Direct evidence of lymphatic function improvement after advanced pneumatic compression device treatment of lymphedema

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Abstract: Lymphedema affects up to 50% of all breast cancer survivors. Management with pneumatic compression devices (PCDs) is controversial, owing to the lack of methods to directly assess benefit. This pilot study employed an investigational, near-infrared (NIR) fluorescence imaging technique to evaluate lymphatic response to PCD therapy in normal control and breast cancer-related lymphedema (BCRL) subjects. Lymphatic propulsion rate, apparent lymph velocity, and lymphatic vessel recruitment were measured before, during, and after advanced PCD therapy. Lymphatic function improved in all control subjects and all asymptomatic arms of BCRL subjects. Lymphatic function improved in 4 of 6 BCRL affected arms, improvement defined as proximal movement of dye after therapy. NIR fluorescence lymphatic imaging may be useful to directly evaluate lymphatic response to therapy. These results suggest that PCDs can stimulate lymphatic function and may be an effective method to manage BCRL, warranting future clinical trials.

OCIS codes: (170.0110) Imaging systems; (170.2520) Fluorescence imaging; (170.2655) Functional monitoring and imaging; (170.3880) Medical and biological imaging

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1. Introduction

In the U.S., the overall rate of cancer survivorship has steadily increased, with cancer stage at time of diagnosis remaining the primary prognostic indicator of five-year survival rate [1]. Despite playing a critical role for defining the most efficacious treatment, nodal staging can

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increase the risk for breast cancer related-lymphedema (BCRL), a progressive and incurable treatment consequence whose risk is further exacerbated by radiation treatment [2–4]. BCRL incidence rates range between 3 to 15% after sentinel lymph node biopsy; 10 to 20% after complete axillary dissection without subsequent radiation; and 30 to 50% after complete axillary dissection followed by radiotherapy [4–7]. Arm lymphedema symptoms include decreased range of motion and function, pain, frustration, anger, and depression [8]. If left untreated or if treated ineffectively, lymphedema can progress to extreme disfigurement, chronic infection, and lymphangiosarcoma.

Standard management of lymphedema (including BCRL) is the use of complete decongestive therapy (CDT), which includes manual lymphatic drainage (MLD), compression bandaging, therapeutic exercise, and skin care [9]. Therapeutic efficacy is typically assessed over several weeks by measuring the change in arm volume as indicated by circumferential arm measurements or water displacement. Depending upon the criteria used to determine response, 50% to greater than 80% of arm lymphedema patients maintain benefits obtained from professionally-administered CDT over a period of 12 months [10–13]. Lack of patient compliance with prescribed self-MLD therapy is a major cause of treatment failure [14]. When used as part of home management, pneumatic compression devices (PCDs) have been proposed as a replacement for or adjunctive to self-MLD treatment. PCDs typically consist of sleeve garments comprised of chambers that, when sequentially inflated and deflated along the length of the arm, are designed to push lymph and extravascular fluids proximally towards the axilla or other functional draining basins within the trunk [15]. Less advanced PCDs consist of simple compressors with a single outflow port to a non-segmented sleeve (HCPC procedure code, E0650) or a segmented sleeve without manual control of pressure in each chamber (procedure code, E0651). While Medicare states that either an E0650 or E0651 device is sufficient to meet the clinical needs of a patient in whom MLD is insufficient [16,17], clinical practice suggests that an advanced, programmable PCD consisting of a segmented sleeve with a calibrated, gradient compressor (procedure code, E0652) provides greater efficacy. Unfortunately, payment for code E0652 is not typically made unless there is documentation that (i) an E0650 or E0651 device has been tried and found insufficient and that (ii) there is "clinical response" to the initial treatment with the E0652 device. Yet there is no method to directly evaluate the response of lymphatic function to an initial treatment.

A method to evaluate lymphatic function prior to and immediately following therapy could result in (i) choosing the most efficacious treatment approaches based upon direct evidence of improved lymphatic function, (ii) improved patient compliance, and (iii) efficient evaluation of new treatments. The objective of this pilot study was to use an investigational imaging technique of near-infrared (NIR) fluorescence imaging [18,19] to evaluate response of the lymphatic function to advanced PCD therapy in normal control subjects and in persons with BCRL.

2. Methods

Nine subjects were enrolled, 3 normal control subjects and 6 women diagnosed with unilateral BCRL, under a combination, Phase 0 IND #: 102,765; Table 1 summarizes the subject demographics. After informed consent was obtained, the subjects received NIR-fluorescent contrast injections, and were imaged for approximately 2.5 hours, during which time PCD treatment occurred (schematic of timeline shown in Fig. 1). Vital signs were monitored during imaging and a follow up phone call was made 24 hours after injections began to monitor adverse events. No adverse events occurred.

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Table 1. Study subject demographics

Subject ID	Sex	Age	PCD Arm	BCRL	Months post diagnosis	Stage at diagnosis	Surgical intervention*	Nodes removed*
BCRL 1	F	51	L	Y	13	I	Mastectomy	Biopsy
BCRL 2	F	58	L	Y	16	I	Lumpectomy	Lymphectomy
BCRL 3	F	51	R	Y	7	II	Mastectomy	
BCRL 4	F	57	R	Y	63	II	Mastectomy plus Radiation	
CTL 1	F	50	R	N	N/A			
BCRL 5	F	65	L	Y	26	I	Mastectomy	
CTL 2	M	24	R	N	N/A			
BCRL 6	F	58	R	Y	56	II	Mastectomy	
CTL 3	F	54	L	N	N/A			

* indicates as reported by the subject

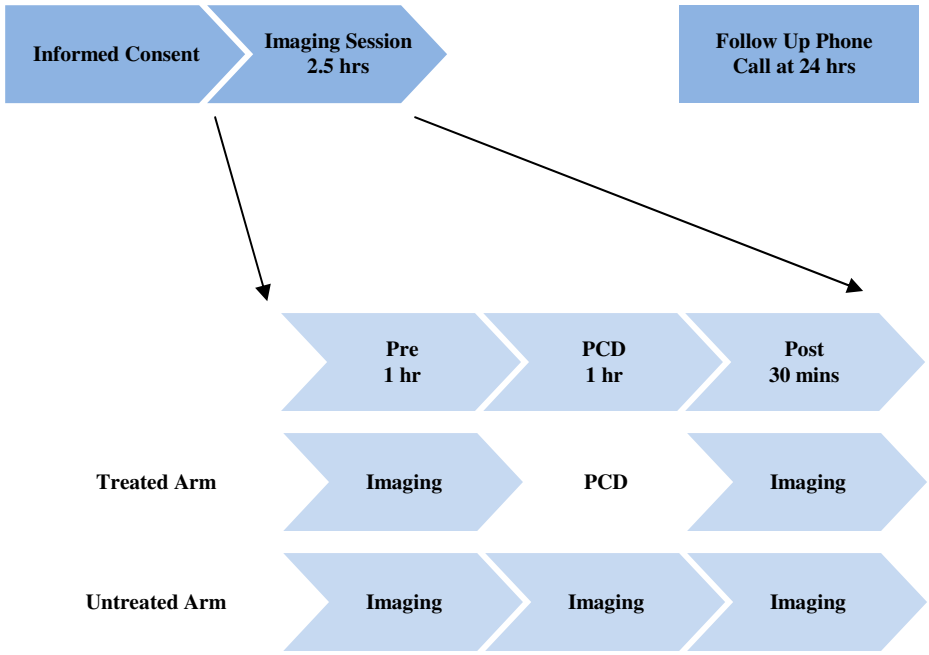

Fig. 1. Timeline for subjects participating in study.

For fluorescent contrast, subjects received up to 6 intradermal injections of 25 µg of Indocyanine Green, USP, (ICG, PULSION Medical Systems AG, Munich, Germany), diluted in 100 µL of saline in each arm. Injection sites were located on the lateral hand (two), on the medial wrist (up to two), and over the lateral and medial antibrachial muscles (up to two). Two custom-built, NIR optical imaging systems were used simultaneously and independently to image both arms of the subject. The imaging systems have been described previously [20,21] but briefly consist of: (i) a 785 nm NIR laser diode, illuminating tissues at fluencies of <1.9 mW/cm^2 over as great as 900 cm^2 area and (ii) a NIR-sensitive intensified charge coupled device (ICCD) camera outfitted with holographic and bandpass filters to efficiently collect fluorescent light at 830 nm, Fig. 2 presents a schematic of the imaging system. All subjects were placed in a supine position and, immediately following agent administration, were imaged for approximately one hour to determine the baseline lymphatic flow and

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function in each arm prior to PCD treatment. During the one hour-long PCD treatment, one imaging system was used to image the contralateral, untreated arm to determine if the treatment caused a systemic effect on the lymphatic system. Because the PCD garment prevented incident excitation of tissue surfaces, no imaging was performed on the treated arm during treatment. After PCD treatment, both imaging systems were again used to determine the effects of PCD treatment on the treated and untreated arms.

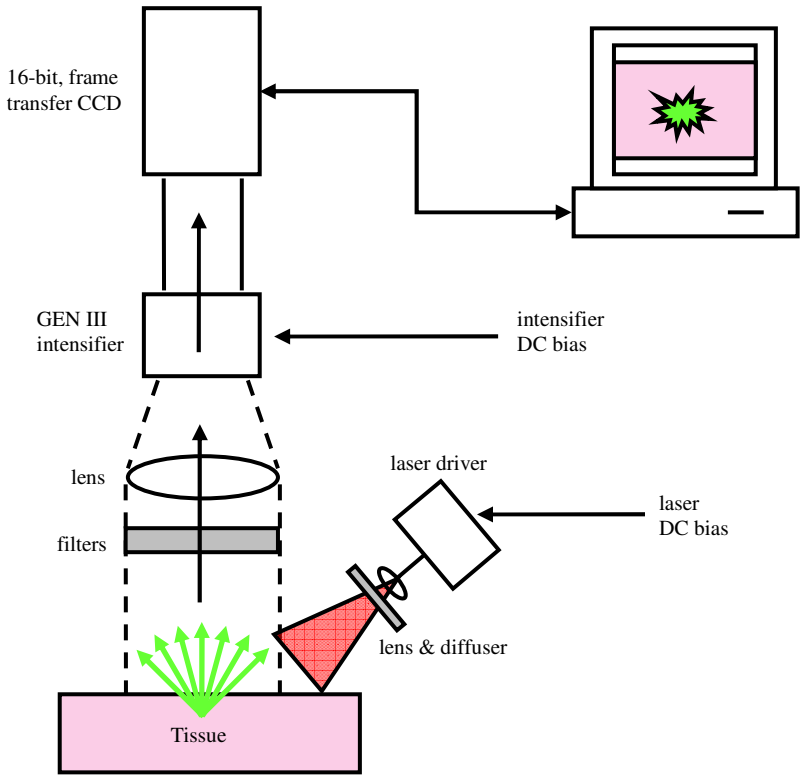

Fig. 2. Schematic of the imaging system, which includes (i) a diffused 785 nm NIR laser with a laser clean up filter, (ii) a NIR-sensitive ICCD camera, (iii) holographic and bandpass filters to efficiently collect fluorescent light at 830 nm, and (iv) a computer to control the system and collect the images.

PCD treatment was applied by the Flexitouch® system (Tactile Systems Technology, Inc., Minneapolis, MN), an automated, calibrated, and programmable PCD specifically designed to treat lymphedema [21,22]. The garments were fitted specifically to each subject according to manufacturer instructions, and placed around the trunk, chest and arm. The PCD treatment began with

- initial truncal decongestion lasting approximately 12 minutes during which a gradient pressure was applied to the trunk and chest areas in a preparative phase that emptied draining basins; and continued with
- initial arm preparation, lasting approximately 18 minutes, during which a gradient pressure was applied to the more proximal areas of the arm; and finally culminating with

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- arm and trunk drainage, lasting approximately 30 minutes during which concerted cycles of mild variable pressure and release were applied sequentially to the limb and trunk in a distal-to-proximal manner.

By initially clearing the adjacent quadrant(s), ipsilateral truncal quadrant, and more proximal areas of existing or normal lymph load, the advanced PCD used mimics MLD, and presumably enables receiving lymphatic basins to more effectively receive and process the lymphatic load from the affected arm.

Image analysis for apparent lymphatic velocity and rate of propulsion was performed as described previously [21]. Briefly, images were previewed in ImageJ (Version 1.43i, National Institutes of Health, Bethesda, MD) to identify subsets with notable lymphatic architecture and with lymphatic flow. Lymphatic transport is defined herein as a "packet" of ICG that travels along a lymphatic vessel. In the images where lymphatic transport was observed, a custom MATLAB (Version 7.6.0 R2008a, Mathworks, Natick, MA) program was used to identify lymphatic vessels and measure the fluctuation of fluorescent intensity across regions of interest over time in order to calculate the apparent velocity of each "packet" of ICG-laden lymph. Positive apparent velocities designate proximal flow, whereas negative values signify distal movement away from the axilla. Rates of lymphatic propulsion were determined by counting the number of propelled "packets" over a period of time. Data of apparent lymph velocity and propulsion rate were grouped into pre-, during, and post-PCD treatment for both treated and untreated arms.

3. Results

Results from the control subjects are summarized in Figs. 3 and 7C. In every control subject, the rate of lymphatic propulsion increased during and post-treatment as compared to pre-treatment, as shown in Fig. 3A. There was no statistical difference in the mean velocities pre-, during, or post-treatment, as shown in Fig. 3B. Negative velocities (or distal movement of "packets") were observed before and during treatment, but none were observed after treatment. Figure 4 displays pre- (4A, Media 1) and post- (4B, Media 2) treatment movies from one control subject, CTL 3, showing improvement in rate of lymph propulsion as well vessel recruitment. Pre-treatment, only one lymphatic vessel clearly delineated with ICG (4A), while post-treatment, a second vessel is well defined (4B). Vessel recruitment was seen in 2 of the 3 control subjects. Lymphatic function improved in all control subjects, as indicated through increased rates of lymphatic propulsion and/or vessel recruitment. Figure 7 C displays the statistically significant difference between the rates of propulsion in the treated arms pre- and post-treatment ($p < 0.05$). The rate of propulsion tended to increase in the untreated arms of control subjects, not only after PCD treatment, but also during the initial preparation phases, suggesting improved systemic lymphatic drainage associated with advanced PCD (see Fig. 9).

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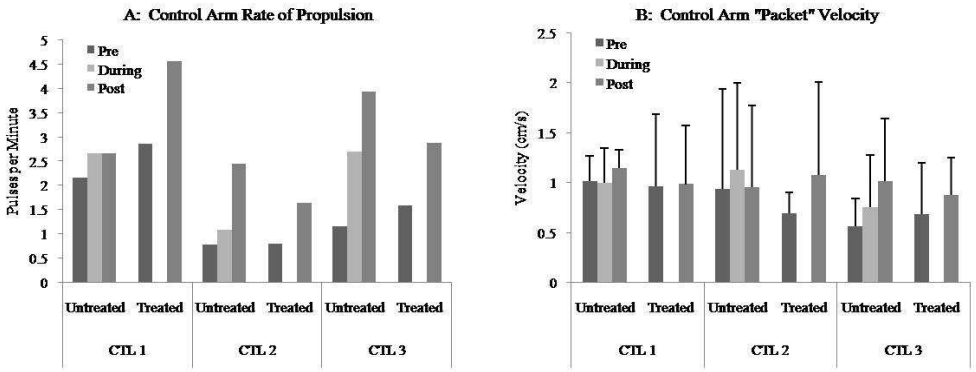

Fig. 3. Comparison of rate of lymph propulsion (A) and velocity (B) in untreated and treated arms of normal control subjects.

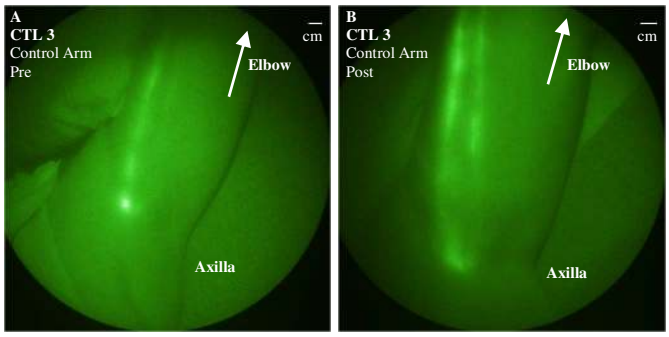

Fig. 4. The upper arm and axilla of Control Subject 3 before PCD treatment (A, Media 1) and after PCD treatment (B, Media 2). After treatment, recruitment of vessels and increased rate of propulsion are observed.

In the affected arm of the lymphedema subjects rate of propulsion and velocity analyses were not possible due to the abnormal lymphatic architecture and obscuration of functional lymph vessels by diffuse and dense ICG-laden dermal lymph vessels within the arm. Proximal advancement of ICG towards the axilla or shoulder was nonetheless observed after treatment in the affected arms of 4 of 6 BCRL subjects and was considered evidence of fluid drainage and stimulation of lymphatic function. Figure 5 presents pre- (A, B, C) and post- (D, E, F) treatment images from three BCRL subjects. Before treatment, ICG was present in two subjects up to the elbow (5A and 5B); after treatment, the ICG travelled proximally above the elbow into the upper arm (5D and 5E). The proximal movement is highlighted by a white circle denoting the same injection site (5B and 5E) seen in each image. In the third subject, prior to treatment, the ICG fluorescence was only present at the injection site (5C), while after PCD treatment, the ICG had moved proximally throughout the entire arm (5F). In 2 of the 6 lymphedema subjects, the proximal movement of ICG continued into the axilla and shoulder, as shown in Fig. 6 (post-treatment proximal movement into the axilla (6B) and shoulder and back (6C) as compared with pre-treatment (6A)). Pre-treatment, ICG fluorescence was not detected in the shoulder or lateral upper arm of any subjects in the study.

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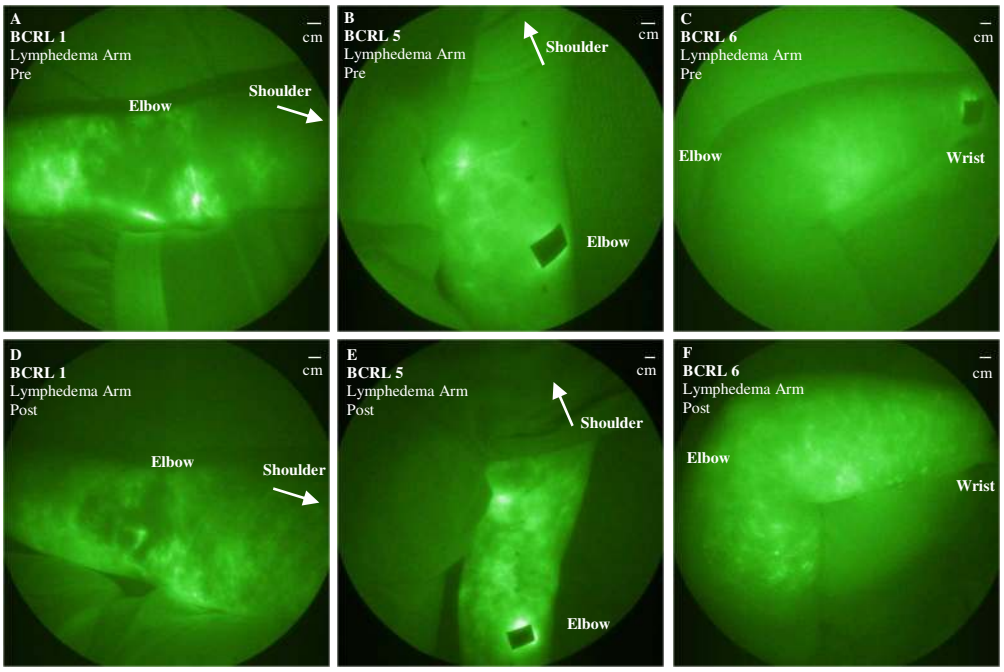

Fig. 5. Advancement of ICG in the affected arms of 3 lymphedema subjects after PCD treatment. In two subjects, BCRL 4 and 5, ICG is not present above the elbow pre-treatment (A and B, respectively), whereas the ICG has advanced past the elbow and into the upper arm post-treatment (D and E). In another subject, BCRL 6, prior to treatment (C), the ICG is present only at the injection site, and after treatment (F), the ICG has spread proximally through the arm.

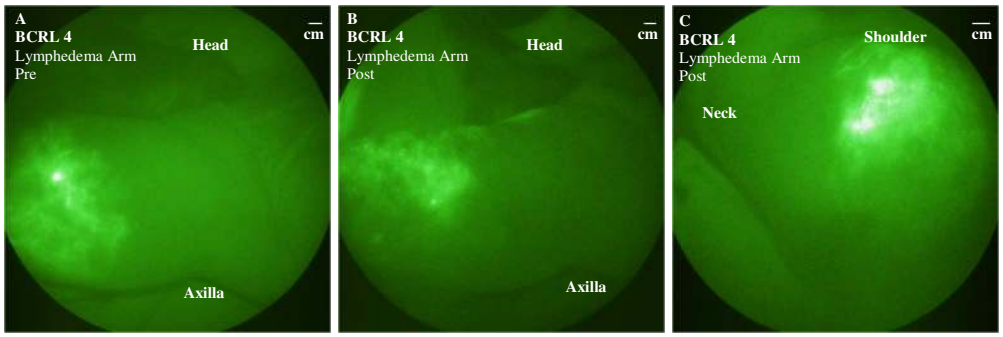

Fig. 6. Pre- (A) and post- (B and C) PCD treatment images of affected arm of lymphedema subject, BCRL 4. Lymphatic fluid moved towards the axilla (B) and into the shoulder (C) after PCD treatment, as compared with pre-PCD treatment (A).

Results from the asymptomatic arms of the BCRL subjects are summarized in Fig. 7. In every BCRL untreated arm, the rates of lymphatic propulsion increased post-treatment as compared to pre-treatment and in 4 of 6 arms, the rates increased during treatment as compared to pre-treatment (Fig. 7A). There was no statistical difference in the mean velocities pre-, during, or post-treatment in the BCRL subjects, as seen in Fig. 7 B. As seen in the control subjects, negative velocities were observed in asymptomatic arms before and during treatment, none were observed after treatment. Figure 7C displays the statistically significant difference between the propulsive rates measured, pre- and post-treatment as well as during

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treatment and post-treatment ($p < 0.05$). This statistical difference is especially notable since there was not a significant difference in the control, untreated arms. Figure 8 displays the top of the hand and wrist of one BCRL subject, BCRL 1, pre- (8A, Media 3), during (8B, Media 4), and post- (8C, Media 5) PCD treatment. The videos show increased rate of propulsion during (8B) and after (8C) treatment as compared to before treatment (8A). Unlike in the control subjects, in the untreated arms of the BCRL subjects, there was a significant increase in the rates of propulsion ($p < 0.05$) during the initial preparation phases and the arm drainage phase of treatment (Fig. 9). This may suggest a systemic compensation mechanism in BCRL subjects in response to preparatory phases of the PCD treatment. Such a compensation mechanism may not be needed in normal, healthy subjects with functioning lymphatics. Lymphatic function improved in all BCRL subjects, as indicated through increased frequency of lymph propulsion in the untreated, asymptomatic arms and proximal movement of ICG in the treated, symptomatic arms.

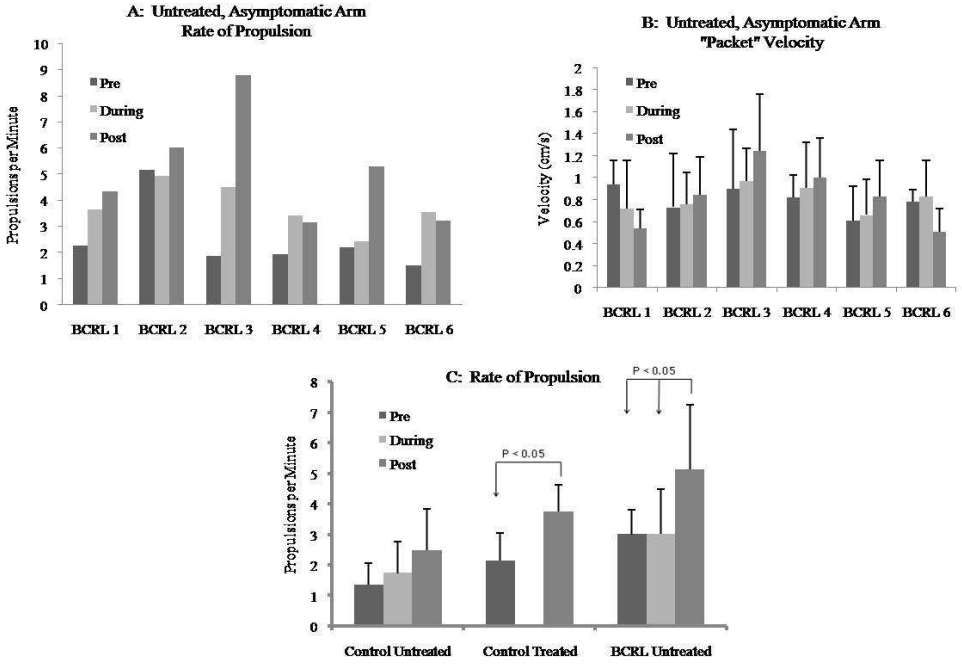

Fig. 7. Comparison of lymph propulsion rate (A) and velocity (B) in asymptomatic arm of BCRL subjects and summary of all rate of propulsion results (C).

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Fig. 8. The top of the hand and wrist of the asymptomatic arm of subject BCRL 1 pre- (A, Media 3), during (B, Media 4), and post- (C, Media 5) PCD treatment. The videos display an increased rate of lymphatic propulsion during (B, Media 4) and after (C, Media 5) PCD treatment when compared with before treatment (A, Media 3).

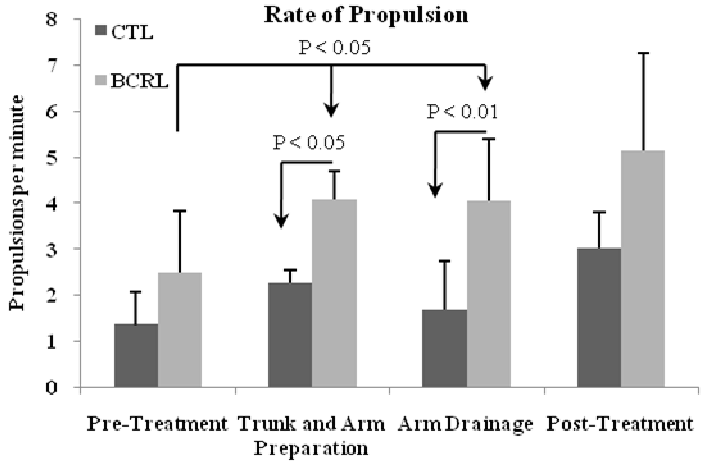

Fig. 9. Rate of propulsion of "packets" in contralateral arm (1) pre massage, (2) during the trunk and arm preparation phase, (3) during the arm drainage phase, and (4) after the PCD treatment.

4. Discussion

The burden of BCRL management is eased with early detection [9,23,24], and adherence to treatment plans [14]. Symptomatic improvement has been demonstrated to varying degrees by different treatment options: CDT, microsurgery, PCDs and structured exercise [14,25–28]. Heretofore, no method existed to directly and immediately evaluate improvement in lymphatic function; therefore, there has been no mechanism by which to assess efficacy of clinical intervention. Using the same approach as described herein, Tan, *et al.,* recently demonstrated the first case of real-time, direct measurement of lymphatic function in lymphedema subjects after MLD treatment [28]. The treatment provided by some PCD systems, such as the Flexitouch, is intended to replicate the magnitude, timing, and sequencing pattern of the gently applied pressures of MLD [15], allowing lymphedema patients to receive MLD at home. Ridner, *et al.,* (2008) found that after incorporating PCD into home, daily lymphedema care, 95% of patients reported limb volume reduction or maintenance [26]. When compared to women with BCRL who used self-administered MLD, significantly greater limb volume reductions and weight loss occurred when using the same PCD system [29] studied herein with NIR fluorescence imaging.

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Within the current study, the lymphatic function improvement that was imaged in both treated and untreated arms of control subjects is an indication that PCD treatment systemically stimulated the lymphatic system. Unfortunately, the BCRL subjects imaged in this study had BCRL diagnosed 7 – 63 months prior to the study, which may have contributed to the abundance of aberrant lymphatic architecture in their symptomatic arms that could have obscured the imaging of deeper functioning vessels. Another explanation may be the progressive loss of functioning lymphatic vessels within the affected limbs. In an earlier study (Rasmussen et al. 2009, 2010), NIR fluorescence imaging captured aberrant lymphatic function in a woman with unilateral BCRL following bilateral mastectomies, where her asymptomatic arm displayed regions of lymphatic hyperplasia connected by functioning dilated lymphatic vessels that displayed reflux or distal transport in addition to proximal flow [18,21].

Longitudinal NIR imaging studies are needed to determine whether such lymphatic abnormalities are present prior to the onset of symptoms and progress with time to the phenotypes presented herein. An understanding of the progression of BCRL is needed to effectively employ evidence-based practices to prevent onset and better manage the disease. For example, Torres Lacomba, *et al*., demonstrated the effectiveness of prophylactic CDT in delaying the onset and possibly reducing incidence of BCRL [30]. The option of home-use of a PCD device could have significant implications as a prophylactic device for women who are not diagnosed with BCRL, but who are at risk for the disease. Until now there has been no diagnostic technique with sufficient spatial and temporal resolution to directly assess or longitudinally image change in lymphatic function and architecture with progressive disease in order to justify the addition of prophylactic treatments. Given the variability of treatment response, a diagnostic technique to assess individual treatment efficacy could improve the efficacy of prescribed treatments and patient compliance, resulting in better management of the disease. In summary, the trends in this pilot study provide (i) evidence of the efficacy of advanced PCDs with truncal treatment, (ii) data to power future evidence-based efficacy trials, and (iii) justification for longitudinal studies to better deploy existing and new treatments to better manage and possibly prevent BCRL.

NIR fluorescence imaging offers unique advantages for imaging the lymphatic system. First of all, the technology involves microdosing of fluorophore, mitigating the potential for adverse events following repeated imaging and enabling quantification of dynamic lymphatic transport. We have observed that the dynamical motion for quantification of lymphatic function seems to depend upon small doses of dye. At high doses of NIR dye, the lymphatic vessels appear to be saturated and stained, preventing observation of propulsive “packets” of lymph flowing through lymphatic vessels. While there have been a number of planar NIR imaging devices described in the literature (for review see Marshall, et al., 2010), lack of sensitivity prevent their use following microdose administration of dye [31]. The large mg amounts of dye may be responsible for the lack of dynamical lymph motion observed using these devices. Secondly, microdosing, defined by the FDA as 1/100th of a pharmacological dose of a labeled therapeutic agent, or less than 100 μg of a peptide- or 30 nanomoles of a protein- based imaging agent, efficiently allows for replacement of dim ICG with brighter, “first-in-human” NIR fluorophores. Previously, we have shown as little as 10 μg of ICG can be detected non-invasively [20] establishing the feasibility for detecting microdosages of brighter, “first-in-humans” NIR agents. Finally, since instrument response falls precipitously with time-dependent operation, NIR optical tomography in both time and frequency-spaces will likely require high sensitivity for clinical relevance [19]. By focusing upon improved sensitivity, we have opened up opportunities to (i) non-invasively visualize lymphatic function in humans; (ii) introduce “first-in-humans” NIR imaging agents, and (iii) conduct tomographic imaging with time-dependent approaches.

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