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Investigating the Short-Term Effects of Manual Lymphatic Drainage and Compression Garment Therapies on Lymphatic Function Using Near-Infrared Imaging

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Abstract

Background: Lymphedema is a chronic peripheral swelling caused by a dysfunction of the lymphatic system, leading to discomfort and loss of upper limb movement. Therapies to treat or manage this swelling have limited evidence, partly because of a paucity in objective lymphatic measures. This study explored the role of near-infrared (NIR) imaging in evaluating interventions. ***Methods:*** Nine healthy volunteers underwent NIR fluoroscopy using a microdose (50 μL, 0.05% w/v) of indocyanine green to quantify lymphatic behavior before and after a 15-minute period of manual lymph drainage followed by compression garment (CG) therapy for a 10-minute period. Images were taken at the forearm and elbow after each intervention. Lymphatic function was defined by the number, size, displacement, and speed of lymph packets. The lymph parameters were analyzed to assess the effects of the interventions compared with basal values. ***Results:*** Baseline (BL) parameters of lymph function revealed high variability in the number, size, and speed of packets between individuals. Despite this variance, both interventions showed statistically significant improvement ($p < 0.05$) in displacement and speed at the forearm compared with BL. The velocity of transient lymph packets increased from a median of 6.7 mm/s at BL to 13.3 mm/s after manual lymphatic drainage (MLD) and 10.5 mm/s after CG. ***Conclusion:*** Lymphatic activity increased significantly after MLD, with relative increases being maintained after a short time period of CG application. NIR fluoroscopy has the potential to both monitor lymph pathology and provide robust parameters in the assessment of interventions.

Keywords: lymphatic system, lymphedema, fluorescence imaging, manual lymphatic drainage, compression garment

Background

LYMPHEDEMA IS A potentially severe and chronic swelling of the limbs triggered by the dysfunction of the lymphatic system. Lymphedema is caused by the inefficiency of lymphatic vessels to drain fluid and proteins, resulting in an accumulation of lymph, leading to an increase in limb volume.[1] This condition leads to a disruption in daily function and adversely affects both gross and fine motor skills, with negative ramifications for work, home, and personal care functions, as well as recreational and social relationships.[2] Several causal pathways have been identified in the pathology, including primary factors such as genetic abnormalities or secondary external factors such as infection, obesity,[3] injury, or cancer treatment. As an example, a recent study estimates that 21% of women who undergo treatment for breast cancer are diagnosed with lymphedema,[4] with a significant proportion of these developing chronic progressive lymphedema.[5] In addition, the presence of lymphedema in breast cancer survivors leads to both higher medical costs and a higher risk of developing an infection in the limb.[6] At present, there are no known curative treatments, either surgical or pharmacological.[7] Typically, conservative treatments, such as compression garments (CGs) and manual lymph drainage are prescribed to manage lymphedema and promote functional restoration in the limb.

Interventions typically involve one or several components of complex decongestive therapy (CDT),[8] involving a four-phase conservative treatment including manual lymphatic drainage (MLD), compression therapy (compression bandages or sleeves), skin care, and lymph-reducing exercises. However, the evidence to support these interventions remains

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limited. Indeed, research involving MLD has revealed contradictory findings ranging from no benefit[9] to substantial benefit.[10] A recent systematic review found a statistically significant benefit favoring MLD for mild-to-moderate lymphedema patients, with circumference reductions from 12% to 24% ($p = 0.05$).[11] To maintain the benefits of MLD, physical therapy is typically used in conjunction with compression therapy.[12] CGs are designed to improve lymphatic uptake and intensify lymphangion pumping.[13] The efficacy of lymphedema interventions is typically measured by limb volume using water displacement or circumferential measurements.[14] This methodology is considered the gold standard as the most accurate for volume, whereas measurements of arm circumference are used more in clinical practice as it is simpler and less intrusive. However, both methods are prone to error and neither give any information about lymphatic function.[15]

Clinical consensus supports the development of surveillance programs to provide both early detection and effective management of lymphedema supported by novel and sensitive diagnostic modalities.[16] Indeed techniques have been developed to image the lymphatic system and diagnose dysfunction.[14] One such technique, near-infrared fluorescence lymphatic imaging (NIRFLI) using indocyanine green (ICG), has recently been adopted to observe the architecture and contractile function of the lymphatic system.[17] This method has proved both easy and safe to use, and provides relatively high resolution in real time, while remaining relatively economical.[18] One group has used NIR fluorescence imaging to quantify the effect of MLD on the lymphatic system and found that lymph velocity increased in both healthy participants and lymphedema patients ($p < 0.05$).[14] However, they did not attempt to assess the effects of CGs on the lymphatic system, although this is a much more commonly used intervention. This study was, therefore, designed to assess the combined effects of MLD and CG and to explore the utility of the NIRFLI technique to assess conservative interventions.

Methods

The study was a case-controlled design using healthy participants. Ethical approval was granted by the University of Southampton ethics committee (REC ID: 19378) before data collection. All participants were provided with complete details of the study before giving their informed consent. Participants with history of thrombosis, liver, kidney, or heart disease were excluded, and contraindications for Cardiogreen injections were monitored.

NIR fluorescence imaging

An NIRFLI methodology developed in the host laboratory provided the basis to measure lymphatic function, as detailed in recent articles.[19,20] To review briefly, a microdose of ICG was tracked by an NIR camera system (Fluobeam® 800; Fluoptics), which included a spectrally confined (780 nm-centered) laser light source that activates ICG with emitted light at a wavelength of 760 nm. The images were recorded by a sensitive charge-coupled device camera. Images were collected at both the right forearm and elbow, where active dermal lymphatic vessels were identified for analysis (Fig. 1). A region of interest was selected around a well-defined vessel

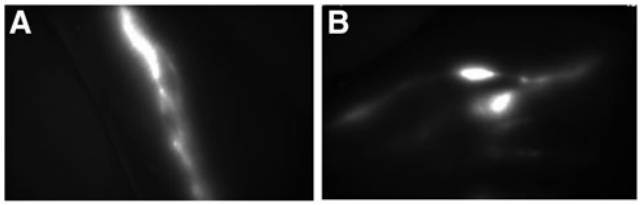

FIG. 1. **(A)** Lymphatic vessels at the forearm. **(B)** Lymphatic vessels at the elbow.

that exhibited contractile activity resulting in transient lymph packets. The camera was located perpendicular to the long axis of the observed vessel to obtain high-quality images.[21] Three videos, each of 5 minutes duration, were captured from the forearm and the elbow at three time phases, namely, baseline (BL) before the intervention, after MLD (post-MLD), and after the application of a CG (post-CG).

MLD protocol

MLD was implemented in the right upper limb for 15 minutes, after the Vodder technique.[22] During therapy, participants were positioned supine with the arm elevated. MLD was then administered with nodal massage in the axillary zone using stationary circles. Lymph node massage was performed by a single researcher (C.L.) with the tips of the fingers, applying slow, deep but gentle pressure. The massage continued from the proximal aspect, working gradually after clearance of each section to the distal regions.[23] The pump technique was used in this phase, applying circle-shaped pressure with the entire palm and the proximal phalanges in a transverse direction. Then the scoop technique was performed, in which the palmar surface of the hand moved over the skin, facilitated by movement of the wrist and combined with forearm pronation and supination.[24] Additional node clearance was made in the anterior aspect at the elbow at the cubital nodes, followed by the pump and scoop technique in the forearm. The final stage of the MLD involved draining the mobilized lymph to the axillary nodes with the pump and scoop technique, performed in a cephalic direction, toward the axilla. Light intensity of MLD was applied throughout the phases to minimize erythema or pain to the participant.

Compression garment

A Juzo class 2 compression arm sleeve was used in the range of 23–32 mmHg, as deemed suitable for moderate levels of lymphedema. The device was made from a knitted material, which allowed for a component of gradient compression decreasing from distal to proximal locations, while avoiding skin damage. The garment was designed to provide a compression effect toward the muscles, promoting lymph drainage during movement. The garment was fitted according to the manufacturer guidelines for sizing using small-, medium-, and large-sized sleeve.

Test protocols

During imaging, each participant remained in a sitting position with their test limb supported at heart level by a vacuum consolidated pillow. Intradermal injections of 0.1 mL of 0.05% w/v ICG were administered by a registered

nurse and delivered equally into the two interdigital spaces between the thumb and the second finger. A 20-minute period was provided for ICG dissemination, after which an appropriate delineated lymphatic vessel was selected separately at the forearm and elbow to provide reference data for the three data collection periods. Initially, images were acquired for 5 minutes at each site, providing BL values for lymphatic function at the forearm and elbow. MLD was then performed by a single researcher trained in the technique (C.L.). Imaging was then repeated for 5 minutes directly after this therapy. Participants were then fitted with a CG for a 10-minute period. Upon removing the sleeve, imaging at the wrist and elbow was repeated. The order in which the interventions were delivered was not randomized.

Video analysis

Robust parameters of lymphatic function from the IR imaging sequences were identified using a customized software application (MATLAB; Mathworks). The output parameters included the frequency of transient packets, the area of each transient packet, in pixels, the distance traveled or ''displacement'' of the packets (mm), and the velocity of each packet (mm/s). To review briefly, the features were established using a droplet morphometry and velocimetry tracking approach.[25] Here image subtraction, binary conversion, and centroid tracking provided the basis to identify and measure each transient lymph packet captured within the 5-minute video sequences. Each transient event was analyzed to provide x and y coordinates of the packet centroids, whereby the resultant displacements could be estimated. An extended Kalman filter was applied to ensure that the centroid axes from distinct packets were isolated between the video frames (Fig. 2).

Statistical analysis

Statistical analysis was performed using MATLAB (Mathworks). Participant lymph behavior was analyzed during each

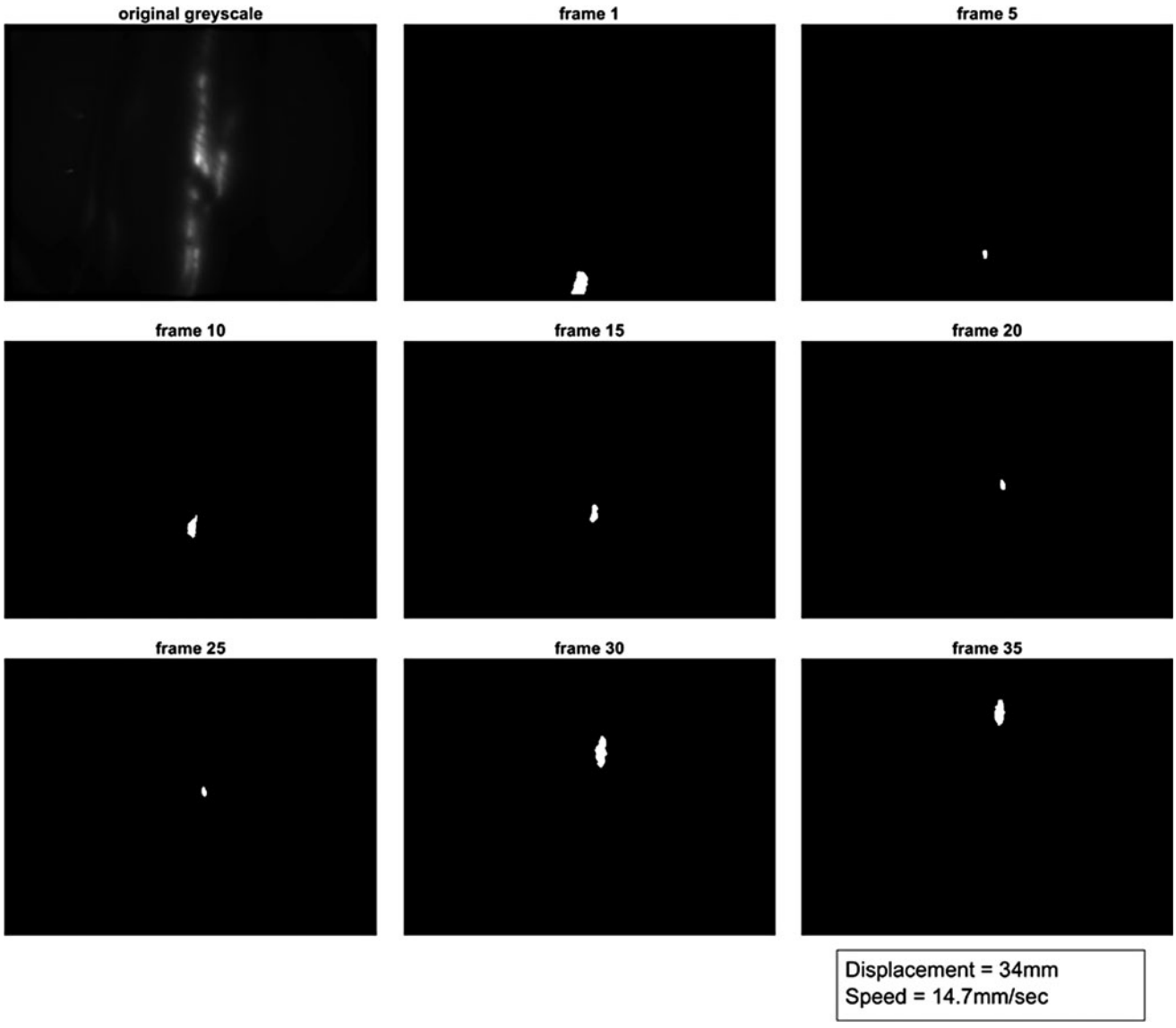

FIG. 2. Track of a single transient lymph packet from participant 5 through time frames at the forearm after manual lymphatic drainage intervention.

of the three test phases. All data were presented in nonparametric descriptors (medians), accounting for the relatively small sample size and distribution of the data. The area, displacement, and speed parameters from each transient packet were averaged over each test phase. Changes across the BL, post-MLD, and post-CG phases were assessed using the Friedman test. Comparisons of lymphatic behavior between individual time points were conducted using Wilcoxon signed-rank test. Differences were considered to be significant at the 5% level ($p < 0.05$).

Results

Participants

Nine healthy participants (five males and four females) were recruited with a mean age of 36 years (range 22–58 years), mean height of 1.66 ± 0.11 m, mean weight of 65.3 ± 10.8 kg, and their corresponding body mass index was 21.15 ± 3.4 kg/m^2.

Lymph function

Table 1 provides a summary of the parameters reflecting lymph function from the three phases of data collection. It is evident that there was considerable intraindividual variability across sites and the four parameters. As an example, the number of packets identified at the forearm at BL ranged between 1 and 10 with a median of 4 packets. Considerable variation was also observed in the size (area) of packets at the elbow with a median of 515 pixels and a range from 214 to 1822 pixels. It should be noted that the BL values at the elbow were generally higher than the corresponding values measured at the forearm for all four parameters.

Despite the interparticipant variability, there were notable increases in lymphatic activity after the interventions. This trend was consistent across the parameters with enhanced median values after MLD and CG. As an example, MLD induced a statistically significant ($p < 0.05$) increase for displacement and speed at the forearm (Table 1). In addition, there was a 100% increase in the median area of transient packets after MLD at the forearm.

The application of CG generally maintained the trend of increased values after MLD when compared with basal values. In some cases, the post-CG values were significantly higher than BL, for example, in displacement values from the forearm. In addition, there was an increase in median value of frequency and area of transient packets at the elbow, with the latter being statistically significant ($p = 0.038$).

Discussion

This study was designed to provide a quantitative assessment of lymphatic function before and after MLD and CG therapy using NIR fluoroscopy. Robust parameters indicative of dermal lymphatic function were extracted using a standardized image processing technique recently developed by the authors.[20] The results indicated that MLD had a significant effect on lymph activity, with increases in both speed and displacement of transient packets at the forearm. These behavioral changes in lymph function were maintained with the application of a CG for a relatively short time period. The methodology was successfully adopted to define suitable dermal lymphatic vessels, which were used to define parameters related to the flow of transient packets. These parameters were sensitive to detect changes pre- and postphysical interventions in a healthy population.

Similar changes in lymph behavior after MLD have been reported by Tan et al.,[14] with five of six healthy subjects

Table 1. Summary of parameters

Subject	*Area (pixels)*			*Displacement (mm)*			*Speed (mm/s)*			*No. of packets*		
Forearm												
	BL	Post-MLD	Post-CG	BL	Post-MLD	Post-CG	BL	Post-MLD	Post-CG	BL	Post-MLD	Post-CG
1	1043	833	291	14	17	15	7.0	8.4	7.7	4	8	2
2	254	2510	968	3	4	17	1.5	20.2	8.5	10	3	11
3	344	950	2399	5	27	22	2.5	13.6	11.1	1	3	4
4	572	1059	1023	8	21	17	4.0	10.7	8.3	4	11	9
5	466	1141	2976	25	23	25	12.3	11.6	12.6	5	10	6
6	1672	609	497	13	24	45	6.7	12.2	22.3	4	3	2
7	1208	1718	834	20	29	16	9.8	14.7	8.2	4	5	3
8	471	1462	1740	7	34	23	3.5	17.2	11.5	7	5	7
9	3988	1432	3846	14	27	21	7.1	13.3	10.5	3	8	6
Median	572	1141	1023	13	27*	21**	6.7*	13.3**	10.5	4	5	6
Elbow												
1	214	297	351	25	21	18	12.5	10.3	9	15	8	9
2	375	378	498	19	24	21	9.7	11.9	10.3	8	7	14
3	1035	2338	1593	26	25	28	12.9	12.3	13.8	4	8	8
4	367	1258	2075	29	27	23	14.4	13.5	11.4	7	6	9
5	406	336	1477	18	04	24	9.1	1.8	12.1	6	4	3
6	515	305	343	13	18	22	6.3	9.2	11.2	1	1	4
7	585	840	2205	13	32	23	6.4	16.2	11.4	3	4	4
8	538	1219	1701	22	21	27	10.8	10.5	13.3	7	7	11
9	1822	1564	3468	26	24	34	12.8	12.2	17.0	8	14	10
Median	515	840	1593**,***	22	24	23	10.8	11.9	11.4	7	7	9

*$p < 0.05$ BL versus post-MLD; **$p < 0.05$ BL versus post-CG; ***$p < 0.05$ post-MLD versus post-CG.
BL, baseline; MLD, manual lymphatic drainage; CG, compression garment.

demonstrating increased lymph velocity after MLD, with three individuals revealing statistically significant differences in one or both arms. The magnitude of velocity changes reported by Tan et al.[14] (range = 7.4%–52.7%) was lower than the changes reported in this study (range = 10%–98%). These differences could be explained by the differences in analytical approaches to quantify velocity, with Tan et al.[14] assessing between 28 and 1095 transient packets and this study choosing an average of 4 packets. Nonetheless, the order of magnitude in velocity was very similar between studies, with velocity in this study ranging from 2.5 to 22.3 mm/s and that in Tan et al's[14] study ranging from 6.2 to 12.7 mm/s. In a separate study, velocities of normal lymph flow were reported to range between 5 and 12 mm/s in 24 healthy control arms.[26] This highlights that despite the differences in settings and protocols, NIRFLI is producing parameters that are consistent in distinct populations.

The changes in transient lymph velocity can be related to the principles of MLD, namely that it enhances movement of lymph fluid by stimulating the natural peristaltic contractions of the lymphangions, reducing hydrostatic resistance to lymph flow and increasing velocity.[11] According to the theory, the distance and speed of an individual packet in the lymphatic vessels will be influenced by the force of the lymphangion contraction. Therefore, stronger contractions would propel fluid further with higher ejection fractions.[27] However, the effects of MLD may not be as pronouced in lymphedema patients, with their tortuous network of capillaries and reduced number of functional lymph vessels,[28] increasing dermal back flow and extravascular lymphatic fluid leakage.[29] The backflow events have also been recently described in lymphatic vessels that have been exposed to a period of uniaxial mechanical compression.[20]

This study also revealed that compared with BL values, the increases in lymphatic activity after MLD were maintained with the application of a CG for a 10-minute period. The specific protocol adopted did not permit the evaluation of whether CGs used in isolation could result in an improvement of lymphatic activity. Indeed, for most parameters, there was a small and insignificant reduction in speed and displacement, with an increase in area. However, the present findings do suggest that hosiery can maintain improvement in lymph function after MLD for a short time period. Further studies are required employing a randomized cross over design with longitudinal measurements to assess the efficacy of MLD and CG therapies in isolation and when they are combined. It is of note that there is limited evidence that active pneumatic compression devices can increase lymph activity in both healthy control and breast cancer-related lymphedema subjects, when assessed with NIRFLI.[30]

The number of participants in the present cohort study limits the generalizability of the results. Indeed, all the participants included were healthy volunteers and thus any extrapolation of the findings to individuals with lymphedema must proceed with caution. However, it has been shown that similar changes in lymph function have been identified in both healthy and lymphedema patients.[14] In addition, the delivery of the interventions was not randomized, with the MLD intervention being applied initially with its inevitable influence on the subsequent CG phase. Further research incorporating longitudinal analyses could derive whether MLD used in isolation has similar effects to its use in combination with CGs. The CG was also applied for a relatively short period of 10 minutes, whereas, in practice, individuals may wear CGs continuously, or at least during waking hours. Evaluation of the temporal effects of CG application warrants further examination. It must also be recognized that the infrared imaging system is limited in terms of depth resolution[31] and thus is sensitive to only superficial dermal lymphatic vessels to a depth of a few centimeters. However, it has been suggested that for both healthy individuals or lymphedema patients with incipient symptoms, the superficial lymphatics may play a greater role in lymph drainage than deep lymphatic vessels.[18]

The valuable information provided using NIR fluoroscopy could enhance the diagnosis and treatment of lymphatic disorders through the observation and quantification of changes in lymphatic transport either before or at the early stages of symptoms. It also offers the opportunity to evaluate MLD methods with a real-time feedback, permitting a spatial resolution of the lymphatic network, indicating the affected areas and the lymphatic vessels that are still functional, allowing for targeted physical therapy.[32] A further benefit might be to use NIR imaging to stratify which subjects could respond to therapy, decreasing unnecessary financial cost for the patient and the health care system.[33] Targeted elements of CDT could be applied to specific subpopulations at varying stages of lymphedema.

Conclusion

The study quantitatively evaluated lymphatic functional behavior after a short period of MLD and CG interventions using NIR fluoroscopy. There was an increase in lymphatic activity in the majority of the participants, with a statistically significant improvement in transient lymph velocity and displacement. NIR fluoroscopy has the potential to provide an insight for investigating who will respond to lymphedema treatment or measure whether contractile function is enhanced by the techniques used to manage this complication. However, further randomized studies are required on symptomatic patients over prolonged periods of intervention.

Ethics Approval and Consent to Participate

This project has been approved by the University of Southampton ethics committee (REC ID: 19378).

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Author Disclosure Statement

No competing financial interests exist.

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