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Case Report

Real Time Visualization of Enhanced Lymphatic Flow When Using a Non-Pneumatic Active Compression Device (NPCD)

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Abstract

Lipedema and lymphedema remain misunderstood and underappreciated diseases. While the conditions appear similar, each presents with unique pathophysiology. Clinically, these diseases both present with edema, adipose tissue enlargement and extracellular tissue matrix remodeling or fibrosis yet they vary with respect to disease progression and molecular regulators of pathophysiology and genetics. Given the inherent challenges in managing these chronic diseases, it is important to understand if standard interventions are efficacious. In consideration of this, a novel ambulatory Non-Pneumatic Compression Device (NPCD) was utilized in this study to support lymphatic flow and improve tissue health while permitting and enabling movement.

The study was designed as a controlled prospective open-label study. Lymphatic pathways and transport of lymph was recorded using Indocyanine Green and a Near-Infrared (NIR) camera. Bioimpedance, Tissue Dielectric Constant (TDC), and skin hardness were measured for all subjects before and after use of device, at baseline (day 0) and at day 90. Subjects were instructed to use the non-pneumatic compression device– Dayspring® in an ambulatory setting at home for approximately 1 hour a day.

Results from this pilot study in evaluating a NPCD demonstrated improved lymphatic flow and uptake through ICG NIRFI. All three subjects presented with less intracellular water in the limbs and less fibrosis post 3 months of NPCD use.

Keywords: Indo Cyanine Green; Fluoroscopy; Intermittent Pneumatic Compression Devices; Lipedema; Lymphedema

Introduction

Lipedema and lymphedema remain misunderstood and underappreciated diseases. While the conditions appear similar, each presents with unique pathophysiology. Clinically, these diseases both present with edema, adipose tissue enlargement and extracellular tissue matrix remodeling or fibrosis yet they vary with respect to disease progression and molecular regulators of pathophysiology and genetics [1].

Lipedema is estimated to affect up to 17 million people, mostly women, in the US and nearly 11% of adult women worldwide [2]. Lipedema is a painful disease of fibrotic loose connective tissue (subcutaneous adipose) characterized by a bilaterally symmetrical and disproportional expansion of the adipose tissue of the extremities relative to the torso, sparing the trunk, hands and feet [3,4]. Additional characteristics include and increased tendency to

bruise, joint hypermobility, and edema formation as the disease progresses, defined as lipolymphedema [5]. Adipose tissue affected by lipedema presents with characteristic abnormalities including microangiopathy (dysfunctional blood and lymphatic vessels), excess interstitial fluid, hypertrophy and hyperplasia of adipocytes, and recruitment of inflammatory immune cells [6-13]. Lipedema is identified by clinical examination and it is graded by stage and location. Lipedematous tissue, Body Mass Index (BMI), metabolic disease and lymphedema increase with stage [14,15].

Lymphedema is a chronic disease resulting from a progressive accumulation of fibro-adipose tissue and protein rich fluid in the interstitium that exceeds the capacity of the lymphatic system to transport the fluid. Lymphedema is either primary (congenital) or secondary (acquired). Primary results from malformations of the lymphatic system mostly related to genetic mutation. It is subdivided into three categories: 1) congenital lymphedema, present at birth or recognized within two years of birth; 2) lymphedema praecox, occurring at puberty or the beginning of the third decade; or 3) lymphedema tarda, which begins after 35 years of age [16]. Secondary lymphedema results from injury, insult, or obstruction of the lymphatic system. The most common cause worldwide is filariasis caused by a parasitic infection, Wuchereria bancrofti. In the US, the most common cause is Chronic Venous Insufficiency (CVI) followed by cancer or treatment related to cancer [17]. Primary lymphedema affects 1 in 100,000 individuals where secondary lymphedema affects 1 out of every 1000 people in the US and up to 250 million worldwide [1,17].

Conservative management for both diseases remains the standard of care. In general, for lipedema, this includes manual therapies, compression garments, pneumatic compression, and a home exercise program [4]. For lymphedema, Complete Decongestive Therapy (CDT) is the mainstay involving two phases. Phase I is the intensive or decongestive phase that is clinician driven involving skin and nail care, Manual Lymphatic Drainage (MLD), compression and education. Once the limb has decongested, Phase II or the maintenance phase begins where the patient continues the components of CDT on their own for lifelong management. In both phases, compression devices are often utilized adjunctively to support or maintain edema reduction. Traditionally, this involves the use of a pneumatic compression device for 1-3 hours per day while seated or supine.

Given the inherent challenges in managing these chronic diseases, it is important to understand if standard interventions are efficacious. In consideration of this, a novel ambulatory Non-Pneumatic Compression Device (NPCD) was utilized in this study to support lymphatic flow and improve tissue health while permitting and enabling movement. ICG imaging was utilized to evaluate lymphatic transport in real time and bioimpedance for intracellular water content were employed to evaluate tissue health. The study objective was real-time near infrared visualization to observe lymph movement at day 0 and after 3 months of use with the NPCD device at home with ambulation.

Materials and Methods

The study was designed as a controlled prospective open-label study. Indo Cyanine Green (ICG) with 10mL sterile water was used to reconstitute 25mg of ICG using a 10cc syringe with an 18-gauge needle. Injection sites were prepped with alcohol and cryospray for numbing prior to injection. Lymphatic pathways and transport of lymph was recorded using a Near-Infrared (NIR) camera. Bioimpedance, Tissue Dielectric Constant (TDC), and skin hardness were measured for all subjects before and after use of device, at baseline (day 0) and at day 90. Subjects were instructed to use the non-pneumatic compression device– Dayspring® in an ambulatory setting at home for approximately 1 hour a day. Figure 1 contains the schematic indicating injection sites and NIR camera utilized for this study.

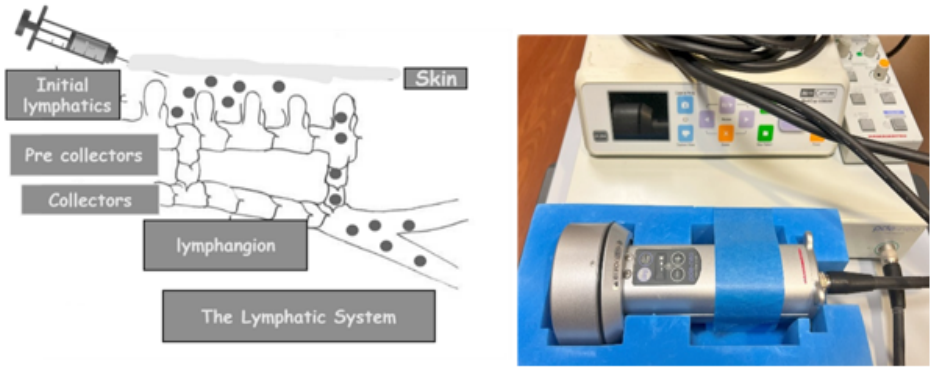

Figure 1: ICG Injection Sites (used with permission from Jane Wiig) and NIR Camera.

Indocyanine Green was injected at the following sites: Posteromedial, Anteromedial, Anterolateral, and the Posterolateral aspect of the right foot. 0.01ml ICG was injected subcutaneously at all four sites using BD 1ml Syringe, Luer-Lok Tip, and 30-gauge 1/2 in needle. Posteromedial was injected 10 minutes after the previous three injections due to a near syncope episode. Black electrical tape was placed over each injection site. Imaging was obtained using PDE Neoll camera.

The Dayspring non-pneumatic compression device is an FDA cleared multi-modal active compression system that is portable, ambidextrous, sized-to-fit, 14 chamber system utilizing a smart metal alloy (Flex Frames™) providing pressures between 0-100 mmHg, as shown in Figure 2. The Koya Dayspring is a prescription only wearable compression system that is intended for use in a clinic or home setting by medical professionals and patients who are under medical supervision to increase lymphatic flow in the upper or lower extremities. It is designed to provide patients with mobility while receiving active compression in the treatment of many conditions such as: lymphedema (primary and secondary), post mastectomy edema, edema following trauma and sports injuries, post immobilization edema, venous insufficiency, lipedema and phlebolymphedema. The Dayspring NPCD may reduce wound healing time and provide treatment and assistance in healing stasis dermatitis, venous stasis ulcers, and arterial and diabetic leg ulcers.

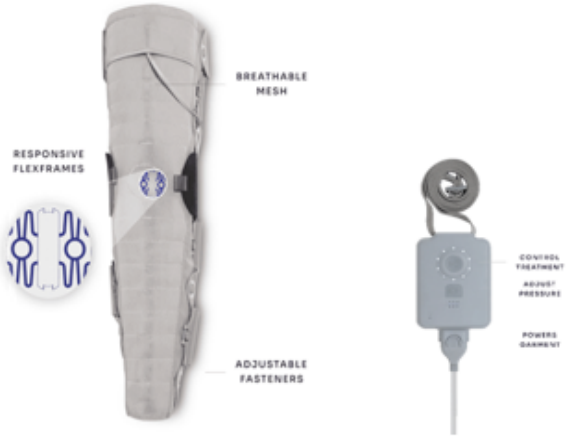

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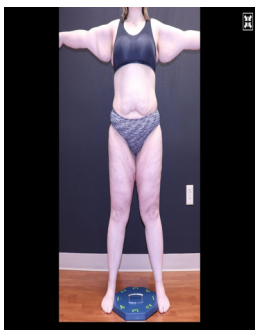
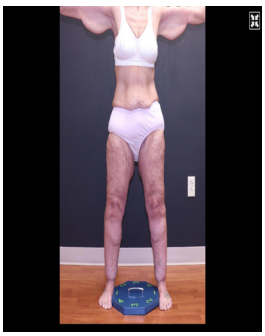
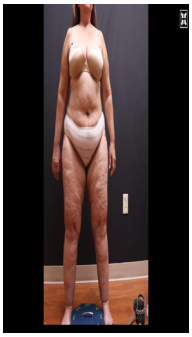
Figure 2: Dayspring Full Leg NPCD with Controller

Case Presentation

Three subjects were consented for this pilot study all with lipolymphedema diagnoses. Subjects were all female Caucasians with a median age of 54.7 (±6.9) years, expressed as mean (±standard error). Table 1 contains the details for the subject's clinical presentation at study initiation.

Subject 001	Subject 002	Subject 003
Type 4, stage 2 Lipedema/Secondary Lymphedema in upper body Type 2, stage 3 Lipedema/Secondary Lymphedema in lower body	Type 4, stage 3 Lipedema/Secondary Lymphedema in Upper body Type 3, stage 3 Lipedema/Secondary Lymphedema in Lower body	Type 4, stage 2 Lipedema/Secondary Lymphedema in Upper body Type 3, stage 3 Lipedema/Secondary Lymphedema in Lower body
		
Lipedema characteristics (+/-)	**Lipedema characteristics (+/-)**	**Lipedema characteristics (+/-)**

(+) Fat overhanging knees (+) Tissue is soft and tender to touch on exam (+) Presentation of legs is column/stovepipe (-) Bilateral Wrist Cuffs (-) Retro malleolar fullness (-) Bilateral ankle cuffs Gait Waddling, Circumduction	(+) Bilateral Wrist Cuffs (+) Retro malleolar fullness (+) Bilateral ankle cuffs (+) Tissue is soft and tender to touch on exam (-) Fat overhanging knees Normal gait	(+) Bilateral Wrist Cuffs (+) Retro malleolar fullness (+) Bilateral ankle cuffs (+) Fat overhanging knees (+) Tissue is soft and tender to touch on exam Gait Waddling, Circumduction

Table 1: Subjects' Clinical Presentation at Study Initiation.

Two of the subjects reported progressive leg enlargement beginning during puberty and the other during menopause. All three subjects presented with fat tissue lobules and nodules in the lower and upper extremities, and all presented with hypermobility in various joints throughout the body. All subjects reported worsening of their symptoms over time, along with weight gain, with negative impacts on quality of life and their ability to do activities of daily living. Specifically, all three reported limitations with ascending/descending stairs, meal preparation due to standing, getting in/out of vehicles and shopping. The subjects reported pain severity related to their lipedema symptoms from 7-8 out of 10, 10 being the worst. The subjects had varied experiences with compression and compression pumps. Two of the three had little to no experience whereas the other had experience with both compression garments and pneumatic compression.

Results

The NPCD technology leverages the muscle pump concomitant with active compression to enhance and support venous and lymphatic flow. In this study, the three subjects all experienced an increase in weight/metabolic rate after 3 months of using the NPCD and all subjects reduced intracellular and extracellular water content after 3 months of NPCD use. Table 2 contains the results from bioimpedance and water content evaluation over the duration of the study. All subjects gained weight in the 90-day period (4.8±3.3 lbs) and an increase in BMI of 0.9±0.6 kg/m2 (Figure 3). Additionally, subjects had a decrease in intracellular water content, extracellular water content, and water content in both arms, both legs, and the trunk over the course of the 90-days (Figure 4).

Change in	Mean	Standard Error
Weight (lbs)	+ 4.8	0.9
Body Metabolic Index (BMI) (kg/m2)	+0.9	0.6
Intracellular Water (lbs)	-1.1	2.0
Extracellular Water (lbs)	-0.4	1.4
Right Arm (lbs)	-0.3	0.2
Left Arm (lbs)	-0.3	0.2
Trunk (lbs)	-2.8	2.1
Right Leg (lbs)	-1.2	0.9
Left Leg (lbs)	-1.0	0.8

Table 2: Change in Characteristics over the 90-day period during use of NPCD

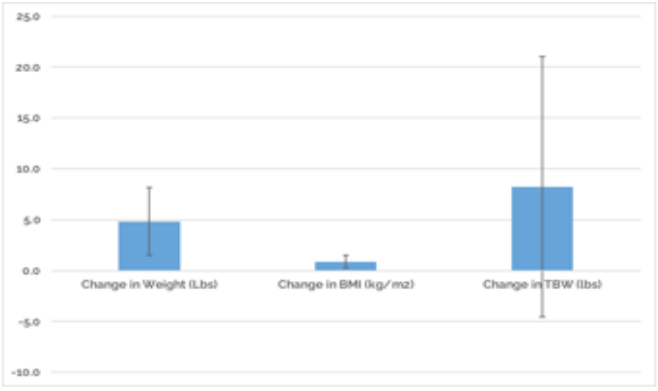


Figure 3: Weight/Metabolic Rate Results (BMI = body mass index, TBW = total body water)

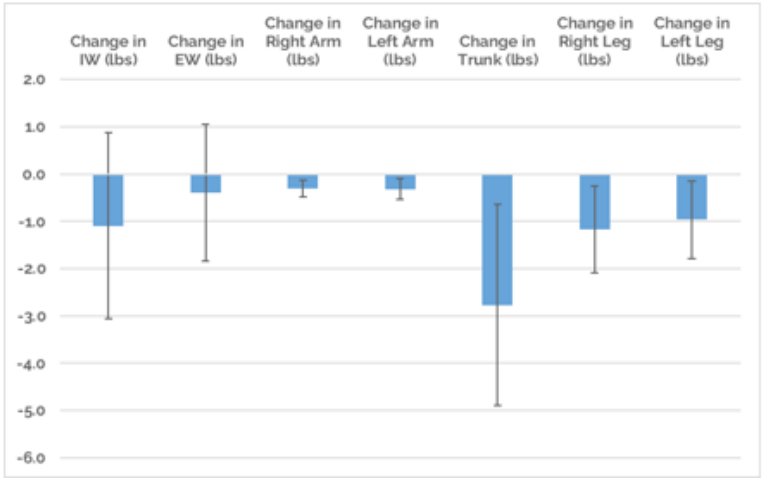


Figure 4: Change in Water Content after 90 Days of NPCD Use (IW = intracellular water, EW = extracellular water)

From a safety perspective, no device-related Adverse Events (AEs) or Severe Adverse Events (SAEs) were reported. All three subjects reported pain described as stinging and burning at the injection site of the ICG that resolved within 5 minutes after injection. All subjects demonstrated increased lymphatic movement and skin softening after 90 days of NPCD utilization. Tables 3-5 reflect the subject's lymphatic flow as visualized through ICG NIRFLI, pre and post NPCD use.

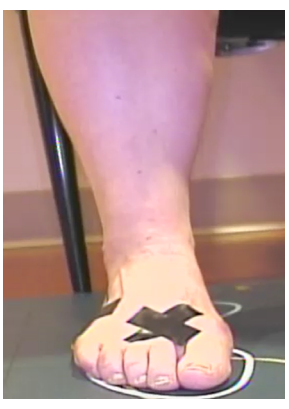
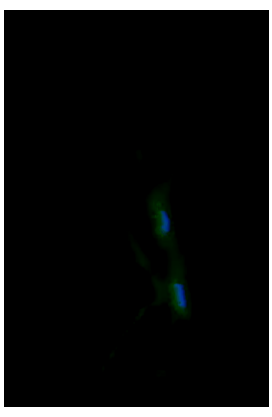
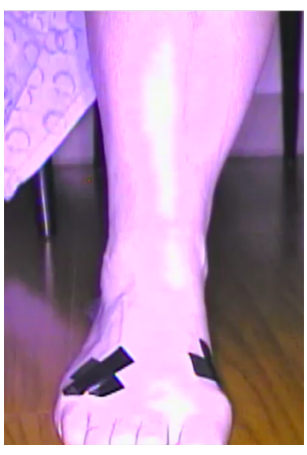
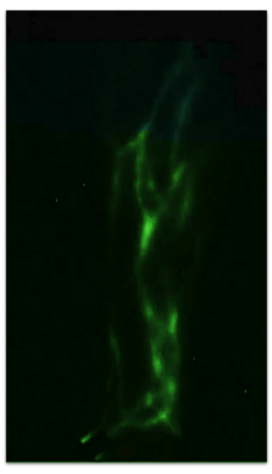
	Ambient Light	**ICG NIRFLI**
Day 0 Pre NPCD-Use		
Day 90 Post NPCD-Use		

Table 3: Subject 1- Pre and Post NPCD Use as Shown with ICG NIRFI

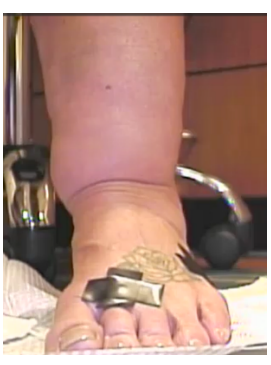
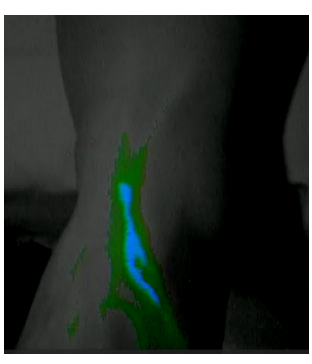
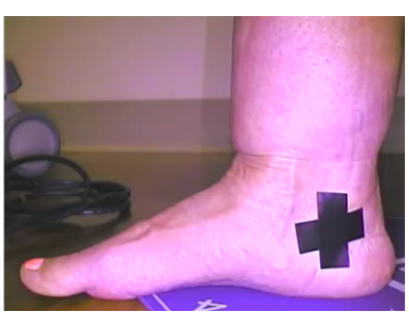
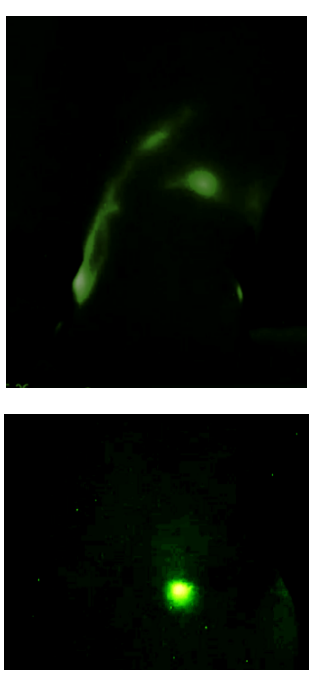
	Ambient Light	**ICG NIRFLI**
Day 0 Pre NPCD-Use		
Day 90 Post NPCD-Use		

Table 4: Subject 2- Pre and Post NPCD Use as Shown with ICG NIRFI

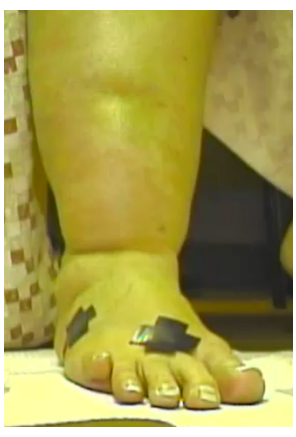
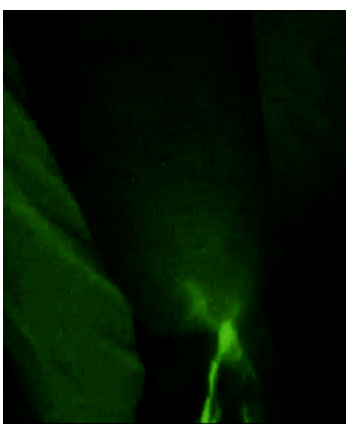
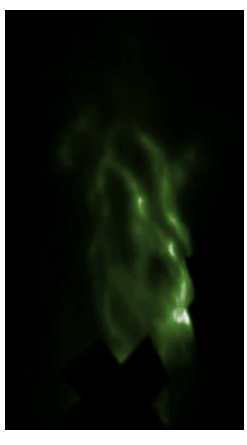
	Ambient Light	**ICG NIRFLI**
Day 0 Pre NPCD-Use		
Day 90 Post NPCD-Use		

Table 5: Subject 3- Pre and Post NPCD Use as Shown with ICG NIRFI

Subject 1 prior to NPCD use presented with some linear uptick flow at the anterior medical aspect of the pretibial region with diffuse pulling above the knee. The popliteal node was vaguely visible. On day 90 post NPCD use, the subject reported her legs were feeling better and her jeans were fitting better. Imaging showed a more clearly defined uptick of linear flow at the right anterior medial calf. There was a clearly defined right popliteal node, diffuse linear uptick at the right anterior medial thigh, and some diffuse pulling at the right inguinal node. Subject 1's post-study participant survey revealed she had not used another PCD prior to this study. She reported she used the NPCD 2-3 times per week, she found she was able to be mobile while using the device and she rated her quality of life while using the NPCD an 8/10 stating it was helpful. Lastly, she did find the device to be portable and easy to use.

Subject 2 prior to NPCD use, had diffuse pulling at her bilateral ankles. Her right popliteal node was visible, and her right leg had diffused linear movement at the mid-anterior thigh. Her left legs had diffused linear flow from the medical knee to the proximal medial thigh. On day 90 post NPCD use, the subject reported her legs were feeling better and her jeans were fitting better. Imaging of the left leg showed linear uptick flow at the dorsum of the foot until the ankle cuff. Diffused pooling at the ankle cuff was noted circumferentially. There was also diffused pooling around the popliteal node. Imaging of her right leg showed linear uptick flow at the dorsum of the foot until the ankle cuff. She had diffused pooling at the ankle cuff circumferentially, and well-defined borders around the popliteal node. Subject 2's post-study participant survey indicated she used the NPCD one time per week and found it difficult to use while walking. She rated her quality of life while using the device a 5/10, however she preferred her PCD.

Subject 3 prior to NPCD use, had diffuse pooling at her left ankle cuff which did not change with positional changes. Her left leg had diffuse linear movement at the mid-anterior thigh. One hour post NPCD use, imaging showed improved uptake at the ankle and diffuse linear movement at the mid-anterior thigh. Imaging post 90-day NPCD use showed linear uptick at the dorsum of the foot with mapping of lymphatic vessels above the malleoli. Further, imaging revealed diffuse linear coursing anteromedially up the calf converging into one linear pathway to the inguinal node. Subject 3's post-study participant survey indicated she did use the NPCD daily during the study timeline. She found the device to be lightweight and easy to pack. She was able to be mobile with the device but found she used it more while lying down. She rated her quality of life while using the device an 8/10 and she reported she preferred the NPCD significantly more than her PCD.

Conclusions

Results from this pilot study in evaluating a Non-Pneumatic Compression Device (NPCD) demonstrated improved lymphatic flow and uptake through ICG NIRFI. All three subjects presented with less intracellular water in the limbs and less fibrosis post 3 months of NPCD use. The combined effects of static and active compression in addition to mobility engaging the muscle pump, allows for a multi-modal approach to manage lymphedema/lipedema. Further, the multi-modal mechanism of action of the NPCD in static and active compression together could aid in remodeling of the fibrotic tissue. The subjects reported improved quality of life while using the NPCD.

Disclosure: Jarren Baldwin Is VP Of Operations And Technology, Koya Medical, Inc.; Heather Barnhart, Director Of Clinical Affairs, Koya Medical, Inc.; Andy Doraiswamy, Chief Executive Officer, Koya Medical, Inc. And Thomas Maldonaldo, Chief Medical Officer, Koya Medical, Inc.

Author Contributions: Conceptualization, TW; Methodology, TW, CS; Validation, TW, TM; Formal Analysis, TW, CS, AD, JB; Investigation, TW, CS; Resources, Data Curation, TW, AD, JB; Writing—Original Draft Preparation Writing, HB, Review And Editing, TW, AD; Supervision, TW, TM

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Institutional Review Board Statement: All subjects signed the consent form after receiving instructions regarding the possible risks and benefits and were granted privacy, confidentiality, and anonymity rights. The subjects were free to stop participating in any stage of the study without giving reasons for their decision.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: Data supporting the study results can be provided followed by request sent to the corresponding author's e-mail.

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Conflicts of Interest: None.

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