LYMPHATIC RESEARCH AND BIOLOGY
Volume 00, Number 00, 2025
© Mary Ann Liebert, Inc.
DOI: 10.1089/lrb.2024.0061

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The Intermittent Pneumatic Compression Influences Edema Fluid Movement and Promotes the Compensatory Drainage Pathways in Patients with Breast Cancer Related Lymphedema

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Abstract

Introduction: Upper limb lymphedema is the most common complication after breast cancer therapy. Suddenly disturbed lymphatic transport in the affected arm causes tissue fluid accumulation in tissue spaces, limb enlargement, and secondary changes in tissue. Early compression therapy is necessary. We aim to evaluate the effectiveness of intermittent pneumatic compression (IPC) in fluid movement along the limb and the possibility of creating compensatory drainage pathways.

Methods and Results: We investigated 25 patients with Breast Cancer Related Lymphedema (BCRL) stages II and III. Indocyanine green observation and measurement of skin water concentration and skin and subcutaneous tissue stiffness were done before and after a single 45-minute session of IPC. After IPC, we observed the movement of edema fluid upper in the arm (92%) and in three main directions not seen before IPC: to the ipsilateral supraclavicular lymph node (30%), to the ipsilateral axilla (22%), and to the axilla, chest, and scapula (26%). We noticed two changes in fluorescent intensity along the entire limb: a decrease in the hand and forearm, an increase in the arm (64%), and a decrease along some parts or the entire limb (36%). Skin and subcutaneous tissue stiffness decreased at all limb levels. The highest, statistically significant reduction of subcutaneous tissue stiffness was noticed in the middle forearm and elbow (36.4% and 33.4%, respectively).

Conclusions: IPC can effectively move edema fluid from the distal to the proximal part of the limb, promote compensatory drainage pathways, and decrease tissue stiffness. This compression type should be applied even in the early stages to prevent limb enlargement and secondary tissue changes.

Keywords: BCRL, indocyanine green lymphography, intermittent pneumatic compression, compensatory drainage pathways, edema fluid movement

Introduction

The most common complication after breast cancer therapy is lymphedema. Surgical treatment, lymphadenectomy, and radiation therapy interrupt the lymph drainage in the affected arm. Consequently, tissue fluid slowly and constantly accumulates in tissue spaces, and limb size and weight increase, causing functional disability and reduced quality of life. According to the literature, the incidents of lymphedema after breast cancer treatment vary between 5% and 75% depending on the type of surgery and additional treatment, such as irradiation.[1–3]

Lymphedema is a lifelong disease associated with high financial costs for patients and health systems.[4,5] So, early diagnosis followed by appropriate therapy is crucial to prevent advanced lymphedema with all possible complications,

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such as subcutaneous tissue fibrosis, massive fluid accumulation with fluid leakage, recurrent skin and subcutaneous tissue inflammations (dermatolymphangioadenitis [DLA]), damage to the shoulder joint, and reducing the financial cost of treatment.[6–8]

The conservative treatment of lymphedema is based on the complex decongestive therapy, which consists of manual lymphatic drainage (MLD), physical exercise, skin care, and bandaging, as well as other methods such as intermittent pneumatic compression (IPC).[9,10]

The main goal of compression therapy is to mobilize and evacuate the tissue fluid accumulated in the tissue space from the more distal part of the limb to the upper part of the limb, where it can enter still-functioning lymphatic vessels (LVs). Starting early and constantly repeating reduces the limb's volume, creates a tissue channel, and promotes compensatory drainage pathways.[11] These facilitate the evacuation of edema fluid and slow down pathological processes such as fibrosis in edematous tissue.[12]

Indocyanine green (ICG) lymphography allows the real-time observation of ICG-dyed lymph/tissue fluid movement in LVs or in the tissue as dermal backflow. ICG is crucial for lymphedema diagnosis as it can detect even LVs' insufficiency, classify lymphedema's advancement, plan therapy, and evaluate treatment effectiveness.[13–16]

Some reports in the literature present on ICG lymphography how MLD facilitates compensatory drainage pathways in patients with upper limb lymphedema after breast cancer therapy.[17,18] However, there is no literature about the similar effect of IPC.

This study aimed to investigate fluid movement from the distal to the proximal parts of the upper limb, visualize possible fluid drainage pathways on ICG lymphography, and analyze how this impacts the skin and subcutaneous tissue stiffness under IPC influence.

Materials and Methods

Patients

Twenty-five patients with lymphedema after breast cancer therapy classified based on clinical investigation as stages II and III appearing for the first time in our outpatient clinic from 2022 to the end of 2023 were included in these studies. All patients were women, with a mean age of 60.4 years ±10.0 (43–75). The mean time since the completion of the breast cancer treatment and duration of swelling was 8.2 ± 8.7 (range 1.2–27 years) and 4.8 ± 4.8 (range 1–25), respectively (detailed patients' information is given in Table 1). Patients with visible signs of inflammation such as redness of the skin, palpation pain, or increased skin temperature are excluded from the studies. None of the patients had previously undergone diagnostic imaging and professional therapy with a reduction phase. In all patients, the ICG lymphography combined with IPC was done to investigate the actual status of lymphatic drainage in the affected upper limbs, plan the individual therapy, and determine the possibility and effectiveness of movement of edema fluid.

All patients were thoroughly informed about the course of the examination and gave their written consent. The Bioethics Committee in the Center of Postgraduate Medical Education, Warsaw, approved the study (69/2022).

Table 1. Patient's Characteristics

Total number of patients/sex	25/F
Age	60.4 ± 10.0, range: 43–75
Stage of lymphedema:	
stage II	16 (63%)
stage III	9 (37%)
Right upper limb edema	12 (46%)
Left upper limb edema	13 (54%)
Time since completion of breast cancer treatment:	1.2–27 years, 8.2 ± 8.7
Radiotherapy	21 (84%)
Chemotherapy	20 (80%)
Lymphadenectomy	20 (80%)
Duration of swelling:	1–25 years, mean 4.8 ± 4.8
DLA	16 (64%)

DLA, dermatolymphangioadenitis.

ICG lymphography

The ICG lymphography was done as previously described.[19] Briefly, 0.2 mL of 0.5% ICG dye (Pulsion, Munich, Germany) was injected subcutaneously into the second, third, fourth, and fifth interdigital tissues. Observation and video recording (Photodynamic Eye, Hamamatsu Photonics, Hamamatsu, Japan) were done 3 minutes after injection, after 1 hour of squeezing the ball, and after a 45-minute compression with IPC. The level reached by ICG-dyed tissue fluid after 1 hour of squeezing the ball was marked on the patient's skin. Observation and analysis were concentrated on the sites and patterns of fluid accumulation (dermal backflow), presence of LVs, fluorescent intensity (FI) along the entire limb (IC-CALC 2.0 software, Pulsion, Munich, Germany) after 1 hour of squeezing the ball, and changes in these parameters and presence of additional pathways of fluid drainage after IPC. For calculation of the FI along the entire limb before and after IPC, the camera was set at a distance of 15 cm from the limb and moved along the limb at the same speed and at the same time before and after IPC.

Compression with IPC

For IPC compression, the device composed with the pump (SC-4008-DL, Bio Compression Systems, Moonachie, NJ) and 8-chamber sleeve sequentially inflated from the distal to the proximal part of the limb was used. The inflation time was set for 120 seconds/8 chambers, compression pressure at the hand level was 60 mmHg and gradually decreased by 20% at the armpit area, and the "focus" (double the inflation time during the first 10 minutes of treatment) therapy (1–3 chambers) was on. The IPC session was 45 minutes.

All measurements were done before and were repeated in the edema limbs immediately after compression with IPC. The measurement levels were marked on the patient's skin to avoid mistakes.

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Skin water concentration

The skin water concentration measurement was done as previously described.[19] The LymphScaner (Delfin Technologies Ltd.) device measuring the water concentration at a depth of 2.5 mm was used. The measurements were done at the medial side at six levels of the upper limb: hand, just above the wrist, middle part of the forearm, at the level of the elbow joint, middle part of the arm, and upper part of the arm at the level of the armpit.

Skin stiffness

Skin stiffness was measured as previously described with a skin fibrometer (Delfin Technologies Ltd., Kuopio, Finland).[19] The device probe was placed on the skin five times at each measured point, and the mean value of the skin stiffness at a depth of 1.25 mm expressed in Newton (1N = 0.0981 kg) was displayed on the device screen.

The measurement points were the same as in water concentration.

Subcutaneous tissue stiffness

The tissue stiffness at a depth of 10 mm was measured at the same points as skin stiffness except for the hand. The deep tissue tonometer comprises a manometer (Wagner, Seattle, WA), and a 10 mm long round-bottom plunger with a 1 cm^2 surface area was used.[19] The subcutaneous tissue stiffness was expressed in g $10^3/cm^2$.

Statistical evaluation

All data were expressed as mean ± standard deviation. A double-tailed Student's *t* test was applied for statistical differences before and after 45-minute IPC sessions and between healthy and edema limbs. The statistically significant difference was set at the $p < 0.05$ level.

Results

ICG lymphography

After 1 hour of squeezing the ball, we observed the accumulation of fluid as a dermal backflow in the hand in 20 (80%), in the forearm in 23 (92%), in the elbow area in 24 (96%), in the lower part of the arm in 22 (88%), in the upper part of the arm in 17 (68%), and in the armpit area in 6 (24%) patients. The dominant dermal backflow pattern was stardust. In some patients, still contracting LVs in different parts of the upper limb were observed. There were present in 5 (20%) patients in the hand, in 2 (8%) in the forearm, in 1 (4%) in the elbow area, in 2 (8%) in the lower arm, and in 2 in the upper part of the arm. The LVs in the arm were faintly visible and did not reach the axilla.

After 45 minutes of compression with IPC, we observed ICG-dyed fluid movement as the dermal backflow upper in the arm in 23 (92%) patients. Among them, in 5 (22%) patients, only movement of fluid upper in the arm without compensatory drainage pathways was seen. In 7 patients (30%), the drainage to the supraclavicular lymph nodes (LNs) was observed (Figs. 1, 2). In 6 (26%) patients, fluid movement to the armpit, chest, and scapula was seen (Fig. 3). Among them, in one patient, the movement of LVs along the chest to the contralateral axillary LN was seen (Fig. 4). Fluid movement to the armpit area was observed in 5 (22%). In 2 patients (8%), no visible changes in the level

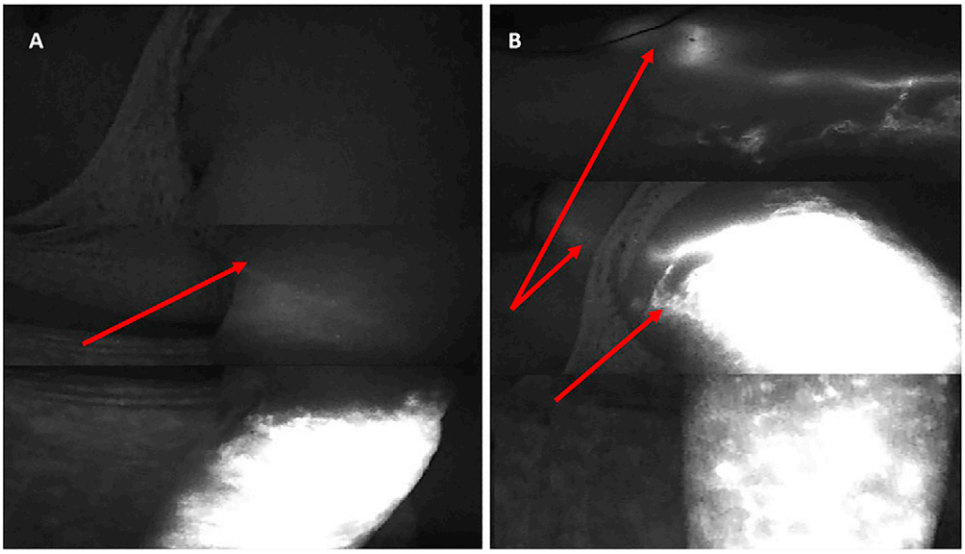

FIG. 1. The examples of changes in ICG-dyed fluid levels before and after 45 minutes with a 60 mmHg IPC compression session and compensatory pathways to supraclavicular LN seem to occur after IPC in a patient with left lymphedema upper limb stage III. Parts A and B comprise the more characteristic video fragments (A, forearm, middle arm, upper arm, and shoulder; B, forearm, upper arm, shoulder, and upper part of the chest wall along the clavicle). **(A)** The ICG-dyed fluid level after 1 hour of squeezing the ball and before the IPC massage. The arrow indicates the exact edema fluid level on the middle arm; no ICG-dyed edema fluid is seen in the upper part of the arm and shoulder. **(B)** After 45 minutes of IPC, the ICG-dyed fluid moved upper in the arm and reached the shoulder level (lower arrow). The upper double arrow indicates the LV going to the supraclavicular LNs. ICG, indocyanine green; IPC, intermittent pneumatic compression; LN, lymph node; LV, lymphatic vessel.

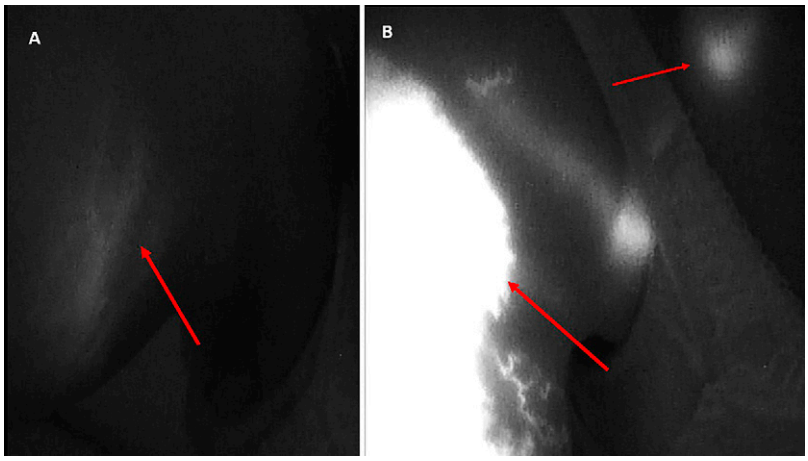

FIG. 2. The example of the ICG-dyed edema fluid location before and after 45 minutes with 60 mmHg IPC compression session and compensatory pathways to supraclavicular LN in a patient with right upper limb stage II. **(A)** The ICG-dyed fluid level in the arm after 1 hour of squeezing the ball and before IPC. The arrow indicates the location of ICG-dyed edema fluid (note the low fluorescent intensity), mainly in the internal site of the arm. **(B)** The change in the location and the fluorescent intensity of edema fluid after IPC (lower arrow) is seen in the arm. The upper arrow indicates the supraclavicular LN that was not seen before IPC. ICG, indocyanine green; IPC, intermittent pneumatic compression; LN, lymph node.

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of ICG-dyed fluid on ICG were seen. In no one patient, the axillary LNs were seen.

Fluorescent intensity

The FI charts showed two types of changes. FI decreased in the hand and forearm, increased in the elbow and arm (16 patients, 64%), and reduced in some parts of the limb or along the entire limb (9 patients, 36%; Figs. 5, 6). A decrease in FI in some regions of the limb was observed even in two patients without visible changes in the level of ICG-dyed fluid.

Skin water concentration

Skin water concentration was statistically significantly higher at all levels in edema than in the healthy limbs. The highest value of skin water concentration in the swollen limb was noticed at the middle forearm and elbow regions, at 55.2% and 52.8%, respectively. After 45 minutes of IPC, the skin water concentration decreased at all limb levels except for the armpit area. A significant reduction of 11.8% (p = 0.0294) was observed in the elbow area (Fig. 7).

Skin stiffness

Skin stiffness was higher at all limb levels in edema than in healthy limbs. The highest values of skin stiffness before IPC were observed in the wrist and middle forearm and were 0.11 N in both areas. After IPC, skin stiffness was reduced in all limb levels, with a more significant decrease in the middle

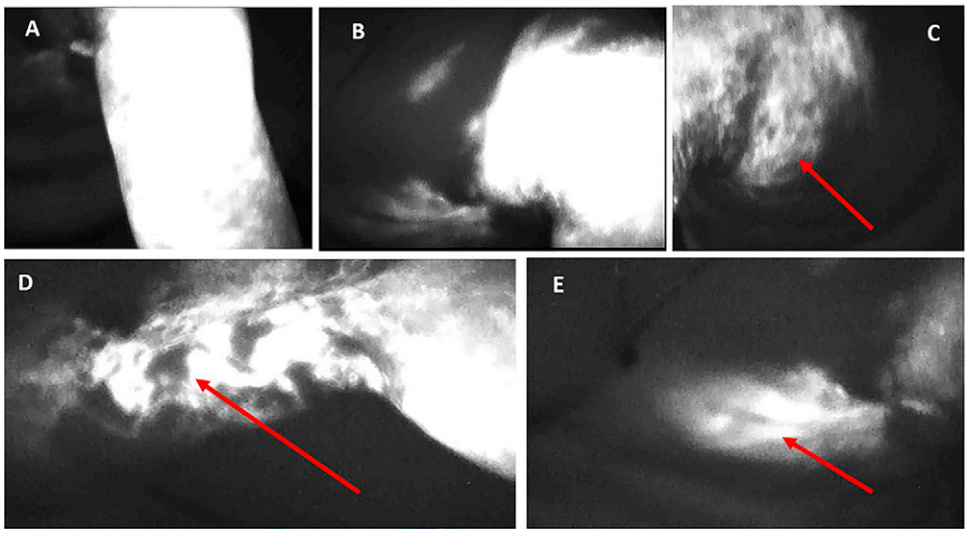

FIG. 3. The example of multiple coexisting alternative drainage pathways appearing after an IPC session in a patient with left upper limb lymphedema stage II. **(A)** The dermal backflow seen in the arm. (**B**). The upper part of the arm is covered by dermal backflow. (**C**). Arrow indicates the dermal backflow seen on the scapula. (**D** and **E**). The arrows show dermal backflow in the armpit **(D)** and the chest wall **(E)**. IPC, intermittent pneumatic compression.

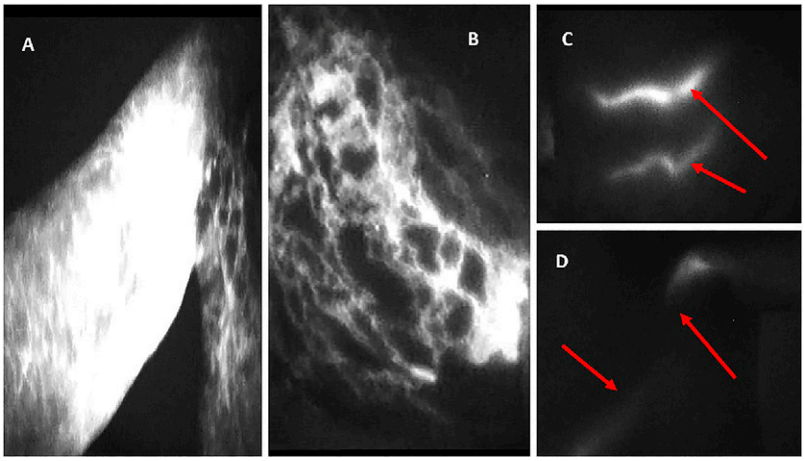

FIG. 4. The example of the alternative pathways of lymph drainage through the chest to the contralateral axilla after IPC in a patient with right upper limb lymphedema stage II. **(A)** Upper part of the arm. (**B**) The dense skin lymphatics network is on the chest wall's right side. (**C**) Two lymphatic vessels go horizontally through the left side of the chest wall. (**D**). Lymphatic vessels go to the contralateral axilla (lower arrow) and reach the contralateral axillary LN (upper arrow). IPC, intermittent pneumatic compression; LN, lymph node.

forearm and the elbow area by 36.4% and 33.4% (p = 0.0217, p = 0.0141), respectively (Fig. 7).

Subcutaneous tissue stiffness

Deep tissue stiffness was higher in edema than in healthy limbs. The highest mean value of deep tissue stiffness before IPC was observed in the wrist and the middle forearm, and it was 0.75 and 0.7 g $10^3/cm^2$, with the highest value of 1.2 g $10^3/cm^2$ in the wrist. The increase in elasticity after IPC was observed at all limb levels, with the highest in the wrist and middle forearm (28.0% and 28.6%, p = 0.0083 and p = 0.0038; Fig. 7).

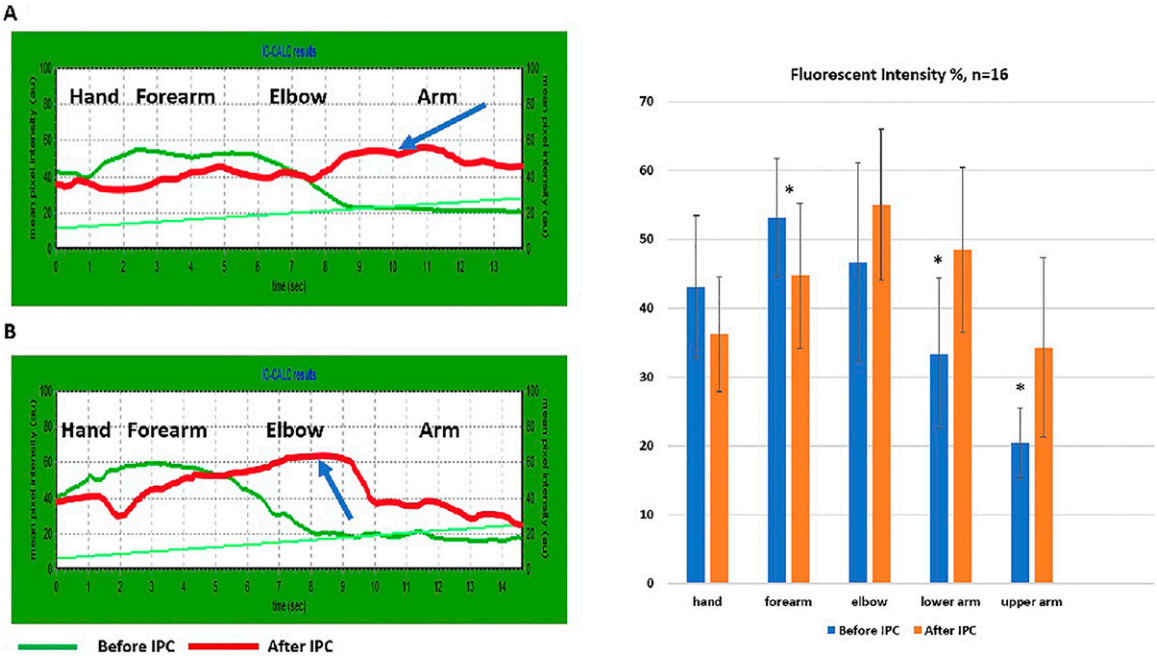

FIG. 5. The changes in fluorescent intensity in the 16-patient group with fluorescent intensity redaction in the forearm and an increase in the arm. The two examples of fluorescent intensity changes along the entire upper limb before and after IPC are on the left side of the figure. The green lines present the fluorescent intensity before IPC and the red lines after IPC. On both charts **(A, B)**, the fluorescent intensity before IPC was highest in the forearm and reached 55% and 60%, respectively, while there was 20% in the arm. After IPC, the fluorescent intensity decreased in the hands and forearms and increased in the arm in the upper chart **(A)** to 55% (arrow) and 60% in the elbow level (arrow) in the lower chart **(B)**. The numerical data of the fluorescent intensity before and after IPC in this 16-patient group are on the right side of the figure. Note the statistically significant reduction after IPC in the forearm (p = 0.0228) and the statistically significant increase in the lower and upper arm (p = 0.0011 and p = 0.0011, respectively). Lower arm—the lower half of the arm; upper arm—the upper half of the arm. *Statistically significant. IPC, intermittent pneumatic compression.

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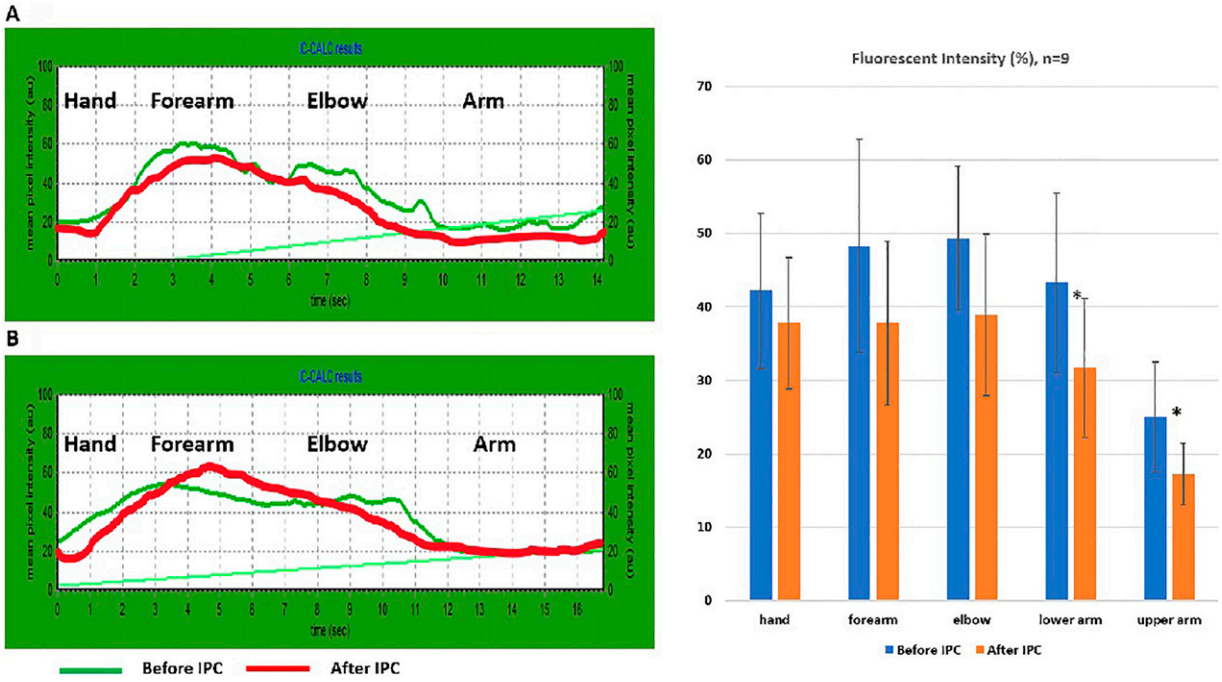

FIG. 6. The changes in fluorescent intensity in the 9-patient group with fluorescent intensity redaction in the part or the entire upper limb. The two examples of fluorescent intensity changes along the entire upper limb before and after IPC are on the left side of the figure. The green lines present the fluorescent intensity before IPC and the red lines after IPC. On the upper chat **(A)**, the decrease in fluorescent intensity is seen along the entire limb by 10%. On the lower chart **(B)**, the reduction in fluorescent intensity is seen in the hand by 10%, then an increase in the forearm (10%), and a decrease in the lower part of the arm. The numerical data of the fluorescent intensity before and after IPC in this 9-patient group are on the right side of the figure. The fluorescent intensity was reduced after IPC at all limb levels, with a statistically significant decrease in the lower and upper part of the arm ($p = 0.0485$ and $p = 0.0202$, respectively). *Statistically significant. IPC, intermittent pneumatic compression.

Discussion

Our studies on fluid movement along the upper limbs on ICG lymphography in patients with BCRL during a single session of IPC revealed the following information: (1) in the majority of patients (92%), we observed the movement of fluid upper in the arm, (2) in 21.7%, we observed fluid movement only in the upper part of the arm, in remained patients additional in 3 main directions: (a) along the clavicle to the supraclavicular LNs (30%), (b) to the armpit area as dermal backflow (22%), and (c) to the armpit, chest wall, and scapula (26%), (3) analysis of FI along the entire limb revealed a decrease of FI in the hand and forearm, an increase in the elbow area and arm in 64% of patients, and a decrease of FI along the part or entire limb in 36% of patients, (4) decreased skin water concentration at all limb levels except armpit area, and (6) decreased skin and subcutaneous tissue stiffness at all limb levels with a more significant reduction in the distal part of the forearm.

Upper limb lymphedema is the most common complication of breast cancer therapy. Surgery with LNs dissection suddenly disrupts the lymphatic pathways draining lymph from the affected arm to the regional LNs. Subsequent radiotherapy causes fibrotic changes in the surrounding tissues and venous and LVs. Consequently, tissue fluid with all its constituents, such as proteins, lipids, and biologically active factors, accumulates slowly in tissue spaces. This fluid should be systematically evacuated from the distal to the proximal part of the limb to prevent limb enlargement and secondary changes such as fibrosis and recurrent skin and subcutaneous tissue inflammation and promote the development of alternative drainage pathways.[12,20] IPC therapy is among the therapeutic methods that can move fluid along the swollen limb.

In most patients included in these studies with lymphedema stages II and III, after 1 hour of activity, which should promote the lymph/tissue fluid transport to the upper part of the limb, we observed the fluid accumulated in the tissue spaces as dermal backflow mainly in the distal part of the limb, hand, forearm, and elbow area without visible drainage to the armpit or other area as chest or supraclavicular LNs. After 45 minutes of IPC, we observed the fluid movement upper in the arm and three main drainage pathways to the ipsilateral supraclavicular LNs, to the ipsilateral axilla, and coexisting pathways to the ipsilateral axilla, chest wall, and scapula. Our data are similar to that of Suami et al. and Koelmeyer et al.[17,18] Both authors studied the compensatory drainage pathways under the influence of MLD. Koelmeyer et al. observed drainage to the ipsilateral axilla in 74.9%, to the ipsilateral clavicular in 41.8%, and to the contralateral axilla in 11.3% of patients. In the studies of Suami et al., the compensatory pathways depend on the severity of lymphedema, with the highest percentage of drainage to the ipsilateral axilla (67%) in the least advanced lymphedema. In comparison, stage III dominated the drainage to the clavicula (55%), and stage IV, lymphedema to the contralateral axilla (17%). In our studies, among five patients with drainage to

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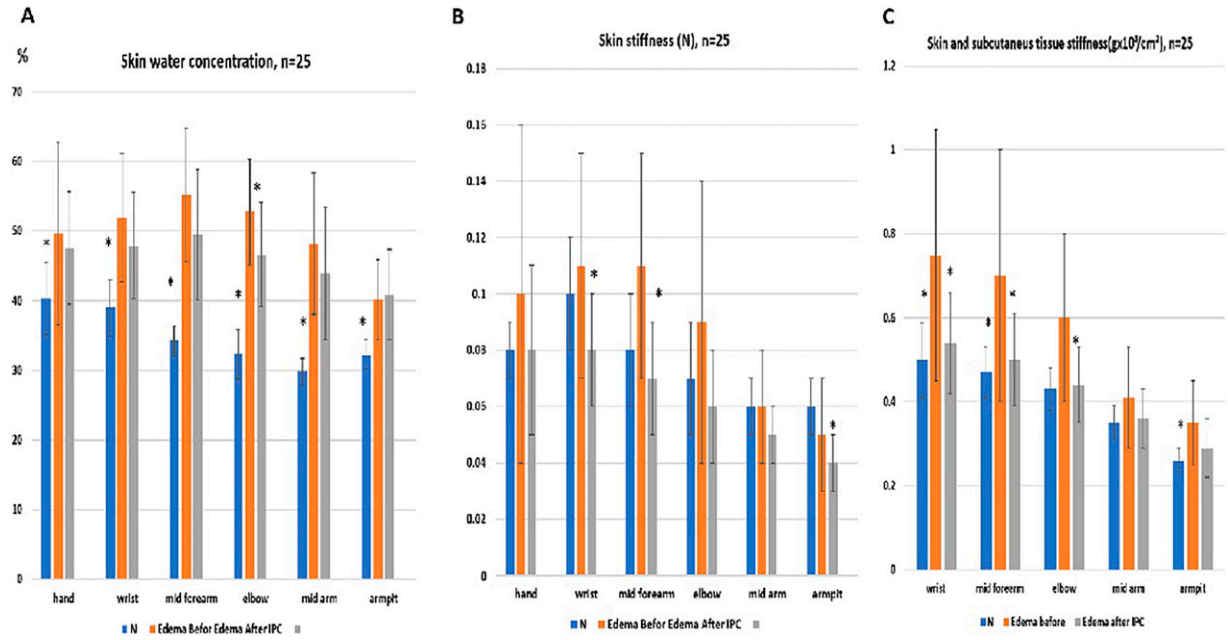

FIG. 7. The values of skin water concentration**(A)**, skin **(B)**, and subcutaneous tissue **(C)** stiffness in healthy and edema upper limbs and the changes in these parameters in edema limbs after IPC. **(A)** The values of skin water concentration were statistically significantly higher in edema limbs at all measured limb levels ($p = 0.00059$, $p = 0.0008$, $p < 0.00001$, $p < 0.00001$, $p = 0.0006$, and $p = 0.0009$, respectively). After IPC, the skin water concentration in edema limbs decreased at all limb levels except the armpit level, with statistical significance at the elbow area ($p = 0.029$). **(B)** The values of skin stiffness were higher in all limb levels except the middle arm in the edema limb than in the healthy limbs. After IPC, there was a reduction in skin stiffness at all limb levels, with a statistically significant decrease in the wrist, mid-forearm, and armpit levels ($p = 0.0216$, $p = 0.014$, and $p = 0.008$). Interestingly, the values of edema limb skin stiffness after IPC were lower than those of healthy limbs at all levels except the hand. A possible explanation is that compression removed the fluid just under the dermis and created an empty space for a very short time. This space fills in quickly, so the compression garment after IPC is necessary. **(C)** The values of subcutaneous tissue stiffness were higher at all limb levels in the edema limb than in the healthy, with statistical significance at the wrist, middle forearm, and armpit ($p = 0.0317$, $p = 0.026$, and $p = 0.0126$, respectively). After 45 minutes with IPC, the deep tissue stiffness decreased at all limb levels with statistical significances at the wrist, middle forearm, and elbow ($p = 0.0083$, $p = 0.0038$, and $p = 0.0142$, respectively). Note that the decrease in subcutaneous tissue stiffness was most expressed after a 45-minute session with IPC in the distal part of the limb, where the tissue stiffness was highest before IPC. *Statistically significant. IPC, intermittent pneumatic compression.

the ipsilateral axilla only, three were classified as lymphedema stage II and two as lymphedema stage III. In the groups with drainage to ipsilateral supraclavicular LNs, five patients were classified as stage II and one as stage III lymphedema. In the group of patients with multiple drainage pathways after IPC, all patients were classified as lymphedema stage II. The more advanced lymphedema stage III patients dominated the group with the only movement of the fluid upper in the arm without visible drainage routes (four patients stage III and 1 stage II). The difference may depend on the criteria of lymphedema advancement classification. In the Suami et al.' study, the classification of the studies was based on the ICG findings in our clinical investigation.[21] However, according to the classification used by Suami et al., the majority of our patients can be classified as stage IV (with no patent LVs) and stage III (with few patent LVs and extended dermal backflow).[17,22,23]

In lymphedema, when the majority of main LVs are obstructed, tissue fluid accumulated in tissue spaces can be moved by an external force (IPC) along the tissue spaces (tissue channels) as dermal backflow to the sites with still existing LVs.[11,24]

The fluid movement and dislocation were visible when we analyzed the FI along the entire limb before and after IPC. Before IPC, we observed the highest FI in the most distal parts of the limb, reaching 43% in the hand and 53% in the wrist level, while, in the upper arm, it was 20–25%. After IPC, we observed two changes in FI: the reduction in the lower and increase in the upper part of the arm and the reduction along the entire or some part of the arm. The first type of changes in FI was observed in all five patients with fluid movement to the ipsilateral axilla, six patients with drainage to ipsilateral supraclavicular LN, and five patients with multiple drainage ways. The second type of FI changes dominated patients with fluid movement upper in the arm only, all five patients. The question arises as to why the FI decreased in patients with the movement of the fluid upper in the arm without visible drainage roots. One of the possible explanations is that tissue fluid is moved along the tissue as a dermal backflow to the site, where it can reach the deep LVs via perforating lymphatics.[18]

The fluid movement was also reflected in changes in skin water concentration and skin and subcutaneous tissue stiffness. The mean skin water concentration measured at a depth

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of 2.5 mm decreased at all limb levels except the upper arm, close to the armpit. Skin and subcutaneous tissue stiffness decreased at all limb levels, with the highest decrease in the forearm, where the fibrotic changes and tissue stiffness are more expressed.

Tissue stiffness progresses along with the duration of lymphedema due to fluid accumulation in the tissue spaces and remodeling and overgrowth of the subcutaneous tissue.[25–27] Our previous studies proved the effectiveness of therapy with IPC on increasing subcutaneous tissue elasticity.[19,28] Studies by Bok et al. also revealed a decrease in both subcutaneous tissue thickness measured in ultrasonography (USG) and subcutaneous tissue stiffness estimated by shear wave velocity after IPC in patients with BCRL.[29]

The limitation of our studies is the low number of patients.[25] A higher number of patients will allow a more detailed analysis of the changes developed under the influence of IPC, such as compensatory drainage pathways, changes in FI, and skin and subcutaneous tissue stiffness in relation to edema advancement.

Taken together, our studies prove the effectiveness of IPC in tissue fluid movement from the distal to the proximal part of the arm, facilitating the compensatory drainage pathways and reducing the skin and subcutaneous tissue stiffness even in patients with more advanced BCRL stages II and III. Systematic and constant evacuation of tissue fluid from the distal part of the limb prevents limb enlargement and the development of secondary changes with hyperkeratosis, fibrosis, recreant DLA, and fluid leakage. This type of therapy, combined with the daily compression sleeves, should be mandatory even in the early stage of lymphedema.

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Author's Contribution

M.T.Z.: conceived the study concept and design, collected data, analyzed the date, wrote the manuscript; N.E.K.: collected data, contributed to the final version of the manuscript.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

No funding was received.

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