic clearance rate during exercise is expected. Exercise causes an increase in arterial blood pressure and cardiac output resulting in greater capillary filtration. Greater capillary filtration leads to a rise in interstitial pressure, which facilitates the entry of fluid and proteins into lymphatic capillaries.[5] Furthermore, during exercise, both extrinsic and intrinsic mechanisms are enhanced, thereby increasing lymph propulsion through lymphatic vessels.

In summary, lymphatic clearance rates during exercise are elevated compared with resting levels. Both studies conducted by Havas et al.[38,40] used subjects who were college-aged males and the effects of short-term exercise on lymphatic clearance in the lower limbs was investigated. It has not been determined if age or sex alters lymphatic clearance rates during exercise. Also, it is not known if the lymphatic vessels in the upper extremity respond in a similar manner to a given exercise bout as do the lymphatic vessels in the lower extremity. Nor is it known how the intensity or duration of the exercise affects lymphatic function. Although Havas et al.[38] demonstrated faster lymph clearance rates in endurance-trained males between exercise conditions, more research is needed to elucidate the effects of training status on lymphatic function during short- and long-term exercise.

4. Breast Cancer-Related Lymphoedema (BCRL)

BCRL is a chronic swelling that can occur in the ipsilateral hand or arm of women treated for breast cancer.[2] Current data suggest that there is a 27%[41,42] to 49%[43] probability of women developing BCRL over a 20-year period following treatment. BCRL may present months or years after initial treatment and the actual onset may be gradual or rapid.[14] Women with BCRL have restricted range of motion in the affected arm, increased risk of infection and impaired limb function. Furthermore, these women report increased anxiety and depression and reduced quality of life.[44] BCRL is essentially an incurable condition, although treatments such as skin care, manual lymphatic drainage, pneumatic pumping and compression sleeves exist to contain swelling.[14,44]

Factors that are known to increase the risk of developing BCRL include dissection of the axillary lymph nodes, radiotherapy to the breast and axilla, pathological nodal status, obesity and tumour stage.[14] There is a greater incidence and severity of subsequent lymphoedema when more axillary

lymph nodes are excised and/or a larger irradiation field and dose is directed at the axilla.[33] A larger radiation dose or field applied to the axillary region may result in damage to lymph nodes, since radiation essentially leaves scar tissue in the area. Older surgical techniques involved radical mastectomy whereby all axillary lymph nodes were removed. Due to advances in technology, specifically the sentinel node biopsy, only potentially cancerous lymph nodes are now excised. Thus, as more surgeons/oncologists use sentinel node biopsy, there could possibly be a lower incidence of BCRL. In fact, Sener et al.[45] have shown that only 3.0% of subjects who underwent sentinel lymphadenectomy alone were determined to have lymphoedema compared with 17.1% who underwent sentinel lymphadenectomy combined with axillary dissection.

4.1 Diagnosis

The diagnosis of BCRL usually involves volumetric or circumference measurements as well as symptoms of heaviness and tightness in the affected arm; however, there is no consistent operational definition in the literature of what describes clinically significant BCRL. Research varies in the method used (arm volume determined by water displacement, arm volume calculated by circumference measures, circumference measurements and patient symptoms) and the reference point on the upper extremity where the measurements are taken. Although the gold standard for limb volume determination is water displacement volumetry, it is neither a portable nor a simple method to perform. Megens et al.[46] examined whether two methods of calculating arm volume using circumference measurements could substitute for water displacement in determining arm volume. Direct and calculated measurements of arm volume were both found to be related and reliable; however, they were not determined to be interchangeable since truncated cone calculations of arm volumes exaggerated actual arm volume. The Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer in Canada[47] reviewed the relevant literature and recommended four points for measuring arm circumference: (i) the metacarpal-phalangeal joints; (ii) the wrists; (iii) 10cm distal to the lateral epicondyles; and (iii) 15cm proximal to the lateral epicondyles. If a difference of >2.0cm between arms at any of the measurement points is found, treatment for lymphoedema may be warranted.

Although arm circumference and volume measurements are non-invasive and simple to perform, they no not indicate changes in lymphatic function. Lymphoscintigraphy was developed to assess lymphatic status in patients with a variety of conditions that cause lymphatic obstruction.[23,48] Now this technique is being used to assess lymph function in women with BCRL. Lymphoscintigraphy has been used in the investigation of the pathology of BCRL as it gives a measure of lymphatic function; however, all published reports[28-33] except one[31] contain data obtained at rest.

4.2 Pathophysiology of BCRL

Originally, it was thought that the primary insult to the axillary lymphatic system due to axillary dissection and/or irradiation caused global impairment of lymph drainage.[14] This traditional view of the pathogenesis of BCRL is analogous to a 'stopcock' effect. The damage to the axillary lymphatics, primarily lymph nodes and vessels, was thought to interrupt lymph flow and thus cause fluid and plasma proteins to accumulate in the affected arm. For this theory to be true then the following findings should be evident in the literature related to BCRL: (i) all breast-cancer survivors who receive identical treatment should develop BCRL; (ii) there should be a similar onset period; (iii) all sections of the arm should be swollen uniformly and lymph flow rates should be similar throughout the affected arm; and (iv) lymph flow should be slower and protein concentration should be higher in the affected arm compared with the non-affected arm.

As reported previously, the incidence of BCRL is ~50% and the onset period may vary considerably. This suggests that other physiological factors in the affected arm are also contributing to the development of BCRL. In addition, recent studies by Bates et al.[49] and Stanton et al.[31] have challenged the

view that BCRL is a result of global impairment of lymph drainage. Specifically, Bates et al.[49] found that protein concentration was lower in the lymphoedemous arm compared with the normal arm, while Stanton et al.[31] discovered that lymph clearance was higher in the non-swollen hand of the affected arm compared with the normal hand.

The finding of a lower, rather than higher protein concentration in the affected arm, suggests haemodynamic abnormalities may also contribute to BCRL development.[49] Lymphoedema in any tissue develops when there is an imbalance between capillary filtration and lymphatic drainage rates.[2,50] A lower than expected interstitial protein concentration could result from increased capillary filtration rates caused by either hyperaemia in the affected arm or a rise in capillary pressure.[49] In fact, Svensson et al.[51] found evidence of increased blood flow in the affected arm, although there are some methodological concerns with the study. Other factors that could explain the decreased interstitial protein concentration are reduced permeability of the capillary wall to plasma proteins and proteolysis within the interstitial compartment.[52]

The discovery by Stanton et al.[31] that lymph clearance is faster in the non-swollen hand of the affected arm compared with the swollen region suggests that regional lymph drainage failure may be occurring. If there is regional lymph drainage failure, then there may be re-routing of lymphatic drainage within the lymphoedemous arm, which could account for the higher clearance rates seen in the non-swollen hand. Re-routing of lymphatic drainage is also supported by the appearance of 'dermal backflow' and the finding of a higher density of lymphatic vessels in the dermis of the lymphoedemous arm of women with BCRL.[53] A higher lymphatic density may indicate that lymphangiogenesis or recruitment of dormant lymphatic vessels is occurring, which could facilitate lymph drainage around regions where lymphatic vessels are failing. Mellor et al.[53] also discovered that breast-cancer survivors who did not present with lymphoedema showed none of the changes in lymphatic density seen in women with BCRL. Thus, the increased lymphatic network appeared to be a result of the oedema and not a result of breast-cancer treatment.

Another finding by Stanton et al.[31] was that lymph flow per unit volume of tracer distribution was slower in the swollen arm compared with the control arm. Although this result lends support to the theory that simple axillary obstruction may be contributing to the development of BCRL, Bates[25] offers another interpretation. He suggests that if the tissues in the affected and non-affected arms respond similarly to injection of the radioisotope protein, then 'tracer fluxes' between arms should be proportional to the relative distribution volumes. Thus, the clearance rates, which are also known, can be used to estimate lymph flow. Based on these assumptions, Bates[25] indicated that lymph flow might be higher in swollen tissue of the affected arm compared with the non-affected arm. More research is needed to verify the theory offered by Bates.

Another factor that may contribute to the development of BCRL is the presence of functioning lymphaticovenous communications.[14] Aboul-Enein et al.[54] evaluated women treated for breast cancer with and without BCRL as well as healthy subjects for the presence of lymphaticovenous communications in the upper extremity. Healthy subjects and breast-cancer patients with lymphoedema showed little lymphaticovenous transfer of the iodinated human serum albumin, while breast-cancer patients who did not present with lymphoedema demonstrated greater radioisotope activity in the venous blood within an hour of injection. Furthermore, radiological detection of lymphaticovenous shunts were assessed in two subjects without BCRL. This study indicates that functioning lymphaticovenous communications in women treated for breast cancer may help prevent the occurrence of BCRL.

In summary, the exact aetiology and pathophysiology of BCRL appears to be multi-factorial and not fully understood. Recent investigations question the view that simple axillary obstruction is the primary determinant of BCRL and instead suggest that regional lymph drainage failure may only be occurring at sites of swelling. If only some lymph vessels of the arm are weakening, then a higher interstitial

pressure would help facilitate lymph flow through these failing vessels. Oedema could provide this driving interstitial pressure. There is also evidence that haemodynamic factors, such as increased capillary filtration, may also be contributing to the development of BCRL. Further research is needed to determine the pathophysiological mechanisms that underlie BCRL so that appropriate treatments can be developed.

5. Effects of Exercise on BCRL

Until recently, physicians, physiotherapists or health professionals erred on the side of caution and recommended survivors of breast cancer to avoid vigorous upper-body exercise for fear of promoting or worsening BCRL.[1] This view stemmed from the belief that simple axillary obstruction of lymph flow was the sole cause of BCRL. Thus, if a woman who survived breast cancer engaged in vigorous exercise on a regular basis, then lymph production would increase, corresponding to an eventual increase in arm volume. Current research,[3,4] however, has not found changes in arm volume and/or circumference in breast-cancer survivors with and without lymphoedema because of participation in an exercise programme.

McKenzie and Kalda[3] found no changes in arm volume in women with BCRL compared with a control group as a result of participation in an 8-week, upper-body exercise programme including both resistance training and upper-body aerobic exercise. Three quality-of-life domains (physical functioning, general health and vitality) showed trends towards increases in the exercise group. Another study[4] measured changes in arm circumference in women with and without BCRL who were competing in dragon-boat racing as well as performing an aerobic and resistance training programme. Over three timepoints separated by 9 months, none of the subjects showed an increase in arm circumference. However, a control group was not included in the study by Harris and Niesen-Vertommen[4] that could be used for comparison purposes.

The fact that exercise was not shown to increase arm volume is promising but not conclusive. A limitation of both studies described above[3,4] is that the measurement techniques used can only provide information on changes in arm volume and circumference and not changes in lymphatic function. So even though it was found that exercise did not lead to the development of lymphoedema or to the worsening of pre-existing lymphoedema, no conclusions can be made about the effects of exercise on lymph function. Measuring anthropometric variables does not give an indication of the physiological changes taking place within the arm. For example, an increase in arm volume in breast-cancer survivors may indicate muscle hypertrophy or an increase in subcutaneous fat or development of BCRL or a combination of factors. Using magnetic resonance imaging could help to elucidate some of the soft tissue changes that may be taking place as a result of exercise training.

As part of the study conducted by Stanton et al.,[31] lymphoscintigraphy was used to investigate the effects of exercise on BCRL. Five subjects who were not wearing compression sleeves performed a total of 5 minutes of intermittent exercise (squeezing a ball in both hands simultaneously at 20 contractions per minute) and lymph clearance was measured for 5–6 hours post-exercise. Exercise was not found to have a significant effect on lymph clearance. However, 5 minutes of exercise may not be of sufficient duration to result in a noticeable change in lymph function over the course of a 5-hour measurement period. It is not known if the subjects wore compression sleeves if different results in response to exercise would have been achieved as it may be necessary for women with BCRL to wear compression sleeves in order for the exercise to be effective.

There is the potential that long-term exercise performed by survivors of breast cancer could lead to improved lymph flow. For example, several physiological changes associated with long-term exercise including increased sympathetic outflow, increased muscular contractions and increased ventilation could facilitate lymph return.[55] Exercise may also result in positive lymphatic changes in the affected arm such as lymphangiogenesis and recruitment of dormant lymphatic vessels. Perhaps, breast-

cancer survivors who were cautioned against performing vigorous, upper-body exercise with the affected arm were fearful of doing even low- to moderate-intensity upper-body exercise. If light to moderate activity is not performed regularly, then the lymphatic vessels of the affected arm may weaken or become dormant as a result of the lack of stress put on mechanisms to assist in lymph return. Studies[41-45] investigating the incidence of BCRL have not differentiated between those survivors who regularly engaged in moderate, upper-body physical activity and those who have abstained from upper-body exercise altogether.

Although exercise has not been shown to cause or exacerbate BCRL,[3,4] caution should still be taken by breast-cancer survivors with and without BCRL when performing vigorous, upper-body exercise until research can conclusively determine that exercising at high intensities will not lead to the development or worsening of BCRL. Wearing a compression sleeve, lifting the arm above the head after exercise and performing a light, active recovery are thought to facilitate lymph return after exercise.[55]

6. Conclusions and Future Directions for Research

The lymphatic system is a one-way transport system that functions to produce, maintain and distribute lymphocytes as well as to assist in the regulation of tissue volume and pressure. Lymphatic vessels have similar structural features to the venous system and rely primarily on extrinsic mechanisms such as the skeletal muscle pump, the respiratory pump and the pulse of nearby blood vessels to facilitate lymph return. Women with BCRL were originally cautioned against performing vigorous, upper-body exercise for fear of promoting lymphoedema. It was originally thought that the primary insult to the axillary lymphatic system (i.e. dissection and/or radiation) caused global impairment of lymph drainage similar to a 'stop-cock' effect. Current research suggests that haemodynamic factors may also contribute to the chronic swelling and lymph vessel failure may only be regional. Thus, the exact aetiology and pathophysiology of BCRL appears to be multi-factorial and not fully understood. Both resistance and upper-body exercise have not been shown to lead to significant changes in arm volume; however, further research is needed using lymphoscintigraphy to better understand the effects of short- and long-term exercise on lymphatic function.

Acknowledgements

K. Lane was supported by the Michael Smith Foundation for Health Research (MSFHR) and the Canadian Institutes of Health Research. The authors have no conflicts of interest that are directly relevant to the content of this review.

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