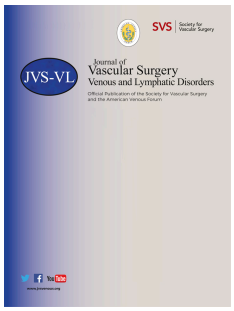
Journal Pre-proof



Safety and Effectiveness of a Novel Non-Pneumatic Active Compression Device for Treating Breast Cancer-Related Lymphedema, a Multi-center Randomized, Crossover Trial (NILE)

Stanley G. Rockson, MD, Pat W. Whitworth, MD, Andrea Cooper, PT, CLT, Sarah Kania, DPT, CLT, Heidi Karnofel, DPT, CLT, Michelle Nguyen, DPT, CLT, Kristin Shadduck, PT, Phyllis Gingerich, RN, BSN, CLT, Jane Armer, RN, PhD, CLT

PII: S2213-333X(22)00338-9

DOI: https://doi.org/10.1016/j.jvsv.2022.06.016

Reference: JVSV 1463

To appear in: *Journal of Vascular Surgery: Venous and Lymphatic Disorders*

Received Date: 13 March 2022

Revised Date: 6 June 2022

Accepted Date: 15 June 2022

Please cite this article as: S.G. Rockson, P.W. Whitworth, A. Cooper, S. Kania, H. Karnofel, M. Nguyen, K. Shadduck, P. Gingerich, J. Armer, Safety and Effectiveness of a Novel Non-Pneumatic Active Compression Device for Treating Breast Cancer-Related Lymphedema, a Multi-center Randomized, Crossover Trial (NILE), *Journal of Vascular Surgery: Venous and Lymphatic Disorders* (2022), doi: https://doi.org/10.1016/j.jvsv.2022.06.016.

Safety and Effectiveness of a Novel Non-Pneumatic Active Compression Device for Treating Breast Cancer-Related Lymphedema, a Multi-center Randomized, Crossover Trial (NILE)

R2WC: 223/2766

Stanley G. Rockson MD[1], Pat W. Whitworth MD[2], Andrea Cooper PT, CLT[2], Sarah Kania, DPT, CLT[3], Heidi Karnofel, DPT, CLT[4], Michelle Nguyen, DPT, CLT[5], Kristin Shadduck, PT[5], Phyllis Gingerich, RN, BSN, CLT[6], Jane Armer, RN, PhD, CLT[7]

[1]Cardiovascular Medicine, Stanford University, Stanford, CA

[2]Nashville Breast Center, 2004 Hayes St. Nashville TN

[3]Good Samaritan Hospital - Mission Oaks Campus, 15891 Los Gatos Road, Los Gatos, CA

[4]Adventist Health Bakersfield, 2620 Chester Ave., Bakersfield, CA

[5]PT Works, Palo Alto, CA

[6]Ginger-K Cancer Center, Morgan Hill, CA

[7]Ellis Fischel Cancer Center, University of Missouri, Columbia, MO

Corresponding Author:

Stanley G. Rockson, MD

Falk Cardiovascular Research Center, Stanford University School of Medicine,

Stanford, CA 94305

rockson@stanford.edu

t: 650.725.7571

f: 650.725.1599

Word Count: 2,282

Presentation Information. NILE interim results were presented at AVLS in Denver in October 2021 and at ILF in Copenhagen in November 2021.

Key words. Breast cancer-related lymphedema, cancer survivorship, quality of life, medical device

ARTICLE HIGHLIGHTS

Type of Research: Prospective, multi-center, randomized, crossover trial

Key Findings: Data from 50 adult women with unilateral breast cancer-related lymphedema demonstrate greater improvements in quality of life and limb edema with a novel non-pneumatic compression device than with a commercially available advanced pneumatic compression device. Patients were also significantly more adherent to self-care treatment (95.6% vs. 49.8%) and more satisfied (90% vs. 14%) with the novel device.

Take home Message: The novel non-pneumatic device is safe and effective for reducing limb volume in breast cancer-related lymphedema, and was more effective and resulted in higher adherence to self-care interventions and greater satisfaction than a commercially available advanced pneumatic compression device.

Table of Contents Summary

A multi-center randomized crossover trial demonstrated that a novel non-pneumatic compression device was more effective and resulted in greater adherence to self-care interventions and satisfaction than a commercially

available advanced pneumatic compression device for treating breast cancer-related lymphedema.

Abstract

Objective. Advanced pneumatic compression devices (APCDs) have been shown to be an effective intervention for lymphedema when used as part of a self-care maintenance treatment regimen. However, adherence to self-care is poor, and APCDs require patients to be immobile during treatment. We sought to evaluate the safety and efficacy of a novel non-pneumatic compression device (NPCD) for treating lymphedema versus an APCD.

Methods. A randomized, crossover head-to-head investigation at five US sites in 2021. Patients were randomized to either the NPCD or a commercially-available APCD. Subjects used the randomly assigned initial device for 28 days with a 4-week washout period prior to a comparable 28-day utilization of the second device.

Results. Data from 50 adult women with unilateral breast cancer-related lymphedema (BCRL) were analyzed. When compared with the APCD, the NPCD was associated with greater mean reduction in limb edema volume (64.6% vs. 27.7%, $p<0.001$), significantly greater mean improvements in quality of life scores, greater adherence (95.6% vs. 49.8%, $p<0.001$), and greater satisfaction with the device (90% vs. 14%, $p<0.001$). Patients indicated that the NPCD facilitated exercise and was convenient for travel. No adverse events were reported.

Conclusions. The novel NPCD is an effective maintenance treatment for reducing limb volume in BCRL patients. The device was more effective than an APCD and resulted in higher adherence to self-care interventions and greater patient satisfaction.

Introduction

Each year there are 1.7 million new cases of breast cancer world-wide,[1] including approximately 270,000 in the US.[2] Cancer survivorship has increased dramatically in the past few decades. The cancer-related mortality rate in the US dropped 40% from 1989 to 2017;[2] it is estimated that more than 3.8 million women are currently living with a history of breast cancer in the US.[2] Targeted therapies that contribute to survivorship may also impose the risk of complications. As the number of breast cancer survivors grows, so does the frequency of these complications.

The disruption of the lymphatic system from cancer treatments can result in breast cancer-related lymphedema (BCRL), characterized by the accumulation of fluid and protein in the ipsilateral upper limb, with associated external swelling, pain, fatigue, restricted motion, and stiffness in the limbs.[3-8] Estimates of the risk of lymphedema following treatment for breast cancer vary depending on diagnostic criteria and follow-up timeframe,[9-11] but multiple studies define the 5-year incidence to be more than 40%.[9, 12] Lymphedema can cause inflammation and fibrosis in the affected limb. Impaired regional immune traffic predisposes to recurrent soft-tissue infection.[13-15] Patients may also experience physical discomfort and a variety of functional impairments.[3, 4, 6, 16-18]

Patients with BCRL often experience anxiety, sadness, fear, and self-consciousness that produce decrements in social and psychological well-being, negatively impacting quality of life (QOL).[4, 6, 8, 19] BCRL is associated with significantly higher medical expenditures overall[15] and higher out-of-pocket costs[20] when compared to patients with breast cancer without lymphedema. Additionally, BCRL can negatively impact patients' work performance, causing distress and hindering their careers.[21, 22]

BCRL is a chronic condition without curative therapy. Therefore, the goal of treatment is to maintain limb health and avoid related complications. Management of BCRL typically involves multiple components. This complex decongestive therapy includes manual lymphatic drainage, the use of compression garments, skin care, and physical exercise.[23] The adjunctive use of pneumatic compression devices (PCDs) as part of a self-care regimen has been shown to reduce limb volume, improve symptoms, and enhance QOL,[24-27] and may help reduce BCRL-related complications and related healthcare utilization and costs.[26-30] Unfortunately, adherence to BCRL self-care is poor; multiple studies have observed that fewer than one-third of patients reach the threshold of 75% adherence.[31-33] Numerous barriers to adherence have been identified, including symptom burden, patient knowledge of lymphedema, complexity of the treatment regimen, and the time required and/or interference with daily activities.[33-35]

The Dayspring® non-pneumatic compression device (NPCD) is an FDA-cleared prescription-only wearable compression system (Figure 1). The device uses Flexframes™-shape memory alloy (SMA)-based actuators and a mobile power source that are programmed to deliver gradient sequential compression. The physical principle of providing pressure underlying both Flexframes and pneumatic compressions is the same, which is force is applied over a given area or $P = F/A$. Flexframes contract and relax to provide pressure using energy from a current that flows through the resistance of the SMA material with a temporal modulation. The number of compression segments in the NPCD (up to 14) is similar to the number available in traditional PCDs (up to 12). In a recent open-label 28-day pilot study of 40 subjects with BCRL, the subjects that utilized the NPCD experienced improvements in limb volume and QOL, and displayed a 98% adherence to therapy.[36] However, a direct, head-to-head comparison of the novel device to a traditional PCD is necessary to demonstrate its clinical non-inferiority. In the current study, we seek to

evaluate the efficacy of, and patient experience with, the NPCD in comparison to that of a commercially available advanced pneumatic compression device (APCD).

Methods

Study Design and Patient Population

This was a multi-center, randomized, crossover head-to-head trial (ClinicalTrials.gov NCT04908254 https://clinicaltrials.gov/ct2/show/NCT04908254). Recruitment began in January of 2021 and occurred at five private lymphedema clinics associated with cancer care centers in the US, including three in California, one in Ohio, and one in Tennessee. The study was approved by the WCG Institutional Review Board. Screening occurred within the 90 days prior to enrollment. Adults aged >18 years, with a diagnosis of primary or secondary unilateral upper extremity edema were eligible. Exclusion criteria included any systemic disorder that might contraindicate sequential compression therapy, including the presence of active cellulitis, open or partially healed wounds. Also excluded were potential subjects with lipedema, active or recurrent cancer (defined as < three months since completion of cancer therapeutics), an acute infection within the previous four weeks, active venous thromboembolic disease within the previous six months, pulmonary edema, uncontrolled congestive heart failure, chronic kidney disease with renal failure, seizure disorder, poorly controlled asthma, or any other condition where augmented venous and lymphatic return might be undesirable. Women who were pregnant, planning a pregnancy, or nursing at study entry and any subjects who had participated any clinical trial of an investigational substance or device during the previous 30 days were also excluded, as were any potential subjects with a cognitive or physical impairment that would interfere with appropriate use of the device.

After informed consent was obtained, the subjects were instructed to discontinue any current pneumatic compression treatment(s) for lymphedema for one month prior to the device trial. Data regarding the type or length of use of prior pneumatic compression were not collected. They were instructed to continue the use of static compression sleeves and/or manual lymph drainage procedures, as previously prescribed. All subjects were taught how to don the study device garments, including placement, duration, and device activation.

Subjects were randomized by each site using a computer-generated block randomization schedule to either the NPCD or a commercially available advanced PCD (APCD – model Flexitouch Plus, PG32-G3) that is FDA-cleared for the same indications as the novel NPCD. All patients used the same commercially available APCD. They were instructed to use the assigned compression device once daily on the study limb only, for a minimum of 60 minutes. Study measures were recorded at day 0 and day 28. Following day 28, there was a 4-week washout period without any use of an active compression device. Following completion of washout, subjects crossed over to the alternate compression device for the next 28 days of use, with volume measurement recorded at day 0 and 28 of that usage.

Measures and Statistical Analysis

This study was designed with the hypothesis that the NPCD is non-inferior to the APCD in reducing edema volume in lymphedema patients, with a non-inferiority primary endpoint for changes in edema volume. We used results from a previous open-label study of 40 patients[36] to estimate that a sample size of at least 30 would be adequate to demonstrate non-inferiority in a randomized cross-over design, and that a sample size of 50 would allow us to demonstrate non-inferiority of changes in affected limb volume as well.

Limb volume quantitation was performed by trained therapists using a calibrated tape measure to quantitate limb circumference at the wrist at the ulnar styloid process and at 4 cm increments to the axilla. Volume (V) was calculated based on a truncated cone cylindrical segment analysis. Both upper extremities were measured. Volume responses to the compression regimens were quantitated as a calculated change in the measured edema volume:

$$\Delta V\ (\%) = [(V_L - V_N)_{pre} - (VL - VN)_{post}]/\ (VL - VN)_{pre} * 100$$

where V_L represents the measured volume of the lymphedematous upper extremity and V_N represents the measured volume of the contralateral normal arm.

The primary outcome assessed the impact of the two compression devices upon these measured volume differences from pre-treatment (day 0) to post-treatment (day 28). Responders were defined as those who experienced >2% reduction in edema volume.

QOL was measured using the Lymphedema Quality of Life Questionnaire (LYMQOL),[37] a 20-item validated disease-specific QOL tool, administered at days 0 and 28 for each device treatment period. LYMQOL assesses the impact of lymphedema on QOL through an overall QOL scale (scored 1-10) and four subscales: symptoms (pain, swelling, and numbness), body image/appearance, function (activities of daily living such as eating, writing, and dressing), and mood (sleep disruption, depression, and irritability). The subscales are scored from 1 (not at all) to 4 (a lot). The total score is calculated by adding all items and dividing by the total number of items. The subscales reflect improvement as a reduced score, whereas the overall QOL scale reflects improvement with a higher score. Changes from day 0 to day 28 for the total score and each subscale score were calculated. Tabulation of the QOL responses was done while blinded to the treatment arm.

Secondary outcome measures included patient-reported treatment adherence (measured as the percent of total prescribed hours), patient-reported usage details including activity, convenience, adjuvant use of static compression sleeves, device preference (measured from patient survey responses at the end of the study, see the Supplemental Material for the survey questions), and the occurrence of any safety events or adverse events. Changes in outcomes from day 0 to 28 were evaluated using paired t-tests; statistical significance was defined at the alpha = 0.05 level.

Results

Fifty-two (52) subjects were enrolled across five sites (Figure 2). All subjects were women with ages ranging from 29 to 84 years. Almost three-fourths were Caucasian (73.1%); 13.5% were Asian, 7.7% African American, and 5.8% Hispanic. The right upper extremity was affected three times more frequently than the left (75% versus 25%). All enrolled subjects were diagnosed with secondary lymphedema from breast cancer and none had primary lymphedema. The average time since cancer-related surgery or radiation was approximately five years, and the average time since lymphedema diagnosis was approximately 4.5 years (Table 1). All subjects were utilizing static compression garments at the time of enrollment. Two patients were lost to follow-up, so that primary and secondary outcomes were assessed for 50/52 subjects.

Twenty-three patients were randomized to receive the novel device first and 27 to receive the APCD first. When comparing these groups there were no significant differences in mean age (60.5 versus 60.3 years, $p = 0.9531$), percent non-White race (30.4% versus 25.9%, $p = 0.9698$), mean months since surgery or radiation (76.5 versus 50.2, $p = 0.2411$), mean months since lymphedema diagnosis (61.4 versus 48.2, $p = 0.4065$), or months between surgery/radiation and lymphedema (18.0 versus 4.29, $p = 0.3396$). There was also no significant difference in Day 0

edema, calculated as the difference in volume between the affected and unaffected arm (293.5 cm^3 versus 284.2 cm^3, p = 0.9276).

With the NPCD, subjects experienced a mean reduction in edema volume in the affected arm of 64.6% (95% confidence interval [CI] = 31.71, 97.58), compared with 27.7% (95% CI = 4.80, 60.14) with the APCD ($p<0.05$, Figure 3a), resulting in a significantly higher overall response rate (88% versus 42%, $p<0.05$, Figure 3b). Volume reduction of the unaffected limb did not differ significantly between devices. With these observations, the primary endpoint of the study was achieved: the NPCD was found to be non-inferior to the APCD in reducing edema volume in lymphedema patients and exceeded the capacity of the APCD to produce volume reduction of the affected limb. No serious adverse events were reported for either device and no additional hand or chest swelling were observed with either device.

The 4-week wash-out period between devices appeared to be adequate as there was no significant difference in the volume of the affected arm at the start of device use (mean difference between Day 0 of the first device and Day 0 of the second device = 35.56 cm^3, p = 0.2772) or in the level of edema (mean difference = 37.52 cm^3, p = 0.2813).

Mean ± standard deviation reported adherence to the prescribed use of 60 minutes per day was 95.6 ± 7% with the NPCD, compared with 49.8 ± 26% with the APCD ($p<0.01$, Figure 3c).

When asked about any differences in use of compression sleeves over the course of each device's use, 86% of patients reported "less" use during the NPCD, compared with 0% reporting "less" use when using the APCD. Additionally, subjects experienced a statistically significant mean 2.44-point increase (improvement) in their overall LYMQOL scores at day 28 of the NPCD use ($p <0.05$, Figure 3d). By comparison, while after the APCD, there was no significant change in overall LYMQOL score. Within the LYMQOL subscales, a significant improvement

in all four subscales (function, mood, appearance, and symptoms) was observed after use of the NPCD. In contrast, all subscale scores worsened during use of the APCD (Table 2).

At the conclusion of the study, 100% of participants indicated that they were able to be active or exercise while using the NPCD, while 0% had a comparable result from the APCD. Similarly, 100% of participants reported that the NPCD was portable or convenient for travel, compared with 0% for the APCD. When asked about their overall satisfaction with the devices, 90% were "somewhat" or "very" satisfied with the NPCD compared with 14% for the APCD; 90% of participants preferred the NPCD to the APCD for daily use (Table 3).

Discussion

Previous studies have highlighted the importance of adherence to self-care in the treatment and management of chronic lymphedema. Patients with BCRL face an increased risk of infection[13-15] and experience considerable detriments to physical functioning, quality of life, and emotional well-being.[8, 17, 19] Those with more symptoms often experience greater declines in QOL.[5] The likelihood of deterioration in the volume response after completion of the initial decongestive physiotherapy is significant; one study observed a mean limb volume increase of 84 ml (95% CI: 56-113) at the end of one year with a 10% volume increase in 52% of patients.[38] Non-compliance to low stretch bandage and elastic sleeve were risk factors for an increased lymphedema after 1-year of maintenance treatment (RR: 1.55 [95% CI: 1.3-1.76]; $P < 0.0001$ and RR: 1.61 (95% CI: 1.25-1.82); $P = 0.002$, respectively).

The use of adjunctive pneumatic compression has been shown to be effective in reducing symptoms, complications, and lymphedema-related healthcare utilization. In addition to improving lymphatic function,[24] their use has been associated with reductions in cellulitis and lymphedema-related health encounters[29, 30, 39] and with increased quality of life.[25, 28, 39]

Additionally, exercise as a treatment for lymphedema, when combined with compression therapy, has been shown to result in significantly greater reduction in limb volume than compression therapy alone.[40, 41] In BCRL specifically, exercise has been associated with improved outcomes.[42]

Unfortunately, adherence to self-care is poor, with adherence to PCD among the worst of all self-care treatments.[31] Manual lymphatic drainage requires in-person visits with certified therapists and compression garments require frequent replacements. PCDs require patients to be immobile for the entire duration of their use, which prohibits exercise and limits the mobility that is needed to perform daily activities. Therapy options that enable mobility and increase adherence may improve self-care effectiveness and improve results.

In the current study, the novel NPCD, which allows for more mobility and less disruption of daily activities than a current, marketed APCD, produced greater adherence and simultaneously achieved greater reductions in edema volume than did the APCD within the same subjects. In addition, subjects experienced greater improvements in QOL and reported higher satisfaction with the NPCD. Patients confirmed that the NPCD allowed them to exercise and that it was convenient for travel purposes. Furthermore, they overwhelmingly preferred it to the APCD. It should be noted that while the study criteria allowed for primary or secondary lymphedema, all enrolled patients had BCRL; therefore, no men and none with primary lymphedema were included. However, we believe our observed results are generalizable to these groups because the underlying mechanism of action and therapeutic benefits from the technology should comparably apply. With any cross-over design there is the potential risk of carry-over when subjects switch treatments. We observed no significant difference in the affected arm volume or edema volume prior to each device's use, suggesting that any carry-over effect is minimal. There could also be a

risk of carry-over for subjects who had used a device prior to the start of the study, as data on prior use of compression devices were not collected. However, subjects were instructed to stop any prior device use a month before the start of the study, a period of time that should be sufficient to minimize carry-over, as demonstrated by the 4-week wash-out period.

These results suggest that the NPCD is non-inferior to the APCD in reducing edema volume in lymphedema patients, and in fact, produced superior outcomes for volume reduction and symptom relief. Subjects are more adherent to therapy and more satisfied with the device than they are when using the APCD. Future studies will explore the impact of early intervention and will assess long-term adherence to the use of the device to prevent progression of lymphedema.

References

1. Ghoncheh M, Pournamdar Z, Salehiniya H. Incidence and Mortality and Epidemiology of Breast Cancer in the World. Asian Pacific journal of cancer prevention : APJCP. 2016;17(S3):43-6.

2. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast cancer statistics, 2019. CA: a cancer journal for clinicians. 2019;69(6):438-51.

3. Fu MR. Breast cancer-related lymphedema: Symptoms, diagnosis, risk reduction, and management. World journal of clinical oncology. 2014;5(3):241-7.

4. Dominick SA, Natarajan L, Pierce JP, Madanat H, Madlensky L. The psychosocial impact of lymphedema-related distress among breast cancer survivors in the WHEL Study. Psycho-oncology. 2014;23(9):1049-56.

5. Hormes JM, Bryan C, Lytle LA, Gross CR, Ahmed RL, Troxel AB, et al. Impact of lymphedema and arm symptoms on quality of life in breast cancer survivors. Lymphology. 2010;43(1):1-13.

6. Anbari AB, Wanchai A, Armer JM. Breast cancer-related lymphedema and quality of life: A qualitative analysis over years of survivorship. Chronic illness. 2021;17(3):257-68.

7. Burckhardt M, Belzner M, Berg A, Fleischer S. Living with breast cancer-related lymphedema: a synthesis of qualitative research. Oncology nursing forum. 2014;41(4):E220-37.

8. Taghian NR, Miller CL, Jammallo LS, O'Toole J, Skolny MN. Lymphedema following breast cancer treatment and impact on quality of life: a review. Critical reviews in oncology/hematology. 2014;92(3):227-34.

9. Armer JM, Stewart BR. Post-breast cancer lymphedema: incidence increases from 12 to 30 to 60 months. Lymphology. 2010;43(3):118-27.

10. Gillespie TC, Sayegh HE, Brunelle CL, Daniell KM, Taghian AG. Breast cancer-related lymphedema: risk factors, precautionary measures, and treatments. Gland surgery. 2018;7(4):379-403.

11. Torgbenu E, Luckett T, Buhagiar MA, Chang S, Phillips JL. Prevalence and incidence of cancer related lymphedema in low and middle-income countries: a systematic review and meta-analysis. BMC cancer. 2020;20(1):604.

12. Norman SA, Localio AR, Potashnik SL, Simoes Torpey HA, Kallan MJ, Weber AL, et al. Lymphedema in breast cancer survivors: incidence, degree, time course, treatment, and symptoms. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(3):390-7.

13. Chakraborty S, Davis MJ, Muthuchamy M. Emerging trends in the pathophysiology of lymphatic contractile function. Seminars in cell & developmental biology. 2015;38:55-66.

14. Douglass J, Graves P, Gordon S. Self-Care for Management of Secondary Lymphedema: A Systematic Review. PLoS neglected tropical diseases. 2016;10(6):e0004740.

15. Shih YC, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz TA, et al. Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: a 2-year follow-up study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(12):2007-14.

16. Ahmed RL, Prizment A, Lazovich D, Schmitz KH, Folsom AR. Lymphedema and quality of life in breast cancer survivors: the Iowa Women's Health Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(35):5689-96.

17. Chachaj A, Małyszczak K, Pyszel K, Lukas J, Tarkowski R, Pudełko M, et al. Physical and psychological impairments of women with upper limb lymphedema following breast cancer treatment. Psycho-oncology. 2010;19(3):299-305.

18. Fu MR, Rosedale M. Breast cancer survivors' experiences of lymphedema-related symptoms. Journal of pain and symptom management. 2009;38(6):849-59.

19. Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact of lymphedema: a systematic review of literature from 2004 to 2011. Psycho-oncology. 2013;22(7):1466-84.

20. Dean LT, Moss SL, Ransome Y, Frasso-Jaramillo L, Zhang Y, Visvanathan K, et al. "It still affects our economic situation": long-term economic burden of breast cancer and lymphedema. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2019;27(5):1697-708.

21. Boyages J, Kalfa S, Xu Y, Koelmeyer L, Mackie H, Viveros H, et al. Worse and worse off: the impact of lymphedema on work and career after breast cancer. SpringerPlus. 2016;5:657.

22. Fu MR. Women at work with breast cancer-related lymphoedema. Journal of lymphoedema. 2008;3(1):20-5.

23. Rockson SG. Lymphedema after Breast Cancer Treatment. The New England journal of medicine. 2018;379(20):1937-44.

24. Adams KE, Rasmussen JC, Darne C, Tan IC, Aldrich MB, Marshall MV, et al. Direct evidence of lymphatic function improvement after advanced pneumatic compression device treatment of lymphedema. Biomedical optics express. 2010;1(1):114-25.

25. Desai SS, Shao M, Vascular Outcomes C. Superior Clinical, Quality of Life, Functional, and Health Economic Outcomes with Pneumatic Compression Therapy for Lymphedema. Annals of vascular surgery. 2020;63:298-306.

26. Fife CE, Davey S, Maus EA, Guilliod R, Mayrovitz HN. A randomized controlled trial comparing two types of pneumatic compression for breast cancer-related lymphedema treatment in the home. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2012;20(12):3279-86.

27. Ridner SH, McMahon E, Dietrich MS, Hoy S. Home-based lymphedema treatment in patients with cancer-related lymphedema or noncancer-related lymphedema. Oncology nursing forum. 2008;35(4):671-80.

28. Blumberg SN, Berland T, Rockman C, Mussa F, Brooks A, Cayne N, et al. Pneumatic Compression Improves Quality of Life in Patients with Lower-Extremity Lymphedema. Annals of vascular surgery. 2016;30:40-4.

29. Brayton KM, Hirsch AT, PJ OB, Cheville A, Karaca-Mandic P, Rockson SG. Lymphedema prevalence and treatment benefits in cancer: impact of a therapeutic intervention on health outcomes and costs. PloS one. 2014;9(12):e114597.

30. Karaca-Mandic P, Hirsch AT, Rockson SG, Ridner SH. The Cutaneous, Net Clinical, and Health Economic Benefits of Advanced Pneumatic Compression Devices in Patients With Lymphedema. JAMA dermatology. 2015;151(11):1187-93.

31. Brown JC, Cheville AL, Tchou JC, Harris SR, Schmitz KH. Prescription and adherence to lymphedema self-care modalities among women with breast cancer-related lymphedema. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2014;22(1):135-43.

32. Brown JC, Kumar A, Cheville AL, Tchou JC, Troxel AB, Harris SR, et al. Association between lymphedema self-care adherence and lymphedema outcomes among women with breast cancer-related lymphedema. American journal of physical medicine & rehabilitation. 2015;94(4):288-96.

33. Ostby PL, Armer JM. Complexities of Adherence and Post-Cancer Lymphedema Management. Journal of personalized medicine. 2015;5(4):370-88.

34. Alcorso J, Sherman KA, Koelmeyer L, Mackie H, Boyages J. Psychosocial factors associated with adherence for self-management behaviors in women with breast cancer-related lymphedema. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2016;24(1):139-46.

35. Zhao H, Wu Y, Zhou C, Li W, Li X, Chen L. Breast cancer-related lymphedema patient and healthcare professional experiences in lymphedema self-management: a qualitative study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2021.

36. Rockson SG, Karaca-Mandic P, Skoracki R, Hock K, Nguyen M, Shadduck K, et al. Clinical Evaluation of a Novel Wearable Compression Technology in the Treatment of Lymphedema, an Open-Label Controlled Study. Lymphatic research and biology. 2021.

37. Keeley VCS, Lytle LA, Gross CR, Ahmed RL, Troxel AB, Schmitz KH. A quality of life measure for limb lymphoedema (LYMQOL). Journal of lymphoedema. 2010;5:26-37.

38. Vignes S, Porcher R, Arrault M, Dupuy A. Factors influencing breast cancer-related lymphedema volume after intensive decongestive physiotherapy. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2011;19(7):935-40.

39. Maldonado TS, Rokosh RS, Padberg F, Rotella V, Miller H, Nassiri N, et al. Assessment of quality of life changes in patients with lower extremity lymphedema using an advanced pneumatic compression device at home. Journal of vascular surgery Venous and lymphatic disorders. 2021;9(3):745-52.

40. Fukushima T, Tsuji T, Sano Y, Miyata C, Kamisako M, Hohri H, et al. Immediate effects of active exercise with compression therapy on lower-limb lymphedema. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2017;25(8):2603-10.

41. Abe K, Tsuji T, Oka A, Shoji J, Kamisako M, Hohri H, et al. Postural differences in the immediate effects of active exercise with compression therapy on lower limb lymphedema. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2021;29(11):6535-43.

42. Baumann FT, Reike A, Reimer V, Schumann M, Hallek M, Taaffe DR, et al. Effects of physical exercise on breast cancer-related secondary lymphedema: a systematic review. Breast cancer research and treatment. 2018;170(1):1-13.

Figure legend

Figure 1. The Novel Non-Pneumatic Active Compression Device

Figure 2. Enrollment Flow Diagram

Figure 3. (A) Mean Percent Volume Difference in Edema Between Day 0 and Day 28 and (B) Response Rate (>2% change in edema volume) in Affected Limb, (C) Adherence to Device, and (D) Mean Change in Overall LYMQOL Score

Table 1. Patient Characteristics

Characteristic	Value
Total N	52
Age in years, Mean (SD; range)	60 (10.8)
Female, N (%)	52 (100)
Race, N (%)	
Caucasian	38 (73.1)
African American	4 (7.7)
Asian	7 (13.5)
Hispanic	3 (5.8)
Other	0 (0)
Affected Arm, N, (%)	
Left	13 (25.0)
Right	39 (75.0)
Sites	5
Months Since Surgery or Radiation, Mean (SD; Range)	59 (59.6; 9-210)
Months Since Lymphedema Diagnosis, Mean (SD; Range)	54 (48.5; 7-196)
Months Between Surgery/Radiation and Lymphedema, Mean (SD)	10 (36.6)

SD, standard deviation

Table 2. LYMQOL results

	Score**				
	Overall (higher is better)	Function (lower is better)	Appearance (lower is better)	Symptoms (lower is better)	Mood (lower is better)
Novel Non-Pneumatic Active Wearable Device					
Day 0, Mean (Standard Deviation)	5.78 (1.88)	2.13 (0.64)	2.53 (0.81)	2.67 (0.75)	2.38 (0.76)
Day 28, Mean (Standard Deviation)	8.22 (1.45)	1.51 (0.47)	1.86 (0.76)	2.00 (0.74)	1.62 (0.48)
Change in Mean Score from Day 0 to Day 28	+ 2.44	- 0.62	- 0.67	- 0.67	- 0.76
p-value*	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Traditional APCD					
Day 0, Mean (Standard Deviation)	7.06 (1.61)	1.69 (0.61)	1.95 (0.82)	2.13 (0.74)	2.01 (0.75)
Day 28, Mean (Standard Deviation)	7.05 (1.92)	1.81 (0.71)	2.17 (0.87)	2.30 (0.69)	2.07 (0.69)
Change in Mean Score from Day 0 to Day 28	- 0.01	+ 0.12	+ 0.22	+ 0.17	+ 0.08
p-value*	0.3843	< 0.001	< 0.001	< 0.001	0.0948

*For change from Day 0 to Day 28

**Higher scores on the overall score reflect better quality of life; higher scores on the individual subscale scores reflect lower quality of life.

APCD, advanced pneumatic compression device

Table 3. Subject Responses at the End of the Study

Measure	Non-Pneumatic Active Compression Device	APCD	p-value
Percent of subjects who indicated that they were able to be active or exercise while using the device.	100%	0%	<0.001
Percent of subjects who indicated that the device portable and convenient for their travels.	100%	0%	<0.001
Percent of subjects who were “somewhat” or “very” satisfied with each device	90%	14%	<0.001
Percent of subjects who preferred each device for lymphedema treatment	90%	10%	<0.001
Percent of subjects who indicated that they reduced use of statis compression sleeves during treatment with device	86%	0%	<0.001

APCD, advanced pneumatic compression device

Figure 2. Enrollment Flow Diagram

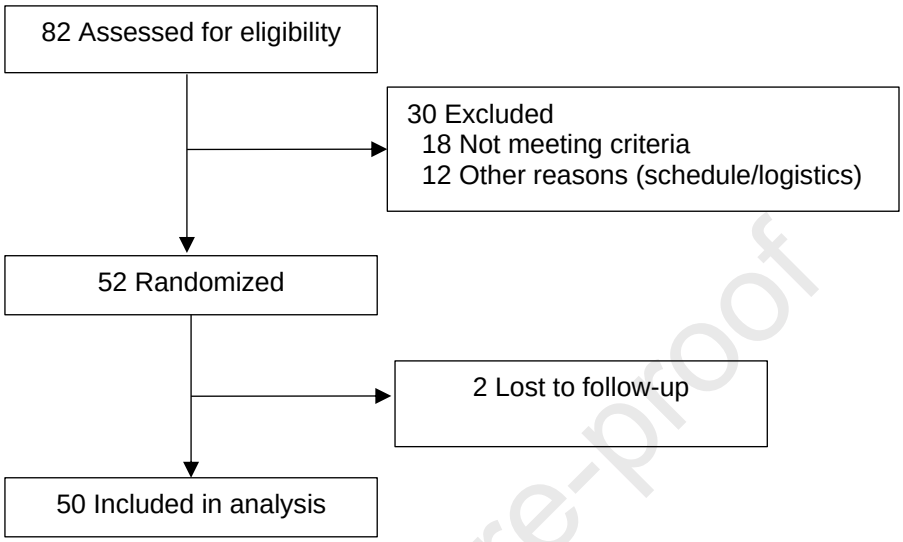
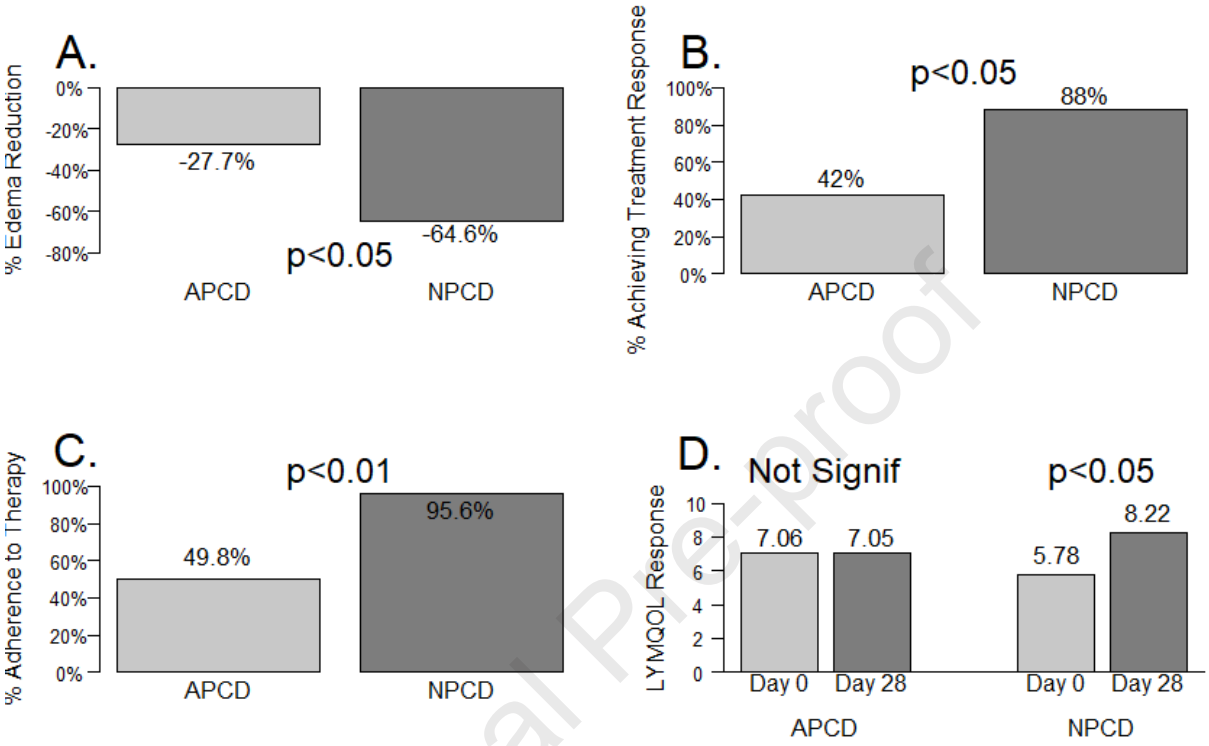


Figure 3. (A) Mean Percent Volume Difference in Edema Between Day 0 and Day 28 and (B) Response Rate (>2% change in edema volume) in Affected Limb, (C) Adherence to Device, and (D) Mean Change in Overall LYMQOL Score



APCD, advanced pneumatic compression device; NPCD, non-pneumatic compression device

Supplemental Material. Subject Satisfaction Survey

1. Were you able to be active or exercise while using this device?
   - ☐ YES
   - ☐ NO
2. Was the device portable and convenient for your travels?
   - ☐ YES
   - ☐ NO
3. How satisfied are you with this device?
   - ☐ Very Dissatisfied
   - ☐ Somewhat Dissatisfied
   - ☐ Neither Satisfied nor Dissatisfied
   - ☐ Somewhat Satisfied
   - ☐ Very Satisfied
4. Which device do you prefer for daily use?
   - ☐ DaySpring Active Compression Device
   - ☐ Flexitouch Pneumatic Compression Device