

## INTERMITTENT NEGATIVE PRESSURE THERAPY IN THE COMBINED TREATMENT OF PERIPHERAL LYMPHEDEMA

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### ABSTRACT

*Intermittent negative pressure devices were initially developed by NASA to enhance blood perfusion and combat a reduction in orthostatic tolerance. Investigational studies have demonstrated that the pressure differential produces changes in the blood and cardiac systems and also documented changes in weight and cellulite in obese patients. Although the mechanisms are not known, previous investigation has also reported changes in lymphedematous limbs. These initial results suggested to us that the inclusion of intermittent negative pressure into a lymphedema treatment protocol would be beneficial. We subsequently undertook a study of 50 patients with lymphedema adding intermittent negative pressure to our CLyFT protocol and compared them to the CLyFT protocol without intermittent negative pressure. We found a significant difference between the groups with an additional 7% reduction in lymphedema volume ( $p=0.008$ ). Our study results indicate that the inclusion of intermittent negative pressure therapy into the CLyFT protocol was beneficial and further incorporation into other protocols should be investigated.*

**Keywords:** lymphedema, lymphedema

treatment, intermittent negative pressure, Vacumed, CLyFT, protocol

### INTRODUCTION

#### *Developmental History of the Device*

A lower body negative pressure device was developed by NASA for use in space to ensure perfusion of astronauts' limbs and combat a reduction of orthostatic tolerance (1-3). The negative pressure is thought to be beneficial for recovery of the baroreceptor reflex and venous tone by astronauts and is used, in combination with medication, as a treatment for orthostatic hypotension in astronauts (4). In addition, beneficial venous effects of intermittent negative pressure therapy have been shown with athletes, and use has been slowly spreading into patient populations.

#### *Principles of Alternating Negative Pressure Therapy*

The lower body (legs and lower abdomen to the level of the iliac crest) is placed into a cylindrical vacuum tube with the person lying on back. The tube is closed with nylon webbing that cinches around the waist to

effectively seal the tube on the lower body. A vacuum pump generates lower pressure in the cylinder that is alternated with periods of normal pressure. This pressure differential leads to an increased flow of blood into the lower body thus improving lower body circulation. The differential lowers blood pressure in the central vein, cardiac stroke volume, cardiac output, and mean arterial pressure (5,6). Cardiac compensatory mechanisms are activated by this shift in fluid towards the lower body, increasing the heart rate and peripheral vessel resistance. This also activates the sympathetic response in the heart and peripheral vessels, increases catecholamine secretion, and reduces release of atrial natriuretic peptide (7). In healthy volunteers, lower levels of body negative pressure (starting at -20mmHg of negative pressure) reduces central venous pressure. At higher levels of negative pressure (e.g., -40mmHg) there is a reduction in stroke volume index and cardiac index. Blood pressure is generally unchanged because of an increase in total peripheral resistance and heart rate but hypotension has occurred at -40mmHg and greater and may be a result of hypovolemia (8,9).

The release of the negative pressure and the return to normal pressure is accompanied by rapid return of blood to the chest and head from the legs, a spike in arterial pressure, and bradycardia (3). The shift of blood volume from distal regions towards the central body leads to vasodilatation in the peripheral blood vasculature because of the baroreceptors particularly in the lower extremities (10). These reports illustrate that the local effect of pressure variation in the lower limbs and abdomen leads to changes in the peripheral blood circulation (11).

#### *Initial Work in Patient Populations*

Initial patient studies applied the rationale of the NASA developers to investigate and attempt to treat the detrimental effects of prolonged bed-rest or patients prone to

orthostatic hypotension (4). Given the effects of intermittent negative pressure therapy on peripheral blood circulation, further studies with patients have been conducted, including diabetic and cardiac patients (12,13).

Löberbauer-Purer et al investigated use of negative pressure therapy combined with dietary controls and exercise in the treatment of obesity (11). All treatment modalities (diet, diet and exercise, diet, exercise, and negative pressure therapy) led to a reduction in weight after 12 weeks. The addition of negative pressure therapy produced positive effects in the appearance of cellulite with significant improvement in subjective rating of cellulite. A widely held hypothesis is that cellulite is caused by a change in the microcirculation and an increased accumulation of fluid in the dermis and in the intra- or interlobular septa (14). Löberbauer-Purer et al concluded that negative pressure therapy promoted movement of extracellular water to reduce the amount of cellulite present on the lower body.

Milicevic et al examined the effect of intermittent negative pressure treatments on the hemostatic system in patients with lymphedema of the lower limbs (15). Eighty-nine patients received 10 treatment sessions in a hypobaric sack (Green sack) with alternating negative and normal pressure. Pre- and post-treatment platelet aggregate test with the addition of ADP, adrenaline, and collagen, as well as CBC and CRP analysis were performed. They concluded that intermittent negative pressure treatment had a beneficial effect by decreasing platelet reactivity in patients with lymphedema.

Milicevic et al did not measure the effect of the negative pressure treatment on the limb volume in their sample of lymphedema patients. Chronic lymphedema is associated with a buildup of fibrous adipose tissue that also contributes to the excess limb volume. If intermittent negative pressure therapy might be effective in reducing this adipose component as it promotes cellulitic tissue lysis and also contributes to weight loss in obese patients who have an excess of adipose tissue.



*Fig. 1. Patient positioned in the intermittent negative therapy pressure device (Vacumed, Weyergans) used as part of the CLyFT lymphedema treatment protocol.*

In addition, the alternating pressure of the intermittent negative pressure system leads to accelerated lymphatic flow and increased micro-perfusion in the peripheral venous system (6). Montgomery et al investigated blood flow in lymphedematous and non-lymphedematous arms (16). They found altered arterial and venous properties in the lymphedematous limbs, lower venous tone, lower venous return, and increased arterial blood flow into the lymphedematous limb. It is possible that the intermittent negative pressure device would have a beneficial effect on the venous and arterial flow and also excess volume in patients with lymphedema, where an overload on the venous system contributes to excess fluid in the affected limb (17).

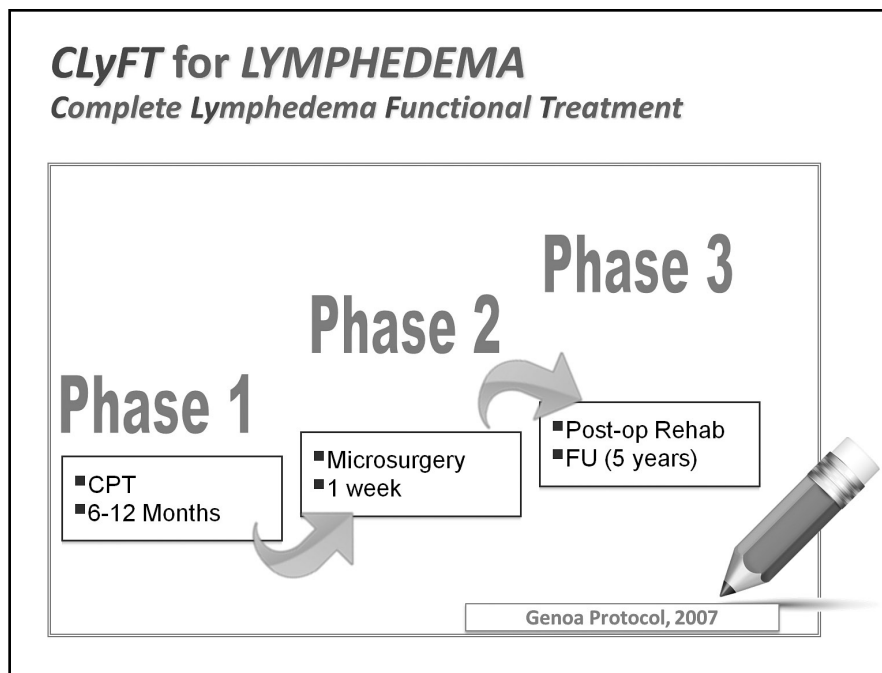
Intermittent negative pressure has been shown to change arterial and venous blood flow as well as effect changes in weight in obese patients with excess adipose tissue. Accordingly, we chose to investigate whether

the inclusion of intermittent negative pressure as part of our lymphedema treatment protocol would result in enhanced improvements for patients with lymphedema.

#### *MATERIALS AND METHODS*

Fifty patients with primary or secondary lower limb lymphedema underwent an integrated treatment protocol including lymphatic microsurgery and pre- and post-surgical physical therapy. This treatment protocol involved daily sessions of intermittent negative pressure therapy in the intermittent negative pressure device (Weyergans Ltd., Germany) (*Fig. 1*), as described below. Excess volume reduction and infection rate at the completion of this treatment protocol were compared to data from 50 patients (as controls) with lower limb lymphedema who completed the analogous protocol prior to the inclusion of the intermittent negative pressure device.

Derivative multiple lymphatic-venous



*Fig. 2. Algorithm of the Complete Lymphedema Functional Treatment (CLyFT) protocol used in the treatment of both primary and secondary lymphedema.*

anastomoses (MLVA) or lymphatic pathway reconstruction using interpositioned vein-grafted shunts (MLVLA) were performed at a single site, in the inguinal-crural region. Healthy appearing lymphatics found at the site of surgical operation are directly introduced together into the vein by a U-shaped stitch and then fixed to the vein cut-end by means of additional stitches between the vein border and the perilymphatic adipose tissue. At the end, the first U-shaped stitch is removed to avoid the risk of closure of lymphatic collectors. With the use of Patent Blue dye (a sodium or calcium salt of diethylammonium hydroxide), properly functioning lymphatics appear blue, and the passage of blue lymph into the vein branch verifies the patency of the lymphatic-venous anastomosis under the operating microscope when the anastomosis is completed.

Microsurgical interventions are part of an integrated treatment protocol called ‘Complete Lymphedema Functional Therapy’

(CLyFT – Fig. 2) (18). The other elements of the protocol consist of manual and mechanical lymphatic drainage and intermittent negative pressure therapy, in conjunction with appropriate compressive garments. Mechanical lymphatic drainage refers to the use of uniform and sequential pneumatic devices. In Genoa, Italy, CLyFT is applied in three phases: an intensive pre-operative phase to reduce the size of the affected limb as much as possible prior to the microsurgical intervention, followed by a gentle post-operative phase in which the pressure of the lymphatic drainage is gradually increased as healing continues, and finally, a long-term maintenance phase of daily mechanical lymphatic drainage and physical exercise (particularly swimming) to strengthen the anastomotic joins over time. The timing of the treatment protocol depends on the pre-operative stage of the disease but in general there is one-to-two weeks of pre-operative CLyFT, the microsurgical intervention, and

then one-to-two weeks of post-operative CLyFT, before patients initiate the maintenance phase. The effectiveness of our derivative and reconstructive lymphatic microsurgery techniques in providing a functional repair of the lymphatic system have been discussed elsewhere (18-22) and are not the focus of this review.

As part of the pre- and post-surgical physical therapy, patients completed 20-minute sessions in the intermittent negative pressure device. The treatment parameters were set on a 30 second cycle of 21 seconds of negative pressure (-35mmHg reaching -40mmHg) and 7 seconds of normal pressure. Each patient completed 12 sessions in the two weeks prior to lymphatic microsurgery and two to three weeks of post-surgical treatment, averaging 14 sessions in this post-surgical period. Thus each patient completed 24-30 sessions of intermittent negative pressure therapy as part of the CLyFT treatment protocol.

Percent volume reduction obtained at the end of the treatment protocol 2-3 weeks post-surgery, as measured by water volumetry and rate of post-surgical infection were assessed for each patient group. Student's two-tailed t-tests were conducted using Microsoft Excel 2011, with a 95% confidence level.

## RESULTS

Average post-treatment percent volume reduction for patients with CLyFT and intermittent negative pressure treatment was  $83.02 \pm 10.78\%$  (Mean  $\pm$  Standard Deviation) compared to  $76.44 \pm 13.48\%$  for the control group. The addition of intermittent negative pressure treatment significantly improved percent volume reduction ( $p = 0.008$ ).

Both groups had a very low rate of post-operative infection with 2 cases in intermittent pressure treatment group and 3 in the controls. This was not significantly different.

## DISCUSSION

The combined treatment protocol CLyFT (including intermittent negative pressure) is an effective treatment regimen for lymphedema. Significant reductions in excess limb volume are achieved almost immediately after surgery and maintained in the long-term (18). Lymphatic microsurgery is effective in restoring the flow of lymph from the affected limb, as demonstrated by long-term lymphoscintigraphy (19-22), and intensive physical therapy is useful to reduce the swelling as much as possible in preparation for surgery. Post-surgery, physical therapy helps to maintain the patency of the anastomoses and stabilize the newly established lymphatic flow from the limb.

It is difficult to determine the effect that the various components of the CLyFT treatment protocol have on the overall outcome as they are applied as a set of therapies, and some components are impossible or not feasible to investigate individually. For example, it is well established that the use of elastic stockings or bandages are necessary to maintain the volume reductions achieved through physical therapy, as without this support limb swelling immediately recommences (23). Thus, given that the aim of treatment is to improve the swelling and reduce the associated risk of infection and increasing physical limitations, removing this component in order to determine its contribution to the treatment protocol would be regarded as unethical. We do know that lymphatic microsurgery can provide greater reduction in limb volume compared to physical treatment alone and, when applied early in the disease course, it offers the possibility of completely restoring lymphatic flow and thus, patients may be able to eventually give up the use of physical treatments and elastic stockings.

Intermittent negative pressure therapy was one of the later components to be added to the CLyFT treatment protocol and therefore data is available on a subset of patients who completed treatment prior to the addition of the intermittent negative

pressure therapy. It appears that intermittent negative pressure therapy contributes an additional 7% benefit in terms of volume reduction to the already significant improvements obtained with the CLyFT protocol. Is this clinically significant? We think so. In some cases of advanced lymphedema, the excess volume can reach extreme levels; up to 3195ml has been reported for the upper limb (24) and 6400 mL in the lower limbs (25). Even an extra 7% reduction in such advanced stages of lymphedema would have a positive impact on the patient's ability to perform daily activities and/or fit into clothing. Treatment with the vacuumed system appears to be an effective way to enhance volume reduction in lymphedema patients. The mechanism of action is not entirely clear, but this improvement may be a result of increased microperfusion enhancing venous flow and lymphatic flow or a reduction in adipose tissue or both.

The addition of intermittent negative pressure therapy did not seem to have any effect on post-operative infection. It is widely recognized that lymphedema, particularly the later stages of disease, is associated with recurrent episodes of cellulitis/erysipelas most likely related to chronic lymph stasis that blocks the movement of macrophages and also provides a perfect environment for bacterial and fungal growth (26,27). A significant reduction in the incidence of infection is typically found with the CLyFT protocol (18-22). Given the very low rates of post-operative infection, it is not surprising that there was no additional benefit from the addition of intermittent negative pressure therapy.

Intermittent negative pressure therapy is relatively simple to add to a lymphedema treatment protocol. Pressure settings and treatment length can be adjusted as needed. The chamber of the machine is padded with foam and the headrest (see *Fig. 2*) can be elevated approximately 20° for comfort. The intermittent negative pressure has a circumference of 170cm where it cinches at the waist

and is therefore able to accommodate patients with large limbs. No patient complained of discomfort throughout the treatment period of this study. In fact, anecdotally, patients seemed to find the treatment relaxing, and many remarked that it was the best part of the therapy. Length of treatment time and number of treatment sessions required to adequately treat lymphedema have yet to be established. In this study, intermittent negative pressure therapy was added to a fixed treatment protocol and therefore the number of sessions was necessarily limited. We also did not have the ability to examine the effect of intermittent negative pressure therapy in isolation. As noted above, compression therapy is the mainstay of lymphedema treatment and so it is highly unlikely an intermittent negative pressure-only treatment protocol would be ethical. However, it would be interesting to see in future studies how intermittent negative pressure therapy compares to pneumatic compression devices or lymphatic massage for patients who maintain compression garments after the treatment period. Given the ease of use and lack of compression involved, intermittent negative pressure therapy may be a preferential addition to a treatment protocol for elderly patients or patients with lipo-lymphedema where the skin is more fragile and the use of mechanical drainage may not be appropriate.

It should be noted that this review is limited by the small cohort of patients who have undergone the inclusion of intermittent negative pressure therapy in the CLyFT protocol and the generalizability of these results to other populations (other than the lower limbs). However, it is likely that the improvement in volume reduction seen with this population sample was achieved by the addition of intermittent negative pressure therapy to the treatment protocol. It is unlikely that these results were due to differences in the patient groups since both patient samples probably contained a similar proportion of stages of disease. We generally

find that most patients are in stage IIA and B or IIIA of the Campisi staging of Lymphedema (28) with only a few patients treated prior to these stages.

In summary, intermittent negative pressure therapy appears to improve micro-perfusion and venous and lymphatic flow in the lower limbs. When added to a combined treatment protocol for lymphedema, it appears to provide additional benefits in terms of volume reduction. This report supports further research and the inclusion of intermittent negative pressure therapy in lymphedema treatment programs.

## REFERENCES

1. Watenpugh, DE, DD O'Leary, SM Schneider, et al: Lower body negative pressure exercise plus brief postexercise lower body negative pressure improve post-bed rest orthostatic tolerance. *J. Appl. Physiol.* 103 (2007), 1964-1972.
2. Cao, P, S Kimura, BR Macias, et al: Exercise within lower body negative pressure partially counteracts lumbar spine deconditioning associated with 28-day bed rest. *J. Appl. Physiol.* 99 (2005), 39-44.
3. Goswami, N, JA Loepky, H Hinghofer-Szalkay: LBNP: Past protocols and technical considerations for experimental design. *Aviat. Space Environ. Med.* 79 (2008), 459-471.
4. Lathers, CM, JB Charles, VS Schneider, et al: Use of lower body negative pressure to assess changes in heart rate response to orthostatic-like stress during 17 weeks of bed rest. *J. Clin. Pharmacol.* 34 (1994), 563-570.
5. Hisdal, J, K Toska, T Flatebo, et al: Onset of mild lower body negative pressure induces transient change in mean arterial pressure in humans. *Eur. J. Appl. Physiol.* 87 (2002), 251-256.
6. Orletskiy, AK, DO Timtschenko: Use of devices for intermittent negative pressure therapy for treatment of athletes. N. Priorov Central Institute, 2009. Accessed online 1/4/2016: <http://vacumed.de/img/media/06415a9402e97420a5b750a21b6aea3a.pdf>
7. Gasiorowska, A, T Mikulski, J Smorawinski, et al: Cardiovascular and neurohormonal responses to lower body negative pressure (LBNP): Effect of training and 3 day bed rest. *J. Physiol. Pharmacol.* 57 (2006), 85-100.
8. Nette, RW, HP Krepel, MA Dospel, et al: Hemodynamic response to lower body negative pressure in hemodialysis patients. *Am. J. Kid. Dis.* 41 (2003), 807-813.
9. Ligtenberg, G, PJ Blankestijn, HA Koomans: Hemodynamic response during lower body negative pressure: Role of volume status. *J. Am. Soc. Nephrol.* 9 (1998), 105-113.
10. Nishiyasu, T, S Hayashida, A Kitano, et al: Effects of posture on peripheral vascular responses to lower body positive pressure. *Am. J. Physiol. Heart Circ. Physiol.* 293 (2007), H670-H676.
11. Loberbauer-Purer, E, N Meyer, S Ring-Dimitriou, et al: Can alternating lower body negative and positive pressure during exercise alter regional body fat distribution or skin appearance? *Eur. J. Appl. Physiol.* 112 (2012), 1861-1871.
12. Wijesundera, DN, GC Butler, S Ando, et al: Attenuated cardiac baroreflex in men with presyncope evoked by lower body negative pressure. *Clin. Sci.* 100 (2001), 303-309.
13. Mathol, H, U Zikeli, CM Brown, et al: Cardiovascular and cerebrovascular responses to lower body negative pressure in type 2 diabetic patients. *J. Neurol. Sci.* 252 (2007), 99-105.
14. Pavicic, T, C Borelli, HC Korting: Cellulite - das größte Hautproblem des Gesunden? Eine. Annäherung. *JDDG* 4 (2006), 8661-8887.
15. Milicevic, B, G Devceverski, N Radakovic, J Jelenc: Effects of intermittent negative pressure treatment on vascular and platelet-component of hemostasis system in patients with lymphoedema of lower limbs. *HealthMED* 7 (2013), 1224-1225.
16. Montgomery, LD, MS Dietrich, JM Armer, et al: Segmental bloodflow and hemodynamic state of lymphedematous and nonlymphedematous arms. *Lymphat. Res. Biol.* 9 (2011), 31-42.
17. Stanton, AWB, WE Svensson, RH Mellor, et al: Differences in lymph drainage between swollen and non-swollen regions in arms with breast-cancer related lymphoedema. *Clin. Sci.* 101 (2001), 131-140.
18. Campisi, C, C Bellini, CC Campisi, et al: Microsurgery for lymphedema: Clinical research and long-term results. *Microsurgery* 30 (2010), 256-260.
19. Murdaca, G, P Cagnati, R Gulli R, et al: Current views on diagnostic approach and treatment of lymphedema. *Am. J. Med.* 125 (2012), 134-140.
20. Campisi, C, MH Witte, E Fulcheri, et al: General surgery, translational lymphology and lymphatic surgery. *Int. Angiol.* 30 (2011), 504-521.

21. Campisi, C, F Boccardo: Microsurgical techniques for lymphedema treatment: Derivative lymphatic-venous microsurgery. *World J. Surg.*, 28 (2004), 609-613.
22. Campisi, C, E Da Rin, C Bellini, et al: Pediatric lymphedema and correlated syndromes: role of microsurgery. *Microsurgery* 28 (2008), 138-142.
23. Lee, BB, M Andrade, PL Antignani, et al: Diagnosis and treatment of primary lymphedema: Consensus document of the International Union of Phlebology (IUP) - 2013. *International Angiology* 32 (2013), 541-574.
24. Brorson, H: From lymph to fat: Liposuction as a treatment for complete reduction of lymphedema. *Int. J. Low. Extr. Wound.* 11 (2012), 10-19.
25. Wollina, U, B Heinig B, J Schönlebe, et al: Debulking surgery for elephantiasis nostras with large ectatic podoplanin-negative lymphatic vessels in patients with lipo-lymphedema. *Eplasty* 14 (2014), e11. eCollection 2014.
26. Rockson, SG: The lymphatics and the inflammatory response: Lessons learned from human lymphedema. *Lymph. Res. Bio.* 11 (2013), 117-120.
27. Shih, Y-CT, Y Xu, JN Cormier, et al: Incidence, treatment costs, and complications of lymphedema after breast cancer among women of working age: A 2-year follow-up study. *J. Clin. Oncol.* 27 (2009), 2007-2014.
28. Campisi, C, CC Campisi CC, S Accogli, et al: Obesity and lymphedema in geriatrics: Combined therapeutical approaches. *BMC Geriatrics* 10 (2010) (Suppl 1), A50.

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