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SUMMARY

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LYMPHOSCINTIGRAPHY OF LYMPH AND TISSUE FLUID FLOW DURING INTERMITTENT PNEUMATIC MASSAGE OF LOWER LIMBS WITH OBSTRUCTIVE LYMPHEDEMA

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Running title: Lymphoscintigraphy during pneumatic compression

ABSTRACT

The open questions remain where does the fluid flow to during sequential pneumatic compression and whether it can be moved to the non-swollen tissues of hypogastrium and gluteal region? During pneumatic massage of the limb we studied the pathways of lymph and mobile tissue fluid flow: a) from the calf and thigh across the inguinal region to the healthy non-swollen tissues of the hypogastrium and b) in the hypogastrium to the lateral and upper abdominal quadrants, with the use of lymphoscintigraphy. To prove that there was effective fluid flow during pneumatic massage, the plethysmographic flow measurements were carried out.

We showed that: (i) pneumatic compression pushed isotope in lymph in the remaining functioning lymphatics and tissue fluid in the interstitial space toward the inguinal region and femoral channel, (ii) there was no isotope crossing the inguinal crease or running to the gluteal area, and (iii) isotope injected intradermally in the hypogastrium did not spread during manual massage to the upper and contralateral abdominal quadrants.

In conclusion, intermittent pneumatic compression is effective in pushing mobile tissue fluid and relocating large fluid volumes toward the groin. However, the question that remains is: how to facilitate further flow toward the non-swollen tissues and local absorption of fluid.

Key Words: lymphoscintigraphy, lymphedema, pneumatic compression, massage.

INTRODUCTION

In obstructive lymphedema of lower limbs most or all lymphatic collectors leading to the superficial and deep inguinal lymph nodes are obstructed following infections, trauma, surgery or irradiation [(1)]. The limited hydraulic function of the damaged collecting lymphatics results in accumulation in the interstitial space of capillary filtrate containing plasma humoral and cellular components, as well as parenchymal cell products. Impairment of flow away of plasma filtered macromolecules and protein–bound ions generate high osmotic pressure. This attracts water from the vascular compartment and further increases the stagnant tissue fluid volume. Furthermore, the accumulating fluid deforms the soft tissue structure and spontaneously creates fluid conducting channels in the subcutaneous tissue [(2)].

This natural hydraulic process remains insufficient in transporting fluid away from swollen regions requiring mechanical forces. They can be provided to the swollen limb as massage squeezing the mobile edema fluid toward the root of the extremity.

In the calf and thigh the natural fluid channels form along large blood vessels, as the saphenous, popliteal and femoral veins and also around small unnamed vessels, leading to the groin region. There they end up at the inguinal crease where skin is connected with the inguinal ligament and external oblique muscle by natural elastic fibers [(3)].

The question arises whether the accumulated tissue fluid can form natural subcutaneous channels across the inguinal crease to

the hypogastrium. This would facilitate absorption of fluid in normal hypogastrium tissues and presumably forming connections with normal lymphatics. Such newly formed flow pathways would justify the common practice of treating the core (truncal) lymphatics as a major therapy component before limb massage [4,5]. The essence of this concept is that treatment must first be directed at lymphatic territories, such as the hypogastrium and trunk, so that they are adequately prepared to receive lymph (tissue fluid) from swollen regions.
In this study we investigated with use of lymphoscintigraphy the pathways of lymph and mobile tissue fluid flow:

a) across the inguinal and gluteal regions to the healthy non-swollen tissues of hypogastrium and

b) in the hypogastrium to the lateral and upper abdominal quadrants, during pneumatic massage of the limb.

To prove that there was effective fluid flow during pneumatic massage, the plethysmographic flow measurements were taken.

MATERIAL AND METHODS

Patients

Study was carried out on 15 patients, age 28-56, mean weight 65 kg (58-72), mean height of 168 cm (161-178), with diagnosis of lymphedema of one lower limb, stage II to IV, duration of 2 to 15 years (Table 1). Eleven patients reported small foot skin abrasions or light trauma of foot in the past followed by development of foot and calf transient edema. Larger edema developed months to years later and in 50% of cases was complicated by 1 to 3 attacks of dermato-lymphangio-adenitis. In 4 patients edema developed without any detectable reason. Cases with acute inflammation, chronic venous insufficiency and systemic etiology of edema were excluded from the study. Five patients without lymphedema with suspicion of enlarged abdominal lymph nodes served as controls. Lymphoscintigraphy and tissue fluid flow measurements are in our hospital the mandatory diagnostic procedures in all cases with lymphedema.
The consent of patients was obtained and the study was approved by Warsaw Medical University ethics committee.

Clinical staging

Staging was based on clinical evaluation: level of edema embracing limb from foot to groin and degree of skin keratosis and fibrosis. Briefly, in stage II pitting edema affected foot and lower half of the calf, in stage III foot and calf were involved, with hard foot and ankle area skin, in stage IV the whole limb was edematous with foot and calf skin hyperkeratosis and papillomatosis of toes [1].

Lymphoscintigraphic staging

Evaluation of lymphatic pathways was done on lymphoscintigraphic images (Table 1). They revealed in stage II spread of tracer in foot and lower part of calf, interrupted outline of a single lymphatic and few small inguinal nodes with irregular outline. In stage III no draining lymphatics were seen with some inguinal nodes of irregular outline appearing 2 hours after isotope injection. Stage IV was characterized by spread of tracer in the foot and entire calf without visualization of collecting lymphatics and nodes.

Lymphoscintigraphy technique

Lower limb lymphoscintigraphy was carried out in each patient in two sessions, the first without pneumatic massage and the second days later following a 45 minutes limb pneumatic massage. Intradermal injection of ^{99m}Tc-Nanocol (3 mCi) (Amersham, Switzerland) was made between the first, second and third toe (to visualize the superficial lymphatic system) and into the subcutis of mid- portion of the sole (to visualize the deep system). Imaging was performed using a gamma camera (Orbiter ZLC 750, Siemens, Germany) immediately after isotope injection and after 45 minutes of pneumatic massage. The images were classified according to the stage of lymphedema. In 5 of these patients (3 stage II, and 2 stage IV) additionally lymphoscintigraphy of skin and subcutis of hypogastrium was performed by intradermal injection of 1/10th of the Nanocoll dose used for limb scintigraphy. The spread of isotope in the limb and its movement toward the groin were observed simultaneously with spread of isotope injected into the hypogastrium.

Table 1. Demographic data of patients with lymphedema of lower limb

M/F	AGE	GROUP/STAGE	LEVEL OF EDEMA	SKIN CHANGES	LYMPHOSCINTIGRAPHY
2M, 3F	28-45	II	mid calf	none	foot & lower calf spread, few collectors and inguinal nodes
3M, 2F	25-52	III	knee	foot keratosis	foot & calf spread, single collector, inguinal node remnants
3M, 2F	26-48	IV	whole limb	foot, calf keratosis	foot & calf spread, no lymphatics and inguinal nodes
2M, 3F	28-52		No lymphedema, controls		limb lymphatics normal

For semiquantitative evaluation of scintigrams, the image of lower leg and thigh lymphatics and lymph nodes was evaluated quantitatively. Lymphoscintigrams were scanned and analyzed using specialized PC software (Olympus Micro Image™ ver. 3.0.0., Olympus Optical Co., Hamburg, Germany). The surface area of the lymphatics (Lv) and inguinal lymph nodes (LN) of both extremities was evaluated in the inguinal area, thigh and calf. Data were expressed as indices obtained from the equations $I_{Lv\ or\ LN} = S_{L\ LV\ or\ LN}/S_{CLv\ or\ LN}$, where $S_{Lv\ or\ LN}$ were surface of lymph vessels or lymph nodes measured on the lymphedema (L) and contralateral normal (C) extremity.

Pneumatic compression appliance

We used a device produced for us by Biocompression (Moonachie, NJ) (Fig. 1). The sleeve was composed of 8 segments 9 cm long each, it was sequentially inflated, inflation pressures were regulated from 50 to 125 mmHg, gradient pressures were decreasing proximally by 20%, inflation time of each chamber was 50 sec, total inflation time equaled 400 sec., there was no deflation of distal chambers, deflation time of all chambers was 50 sec at the end of each cycle. The sleeve embraced the whole limb to the inguinal crease.

Manual massage of hypogastrium

Manual massage for hypogastrium fluid clearance was performed for 10 minutes at the site of isotope injection in the upper and lateral direction.

Measuring tissue fluid flow volume

Strain gauge plethysmography was used to measure sequential changes of circumference changes in the calf and thigh during massage (Fig.1). The obtained data served for calculation of volume changes of the massaged limb segments. A plethysmograph (Hokanson, Bellevue, WA, type EC6) in a recording vein mode was applied. Six mercury strain gauges of a length of 22 cm to 53 cm were put around limb at chamber levels 3 to 8 (Fig. 1).

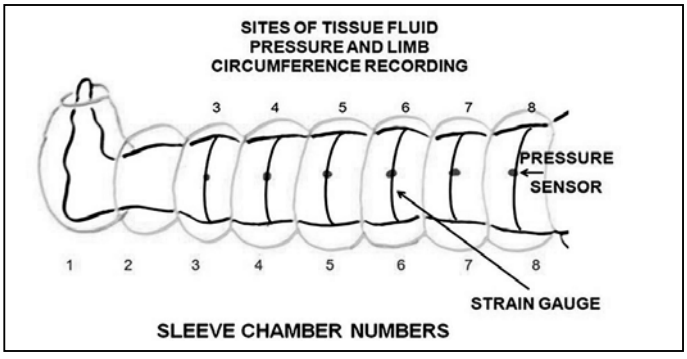

Figure 1: Schematic presentation of lower limb in a pneumatic sleeve with 8 chambers 9cm wide each. Tissue fluid pressure was measured at 6 points indicated by large dots. The lowest point in the calf was at chamber 3 level, then at levels 4 and 5. In the thigh, pressures were measured at chamber levels 6, 7 and 8. The lines encircling calf and thigh show the site of strain gauge placement for continuous measuring of circumference changes during compression.

Increase in circumference caused elongation of the gauge that was read off on the recorder graph scale in mm. The obtained numerical data were used for calculation of volume by multiplying the cross area of limb segments by 90 mm (length of the compressing chamber). Subtracting the volume value before compression from that during compression provided data on the proximally transferred volume.

Statistical evaluation

For comparison of numerical data of lymphoscintigrams' densitometry Students t-test was applied with significance at $p<0.05$.

RESULTS

Lymphoscintigraphic evaluation of lymph and tissue fluid flow in the massaged limb

Lymphoscintigraphic and volumetric evaluation of lymph and tissue fluid flow has been presented on Tables 2 and 3.

Table 2. Comparison of lymphoscintigraphic images and lymph and tissue fluid flow after intermittent pneumatic massage.

	Lymphoscintigraphy		Calculated flow (ml/cycle) Total volume reaching groin
	Before massage	*After massage*	*During massage*
Stage II	Tracer spread in foot and calf, single vessel, few small inguinal nodes, no iliac lymphatics	Tracer spread in foot and calf, lymphatics up to the groin, inguinal nodes, iliac lymphatics	20-30
Stage III	Tracer spread in foot and calf, fragments of vessels, sporadically small inguinal node no iliac lymphatics	Tracer spread in lower thigh, lymphatics and fragments of nodes visible, no iliac lymphatics	40- 60
Stage IV	Tracer spread in foot and calf, no vessels and nodes visible	Tracer spread in foot, calf and thigh up the inguinal crease, no lymphatics and nodes visible, tracer in femoral canal	60-120

Table 3. Semiquantitative densitometric evaluation of lymphoscintigrams before and after intermittent compression (ratio edematous/ normal limb).

	Limb area (incl. lymphatics and tissue spread of tracer)		Inguinal lymph nodes
	Calf	*Thigh*	
Before	2.4 ± 4.5	1.2 ± 2.5	0.3 ± 0.4
After	2.8 ± 5.0	2.5 ± 3.0*	0.6 ± 1.0*

(*) After vs before treatment $p<0.05$

The pathways of lymph and tissue fluid flow during pneumatic massage have been shown on Figs 2-7 and evaluation presented in Table 2. After massage in stage II (Fig. 2) and some cases in stage III (Fig. 3,4) the tracer filled the upper parts of the thigh tissues. It flowed along lymphatics to the femoral canal and retroperitoneal space. In stage IV, it reached the inguinal crease and accumulated in the upper thigh (Fig. 5,6,7). No pictures of isotope flow from the thigh across the inguinal crease to the lower abdominal quadrant were observed. In normal limbs isotope flowed along the superficial and deep lymphatic system to the inguinal nodes and through the femoral canal to iliac lymph nodes.

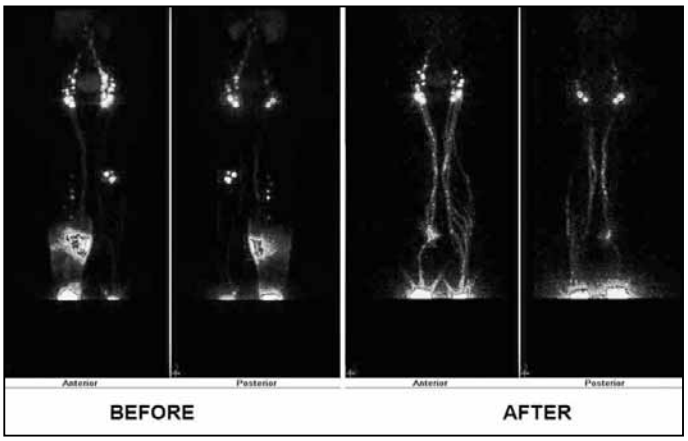

Figure 2: Lymphoscintigrams in postinflammatory lymphedema of the right lower limb, stage II. A. Before massage. Accumulation of isotope in the swollen calf. Weak outline of the superficial lymphatics. Inguinal and iliac lymph nodes visualized. B. After 1 hour of pneumatic massage most isotope was moved along normal thigh lymphatic to the groin and iliac vessels. This proved efficacy of the pneumatic massage.

Figure 3: Lymphoscintigrams in postinflammatory lymphedema of the left lower limb, stage III. A. Before massage. Isotope accumulated in the subcutaneous space of the swollen calf. No superficial and deep lymphatics are seen. Some subepidermal flow in the thigh and a small inguinal lymph node. No iliac nodes. B. After 1 hour of pneumatic massage most isotope was moved along the subcutaneous space to the groin to visualize single small inguinal nodes. Further isotope flowed through the femoral canal along large iliac blood vessels visualizing single iliac nodes. It did not flow to the hypogastrium or gluteal region.

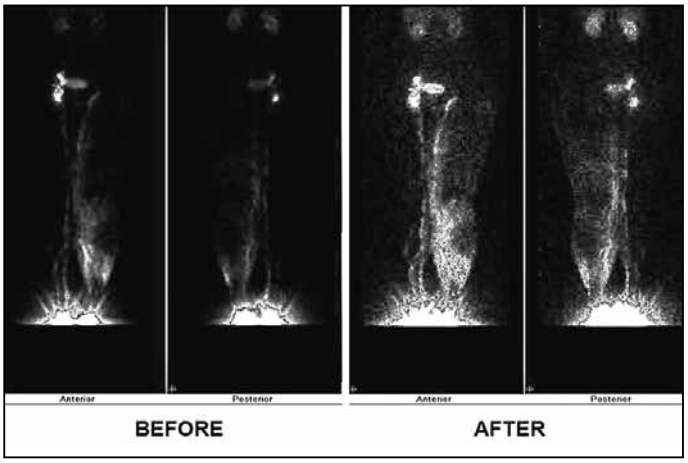

Figure 4: Lymphoscintigrams in posttraumatic lymphedema of the left lower limb, stage IV. A. Before massage. Isotope accumulates in the internal aspects of the calf with a faint outline in the thigh. No lymphatics are seen. B. After 1 hour of pneumatic massage only some isotope moved along the internal aspect of the thigh to the groin level but did not visualize inguinal nodes. This was caused by obliteration of lymphatics and fibrosis of inguinal nodes proved by biopsy. There was no flow to the hypogastrium or gluteal region.

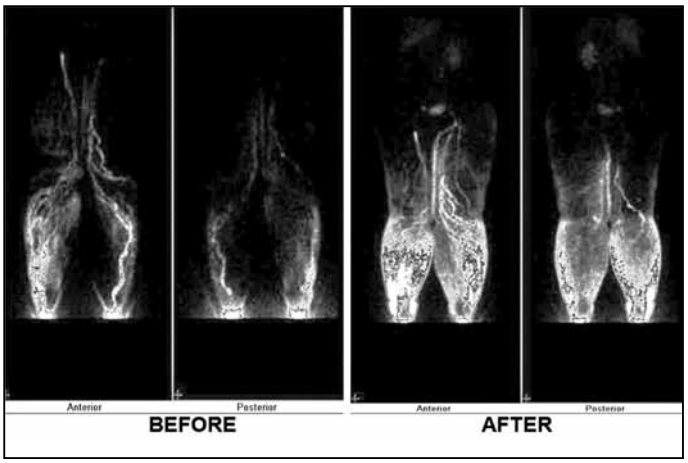

Figure 5: Lymphoscintigrams in postinflammatory lymphedema of both lower limbs, stage IV. A. Before massage. Isotope in dilated calf lymphatics and tissue subcutaneous spaces reaching mid-thigh level. B. After 1 hour of pneumatic massage most isotope was moved to the thigh but did not reach the groin. This was presumably due to the resistance to flow in the fibrotic inguinal lymph nodes. There was no flow to the hypogastrium or gluteal region.

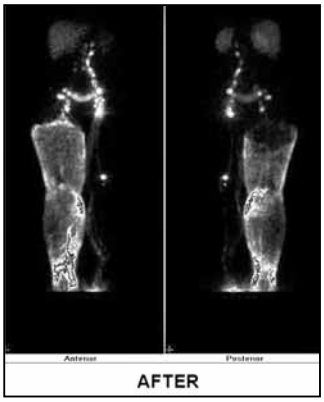

Figure 6: Lymphoscintigrams in postinflammatory lymphedema of the right lower limb, stage IV after one hour of pneumatic massage. The isotope visualized dilated subcutaneous spaces up to the inguinal level but not lymphatics. Note a sharp border for isotope flow at the inguinal ligament level. Further, isotope moved along the femoral canal to the iliac region and visualized two small lymph nodes. There was no flow to the hypogastrium or gluteal region.

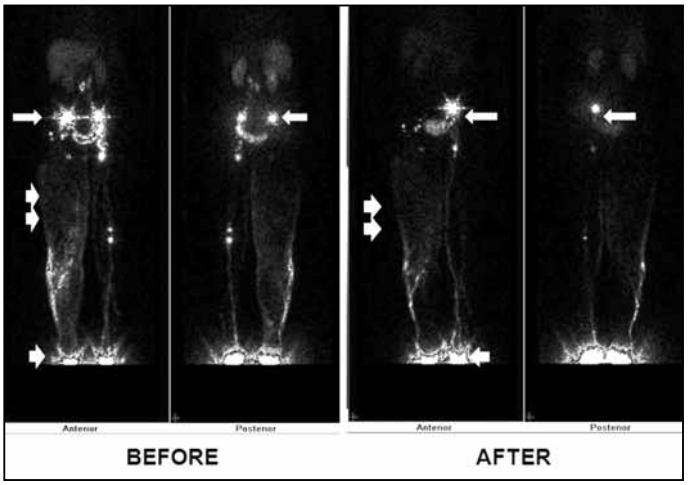

Figure 7: Lymphoscintigrams in postinflammatory lymphedema of the right lower limb, stage III. A. Before massage. Left normal side. 99Tc Nanocoll was injected into the toeweb of foot (arrow) and it visualized the superficial and deep lymphatics. To visualize lymph drainage from the hypogastrium another dose of Nanocoll was injected intradermally in the left lower abdominal quadrant (arrow). Right lymphedema side. Nanocoll injected into right foot (with lymphedema) showed few calf lymphatics (two arrows). B. After 1 hour pneumatic sequential massage of the lymphedematous right limb isotope spread in the subcutaneous tissue of calf and partly thigh but did not cross the groin level despite high pressure sequential compression. Isotope did not move to the abdominal area. Moreover, isotope injected bilaterally into hypogastrium spread slightly radially, however, did not flow to the upper or lateral quadrant.

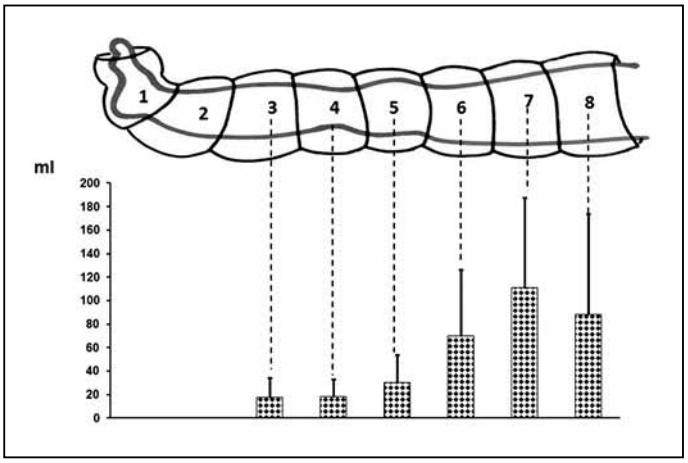

Figure 8: The calculated tissue fluid flow during intermittent pneumatic compression from the calf to the groin (ml/cycle, mean+-SD of 15 patients stage II-IV). The sleeve chambers have been numerated. Inflation from 1 to 8 at 120mmHg, each chamber 55 sec, no distal deflation.

Semiquantitative evaluation of lymphoscintigrams before and after intermittent compression

In the whole group of patients there was increase in the spread of tracer to the thigh and inguinal region including inguinal lymph nodes (Table 3). There were wide individual variations.

Lymphoscintigraphic evaluation of lymph flow from hypogastrium during limb massage

There was minimal radial spread of the isotope from the site of injection with no signs of its movement toward the upper or contralateral quadrants (Fig. 7) In two patients flow was directed toward inguinal nodes.

Tissue fluid volume transfer during pneumatic massage

Continuous recording of circumference changes during sequential compression gave indirect insight into the volumes of fluid translocated from the compressed segments to the proximal ones. The increase in circumference at each level was recalculated into increase in volume. Summarized data of 15 patients are presented on Fig. 8. The tissue fluid flow ranged from 20-30 ml/cycle in the calf to 60-105 ml/cycle in the thigh.

Relationship between the isotope spread and tissue fluid flow

Pneumatic compression caused flow of tracer toward groin both in the lymphatics and interstitial space (stage II and III). In stage IV tracer spread in the interstitial space of entire limb with a sharp border at the inguinal crease, not entering the femoral channel. The proximal flow of tracer was accompanied by tissue fluid flow (Table 2, Fig. 8). Most of tracer and massaged fluid accumulated in the thigh.

DISCUSSION

This study provided the following information: (i) pneumatic compression of the lower limb pushed isotope in lymph in the remnant lymphatics and tissue fluid in the interstitial space toward the inguinal region and femoral canal, (ii) no isotope filling fluid channels crossing the inguinal crease or running to the gluteal area was visualized, (iii) there was no isotope flow either in lymphatics or in tissue fluid to the hypogastrium, and (iv) the isotope injected intradermally in the hypogastrium did not spread during both manual and pneumatic massage to the upper and contralateral abdominal quadrants.

Our study showed that sequential pneumatic compression with high inflation pressure are very effective in pushing stagnant lymph and tissue fluid in cases with obstructive lymphedema. The lymphoscintigrams showed that tissue fluid finds its way toward the root of the extremity along the natural pathways with least hydraulic resistance. These are the perivascular spaces and spontaneously formed by tissue deformation subcutaneous channels [(2)]. Isotope accumulated along the great saphenous vein and internal aspect of the thigh. Even if there was some flow along femoral and iliac lymphatics, tissue fluid reaching the inguinal crease did not pass it. In advanced stage IV tissue fluid moved to the knee or lower thigh level only.

The flow of tracer followed during pneumatic compression the tissue fluid flow. Large volumes of proximally moved fluid indicated that it was not only lymph in the subepidermal plexus and the remaining patent lymphatics but also the tissue fluid accumulating in the spontaneously formed tissue spaces, where the bulk of edema fluid is usually found [(2)]. The qualitative comparison of lymphoscintigraphic pictures and flow data clearly showed that

sequential compression propelled lymph and stagnant tissue fluid toward the groin. Most of the fluid accumulated in the groin, which was expected. However, in contrast to the general view, it did not move toward the hypogastrium but to the femoral channel. Results of our study revive the questions of: what is the fate of fluid accumulating in the groin. Does it find its way to the pelvis through the femoral and obturator channels? How are large portions of fluid is absorbed in the upper thigh and genitals? It cannot be water only as tissue fluid protein concentration remains at low level and at the same concentration as in the calf fluid (personal observations)

There are only few publications on lymph and tissue fluid flow during pneumatic compression of swollen limbs [6,7]. Based on the results of lymphatic vascular factorial analysis, a beneficial effect of intermittent pneumatic compression was detected in 18 of 22 limbs examined. It facilitated radiocolloid transport in the proximal portion of the limb and also pushed tracer from the injection site toward the lymphatics. The effect was evident as soon as external compression therapy began [6]. In another study, pneumatic compression brought about decrease in the volume of the massaged limb, however, no flow of tracer toward the groin was observed [7]. The authors concluded that water was absorbed but fluid proteins remained in the massaged regions. No data on applied pressure and inflation timing were presented which would allow analysis of tissue fluid flow. None of these papers addressed the problem of massaged fluid flow through the groin to the hypogastrium or pelvis through the femoral channel.

There is a widely accepted notion that emptying of the hypogastrium by manual or pneumatic massage prior to limb massage creates space for lymph and tissue fluid from the massaged tissues. The essence of this concept is that treatment must first be directed at lymphatic territories, such as the trunk, so that they are adequately prepared to receive lymph from subsequently treated lymphedematous regions such as the arm or leg. This truncal clearance or decongestion approach makes intuitive sense to most intensively trained practitioners.

According to Foeldi [4] lymphatic tributary regions or territories are separated by lymphatic watersheds. The term watershed is borrowed from hydrology, where it can be thought of as a drainage basin usually bounded by ridges of higher ground. Although lymphatic watersheds are not true anatomical structures, their dividing lines delineate the direction of lymph flow [5]. Although treatment of the trunk has long been a standard MLD (manual lymphatic drainage) process, there have been no anatomical studies confirming presence of watersheds either randomized clinical trials comparing manual lymphatic drainage with and without truncal decongestion .

In our studies we were not able to confirm lymph and tissue fluid flow to the hypogastrium and from there to the neighboring quadrants. The isotope containing lymph and tissue fluid were stopped at the inguinal crease and flow was directed toward the femoral channel. Also isotope flow away from the hypogastric subcutaneous tissue was not observed. Manual massage of this region revealed radial spread of isotope but not flow to the upper or lateral quadrant. We think the concept of proximal clearing-hypogastrium clearance should be reevaluated basing on objective physiological studies of tissue fluid hydraulics.

Taken together, sequential intermittent compression of the lymphedematous lower limbs is effective in propelling lymph and tissue fluid toward the groin. It is directed toward the femoral canal but not to the hypogastrium. These findings point to the necessity of applying high compression pressures at the groin region and also searching for pharmacological and surgical methods facilitating fluid flow across the inguinal crease.

REFERENCES

1. Olszewski W.L. (1991): *Clinical picture of lymphedema.* In: W. L. Olszewski (Ed.), "Lymph stasis: Pathophysiology, diagnosis and treatment", CRC Press, Boca Raton, FL. pp. 351.
2. Olszewski W.L., Jain P., Ambujam G., Zaleska M., Cakala M. (2009): *Where do lymph and tissue fluid accumulate in lymphedema of lower limbs caused by obliteration of lymphatic collectors.* Lymphology, 42: 105-111.
3. Lechner G., Jantsch H., Waneck R., Kretschmer G. (1988): *The relationship between the common femoral artery, the inguinal crease, and the inguinal ligament: a guide to accurate angiographic puncture.* Cardiovasc Intervent Radiol.,11: 165-169.
4. Földi E., Földi M., Clodius L. (1989): *The lymphedema chaos: a lancet.* Ann Plast Surg., 22: 505-515.
5. Földi E., Földi M. (1991): *Conservative treatment of lymphedema.* In: W.L. Olszewski (Ed.), *Lymph stasis: Pathophysiology, diagnosis and treatment.* CRC Press, Boca Raton, FL. pp. 469-473.
6. Baulieu F., Baulieu J.L., Vaillant L., Secchi V., Barsotti J. (1989): *Factorial analysis in radionuclide lymphography: assessment of the effects of sequential pneumatic compression.* Lymphology, 22: 178-185.
7. Miranda F. Jr, Perez M.C., Castiglioni M.L., Juliano Y., Amorim J.E., Nakano L.C., de Barros N. Jr, Lustre W.G., Burihan E. (2001): *Effect of sequential intermittent pneumatic compression on both leg lymphedema volume and on lymph transport as semi-quantitatively evaluated by lymphoscintigraphy.* Lymphology, 34: 135-141.

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TREATMENT AND PREVENTION OF LYMPHATIC INJURIES IN SURGERY AND TRAUMA

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ABSTRACT

Authors describe their clinical experience in the treatment of patients referred to the Unit of Lymphatic Surgery and affected from injuries to the lymphatic system due to surgery or trauma . Epidemiological data point out the significant prevalence of lymphatic injuries correlated mainly to oncological operations in the ambit of general, gynaecological and urological surgery. Moreover, also venous and arterial surgery may be responsible of the appearance of early and late lymphatic complications. Diagnosis includes ultrasonography, CT, MRI, lymphoscintigraphy and oil contrast lymphography. Prevention is based on different technical details, for example a proper skin incision, lymphnodal dissection, adeguate use of drain tubes, right compressive medications on wounds, etc.. It is very important to follow-up the patient not only clinically but also by lymphoscintigraphy. For the treatment, different procedures are used including microsurgical methods, CO2 LASER, laparoscopic approach, etc.
It was identified a protocol of prevention of secondary limb lymphedema that included above all, from the diagnostic point of view, lymphoscintigraphy and, as concerns therapy, it recognized also a role to early microsurgery. Authors conclude that it is necessary to accurately follow-up the patient who has undergone an operation at risk for the appearance of lymphatic complications and, even better, to assess clinically and by lymphoscintigraphy the patient before the surgical operation.

Key words: Lymphatic injuries, Surgery, Trauma, Microsurgical Treatment, Prevention.

INTRODUCTION

In the prevention of injuries to the lymphatic system we must consider a primary and a secondary prevention.
Primary prevention includes anamnesis, which aims at pointing out risk factors, such as biological factors (constitution, sex-hormonal status, familiarity, etc.), hygienic, environmental and climatic factors, working activity and the most significant events in remote pathological anamnesis, and protective factors, such as style and habits of life (diet, sanitary measures, sports activity, etc.), social-sanitary culture of Preventive Medicine and epidemiological studies. However, for most of risk and protective factors, mechanism of action are not known yet [(1-4)].
The rate of occurrence of post-operative complications after inguinal lymphadenectomy reported in Literature is of 6-40% for seromas or lymphocele, 2-4% for haematomas, 17-65% for wound dehiscence, 6-20% for wound infection and 22-80% for lymphoedema [(5-7)].
The problem of prevention of lymphatic injuries in surgery is extremely important if we think about the frequency of both early complications such as lymphorrhea, lymphocele, wound dehiscence and infections and late complications such as lymphangites and lymphedema. Nowadays, it is possible to identify risk patients and prevent these lesions or treat them at an early stage [(8-11)].
We tried to perform a protocol of prevention which includes diagnostic investigations such as lymphoscintigraphy and early therapeutic strategies which involve both physical and surgical procedures.

MATERIALS AND METHODS

The main causes of secondary lymphatic injuries are represented by surgical operations, irradiations, infections, infestations (filariasis), traumas, metastatic lymphnodal involvement, etc.
The high risk surgical operations include: radical mastectomy, Wertheim-Meigs operation, oncologic operation in urology, abdominal surgery, lymphadenectomies in "critical sites" (groin and axilla).
Other operations are represented by exeresis of lipomas in critical sites, saphenectomy, inguino-crural hernioplasty, etc.
Our experience includes the treatment of a patient with left supraclavicular chylocele due to thoracic trauma, in which we could repair the thoracic duct fistula by microsurgical technique avoiding its surgical closure. In a similar case of thoracic duct fistula, but due to bioptic excision of a supraclavicular lymphnode, we could reconstruct the thoracic duct preventing its ligation. In another patient with wound infection and lymphangitis at the groin after groin lymphadenectomy due to vulvar carcinoma, we had to excise the infected soft tissues and cover the wide gap with a muscular flap from the rectus abdominis, preserving lymphatics coming from the leg thanks to the blue dye injected at the thigh, to avoid secondary lymphedema of the leg. Seven patients with pelvic lymphocele were treated by conservative method by putting two drain tubes through the skin guided by ultrasounds and using sclerosing agents and maintaining the tubes in deep aspiration.

Three patints with inguinal lymphocele were treated by removing the lymphocele and performing lymphatic-venous anastomoses to prevent secondary lymphedema of the corresponding limb. In these cases, lymphoscintigraphy is of great help in showing the lymphatic way that fills and maintain the lymphocele. Our widest experience is in the prevention and early treatment of arm lymphedema after breast cancer treatment (195 patients followed-up at 5-7 years). This experience includes the possibility to perform lymphatic-venous anastomoses directly at the same time of axillary lymphadenectomy or very early after breast cancer surgery, following the patient both clinically and by lymphoscintigraphy. Another important clinical experience is in the prevention of lymphatic injuries in venous surgery, by using blue dye and preserving lymphatic and lymphnodal structures or performing lymphatic-venous shunts at the same time of the vein surgery, depending on the entity of the lymphatic damage associated with the venous dysfunction.

In patients with anamnestic potential risk, it is important to educate the patient to examine himself, to visit him periodically and to perform a lymphoscintigraphy. On the other hand, patients without anamnestic risk can be educated to examine themselves and to visit them at distance of time from primary operation.

Secondary prevention includes clinical examination and lymphoscintigraphy, which can point out an initial lymphatic impairment before its clinical manifestation (Figs.1,2).

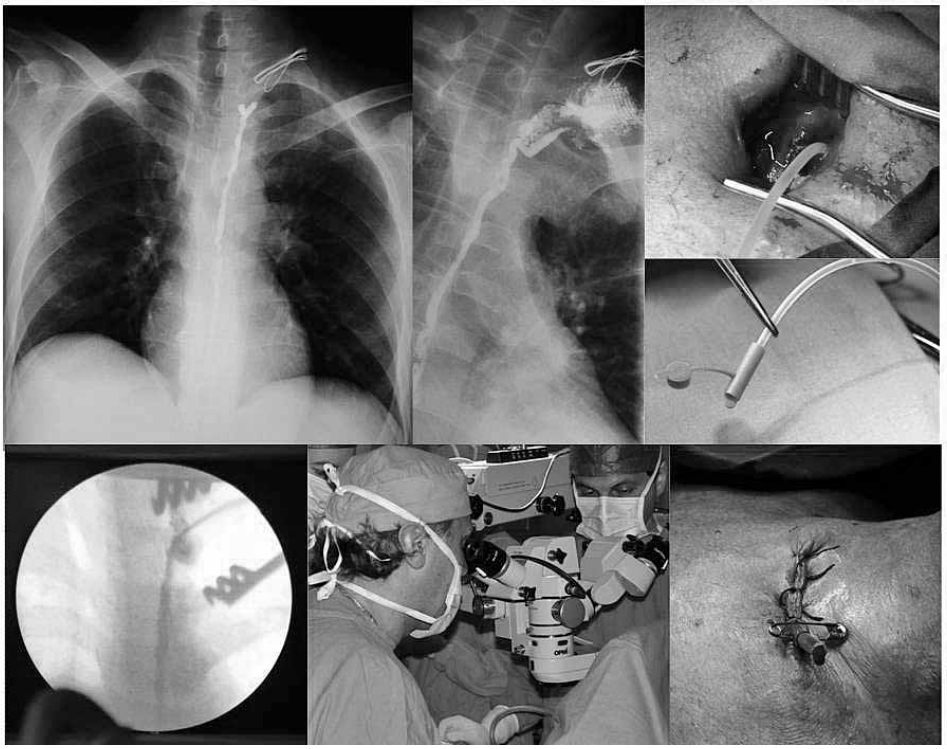

Fig. 1: The patient was addressed to our hospital because he was affected by a chylous fistula at the left supraclavicular region occurred after a lymphnodal biopsy. Traditional oil contrast lymphangiography allowed to visualize chylous leakage and the fistula and the thoracic duct was repaired by microsurgical technique.

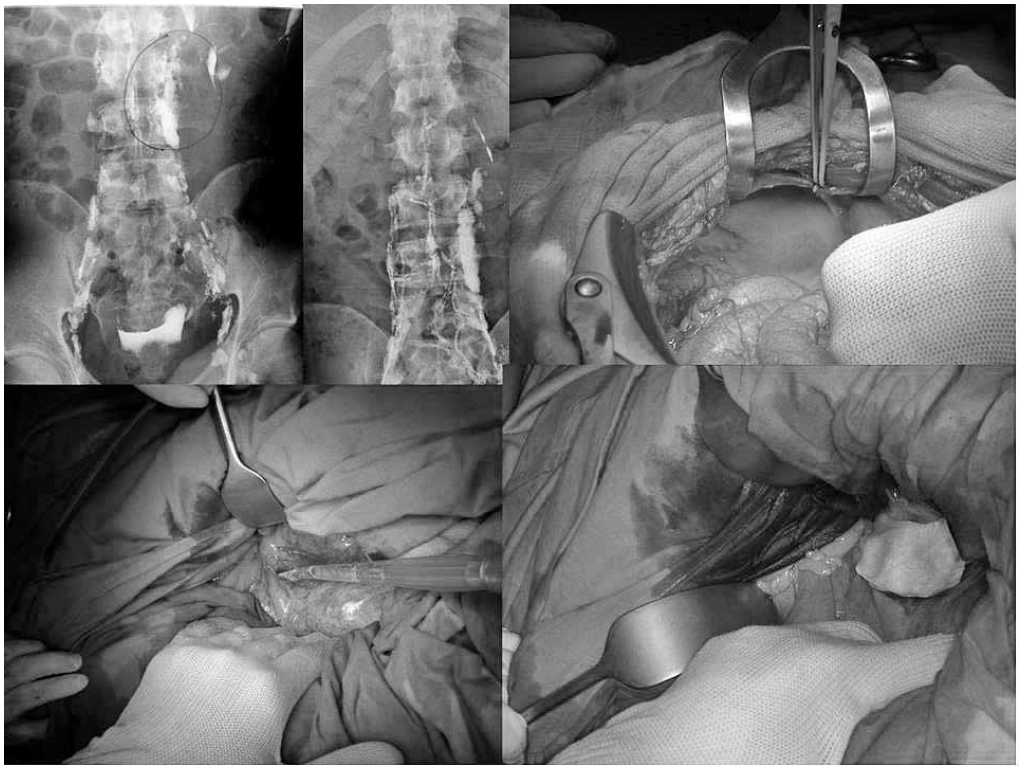

Fig. 2: The patient was addressed to our hospital because he was affected from chylous ascitis appeared after an urological oncological operation with extended lymphoadenectomy. Lymphangiography demonstrated the site of lymphatic leakage and a laparotomy after a fatty meal allowed us to find the lymphatic injury and repair it by microsurgical techniques and placing biological sealing material.

RESULTS

Our results were evaluated both clinically and instrumentally (lymphoscintigraphy, ultrasounds, CT, etc.). As concerns the treatment of supraclavicular lymphocele and chylocele, a long term follow-up has shown the complete disappearance and the absence of any relapse of the pathology. Also ultrasounds and CT scan confirmed the good long term outcome. The lymphatic drainage of patients after groin surgery with lymphatic prevention using the blue dye was investigated by lymphoscintigraphy performed at medium and long term after surgery, and it was demonstrated a good lymphatic sparing and a consequent sufficient lymphatic drainage of the limb. There was no relapse of pelvic lymphocele even at long term follow-up (over 3-5 years), demonstrating how the conservative treatment of these disorders might be to consider as first choice before a second surgery. The treatment of inguinal lymphocele, removing the lymphocele and performing lymphatic-venous anastomoses to prevent secondary lymphedema was successful. There were no relapse of the lymphocele and there was no appearance of secondary leg lymphedema. Early treatment of arm lymphedema following breast cancer therapy proved to carry out a complete recover of the disease with the stable disappearance of lymphedema and no necessity to wear any compression garment. The same outcome was for the primary surgical prevention of secondary arm lymphedema, performing lymphatic-venous shunts at the same time of axillary dissection, In venous surgery, results of the use of the blue dye and of lymphatic-venous shunts during surgical operation for varices demonstrated to bring about positive results, in treating patients with both venous and lymphatic disorders or in preventing lymphatic injuries during vein surgery.

DISCUSSION AND CONCLUSIONS

The wide clinical experience above reported in the prevention of lymphatic injuries in general, oncologic, vascular and other specilistic (urologic, gynaecologic) surgery allows us to say that it is nowadays possible to identify patients at low, medium and high risk to develop lymphatic diseases and to prevent them, besides treating lymphatic complications early in order to obtain better results.
The diagnostic investigations that can help us in this sense are represented by ultrasonography, CT scan, MRI, lymphoscintigtaphy and lymphangiography (12-14).
From the operative point of view, it is important to pay attention to lymphatic vessels also during skin incision and to use magnification devices during lymphnodal dissection, using suture

material for lymphatic ligations instead of electric coagulation. It is important to use properly the drain tubes, to put them in adequate aspiration associated with proper compression medication on wounds, which might be closed without excessive tension. Proper postural immobilization have to be considered as well (15).

Finally, a proper follow-up of these patients helps in identifying any possible lymphatic complications precociously and thus to treat it very early allowing to overcome the problem completely. This is, therefore, a proposal of prevention and early treatment of secondary lymphatic injuries, which might be applied by all different specialists (general surgeons, urologists, gynaecologists, oncologists, radiotherapists, etc.) during their daily clinical activity to try to get to the aim of preventing the patients, who undergo "risk" operations, from fighting also against complex lymphatic acquired disorders such as lymphorrhea, lymphocele, lymphedema, etc, besides their already more or less serious primary pathological condition.

REFERENCES

1. Pain S.J., Purushotham A.D.: *Lymphoedema following surgery for breast cancer.* British Journal of Surgery, 2000; 87: 1128-1141.
2. Clodius L.: *More on axillary lymphadenectomy.* Lymphology, 2003; 36: 1-6.
3. Roses D.F., Brooks A.D., Harris M.N., Shapiro R.L., Mitnick J.: *Complications of level I and II axillary dissection in the treatment of carcinoma of the breast.* Annals of Surgery, 1999; 230(2): 194-201.
4. Burstein H.J., Winer E.P.: *Primary Care for Survivors of Breast Cancer.* N Engl J Med, 2000; 343: 1086-1094.
5. Tonouchi H., Ohmori Y., Kobayashi M., Konishi N., Tanaka K., Mohri Y. et al.: *Operative morbidity associated with groin dissections.* Surg Today, 2004; 34: 413-8.
6. Paley P.J., Johnson P.R., Adcock L.L., Cosin J.A., Chen M.D., Fowler J.M. et al.: *The effect of sartorius transposition on wound morbidity following inguinal-femoral lymphadenectomy.* Gynecol Oncol, 1997; 64: 237-41.
7. Urist M.M., Maddox W.A., Kennedy J.E., Balch C.M.: *Patient risk factors and surgical morbidity after regional lymphadenectomy in 204 melanoma patients.* Cancer, 1983; 51: 2152-6.
8. Hoe A.L., Iven D., Boyle G.T., Taylor I.: *Incidence of arm swelling following axillary clearance for breast cancer.* Br J Surg, 1992; 79: 261-262.
9. Olszewski W.L.: *Axillary dissection for breast cancer.* Lymphology, 2002 Mar; 35(1): 41-2.
10. Nos C., Lesieur B., Clough K.B., Lecuru F.: *Blue dye injection in the arm in order to conserve the lymphatic drainage of the arm in breast cancer patients requiring an axillary dissection.* Ann Surg Oncol, 2007; 14(9): 2490-2496.
11. Boneti C., Korourian S., Bland K., Cox K., Adkins L.L., Henry-Tillman R.S., Klimberg V.S.: *Axillary reverse mapping: mapping and preserving arm lymphatics may be important in preventing lymphedema during sentinel lymph node biopsy.* J Am Coll Surg, 2008 May; 206(5): 1038-42.
12. Campisi C., Boccardo F.: *Microsurgical techniques for lymphedema treatment: derivative lymphatic-venous microsurgery.* World J Surg, 2004 Jun; 28(6): 609-13.
13. Campisi C., Boccardo F., Padula P. et al.: *Prevention of Lymphedema: Utopia or Possible Reality?* Lymphology, 1994; 27(S): 676.
14. Campisi C., Boccardo F.: *Prevention of Secondary Lymphedema. Possible Role of Microsurgery.* Lymphology 1996; 29 (S): 41-43.
15. Boccardo F., Casabona F., De Cian F., Friedman D., Villa G., Bogliolo S., Ferrero S., Murelli F., Campisi C.: *Lymphedema Microsurgical Preventive Healing Approach: A New Technique for Primary Prevention of Arm Lymphedema After Mastectomy.* Ann Surg Oncol, 2009 Mar;16(3): 703-8.

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PRIMARY LYMPHEDEMA: PRODIGAL SON OF LYMPHATIC MALFORMATION

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EDITORIAL

Through many decades, no one paid enough attention on the obscure but unique origin of the primary lymphedema but considered harmless to deal as one of chronic lymphedema [1, 2]. Indeed, through the last century our knowledge on primary lymphedema has been so limited that we did not know the full nature of the primary lymphedema as a tip of the iceberg of the lymphatic malformation (LM); it is still considered not much serious issue to the clinicians [3, 4].

On the contrary, the secondary lymphedema, mostly involved to the cancer management in the developed countries, has been well investigated for advanced management to reduce if not prevent the condition by appropriate measurement [5, 6].

Nevertheless, the efforts to define the relationship of the primary lymphedema with the rest of lymphatic malformation for more than two decades began to deliver substantial new information to help us to understand this neglected condition better. Recently published "IUP Consensus on Primary Lymphedema-2009" is one of these contribution [7].

This consensus group, however, decided to limit its scope strictly to the subject linked to the clinical aspect of primary lymphedema as the most crucial message to be delivered at this time; the other side of the coin from the LM's point of view as one of vast groups of the congenital vascular malformations (CVMs) was intentionally left to avoid unnecessary confusion [8].

Regardless, conventional concept defines primary lymphedema based on this anatomical defect on the lymph transporting system, classified to the LM even though some of the primary lymphedema by definition has a limited pathology in the functional level with no morphological/ anatomical defect involved [7].

Therefore, additional knowledge on the LM side view will be certainly helpful to understand the nature of the primary lymphedema as one of the LM, and subsequently for improved management as one of the LM with a bird eye's view, which we can no longer afford to ignore.

The LM is the outcome of defective development of the lymphatic system during various stages of the lymphangiogenesis either alone or combined with other vascular defects affecting the capillary, arterial, and venous system. Such combined condition with other CVMs is distinctively different from independent condition on its clinical behavior so that it is now separately classified as "hemolymphatic malformation" to improve its management [9, 10]. (Table 1)

Therefore, thoughtful consideration on this risk combined with other CVMs (e.g. Klippel-Trenaunay Syndrome) is mandated on every primary lymphedema even if the condition is clinically obvious as a solitary LM lesion [11].

The majority of primary lymphedema represent the clinical manifestation of this LM developed during the "later" stage of the lymphangiogenesis, which is grouped as the "truncular" lesions. Such embryological subclassification is extremely important because the "extratruncular" lesion from the "early" stage keeps its evolutional potential originated from the mesenchymal cells while the truncular lesion from the 'later' stage does not [12, 13].

Another words, the "truncular" LM lesion to cause primary lymphedema is a "stable" lesion involved to fully matured lymphatic vessel trunk/system in general as defective conditions of hypoplasia, aplasia, numerical hyperplasia, or dilation (lymphangiectasia) with valvular incompetence. But the "extratruncular" LM lesion, often known as "lymphangioma", is such "unstable" condition to grow when stimulated (e.g. female hormone, menarche, pregnancy, trauma, surgery) [14, 15].

Infrequently, we clinicians encounter the primary lymphedema/truncular LM coexisting with the extratruncular LM (e.g. capillary/cavernous lymphangioma) often in a hidden condition; a fair portion of such condition is further combined with additional CVM lesions (e.g. truncular & extratruncular venous malformation) to make its clinical management much complicated. Without proper management of coexisting extratruncular LM lesions with priority, the truncular LM as primary lymphedema would not respond to DLT (decongestive lymphatic therapy) - oriented conservative care effectively [16] and often deteriorate fast following increased frequency of the local-regional-systemic infection with/without lymphatic leakage from the extratruncular LM lesions. When the primary lymphedema is further combined with venous malformation (VM) [17, 18], the VM lesion should have a priority to any of coexisting extratruncular LM lesions except life-threatening lymphangioma (e.g. infected cystic hygroma affecting the upper airway).

By timely care on coexisting VM - truncular and/or extratruncular - lesions (e.g. Klippel-Trenaunay Syndrome), the DLT-based primary lymphedema care will be more effective with much better long term prognosis.

When the arterio-venous malformation (AVM) [19, 20] is further combined with the VM to the LM, known as Parkes-Weber Syndrome, the AVM lesion should be controlled with priority whenever feasible with no delay. Otherwise, the lymphedema will progress rapidly resisting to the conventional DLT.

Table 1. Hamburg Classification of Congenital Vascular Malformation (CVM), modified*

Main classification based on its predominant vascular component:

- Arterial malformation
- Venous malformation
- AV (arteriovenous) shunting malformation
- Lymphatic malformation
- Capillary malformation
- Combined vascular malformation

Embryological subclassification:

- Extratruncular forms - developmental arrest at the earlier stages of embryonal life:
  - *Diffuse, infiltrating*
  - *Limited, localized*
- Truncular forms - developmental arrest at the later stages of embryonal life:
  - *Obstruction & Stenosis*
    - *Hypoplasia; Aplasia; Hyperplasia*
    - *Membrane; Congenital spur; Web*
  - Dilatation
    - *Localized (aneurysm)*
    - *Diffuse (ectasia)*

(*) Both extratruncular and truncular forms may exist together in same vascular malformation; may be combined with other various malformations (e.g. capillary, arterial, AV shunting, venous, hemolymphatic and/or lymphatic); and/or may exist with hemangioma.

(*) Based on the consensus on the CVM classification through the international workshop in Hamburg, Germany, 1988, which was upheld by subsequently founded ISSVA (International Society for Vascular Anomaly).

CONCLUSION

Primary lymphedema is mostly clinical manifestation of the truncular LM lesion; it should be managed with full consideration on closely existing extratruncular LM as well as other CVM lesions for fail-proof management.

REFERENCES

1. Lee B.B.: *Lymphedema-Angiodysplasia Syndrome: a Prodigal form of Lymphatic Malformation (LM).* Phlebolymphology, 2005; 47: 324-332.
2. Lee B.B., Kim Y.W., Seo J.M., Hwang J.H., Do Y.S., Kim D.I., Byun H.S., Lee S.K., Huh S.H., Hyun W.S.: *Current concepts in lymphatic malformation (LM).* J Vasc Endovasc Surg, 2005; 39(1): 67-81.
3. Lee B.B.: *Current issue in management of chronic lymphedema: Personal Reflection on an Experience with 1065 Patients. Commentary.* Lymphology, 2005; 38: 28-31.
4. Lee B.B.: *Chronic lymphedema, no more stepchild to modern medicine!* Eur J Lymphol, 2004; 14(42): 6-12.
5. Lee B.B.: *Lymphatic Malformation,* Pages 31-42, Chapter 4, *Lymphedema-Diagnosis and Treatment.* Tredbar, Morgan, Lee, Simonian, Blondeau (eds). Springer-Verlag London Limited 2008.
6. Lee B.B.: *Lymphoedeme post-chirurgical: un terme frappe d'interdiction pour les chirurgiens.* Angeiologie, 2004; 56(4): 7-8.
7. Lee B.B., Andrade M., Bergan J., Boccardo F., Campisi C., Damstra R., Flour M., Gloviczki P., Laredo J., Piller N., Michelini S., Mortimer P., Villavicencio J.L.: *Diagnosis and treatment of Primary Lymphedema - Consensus Document of the International Union of Phlebology (IUP)-2009.* International Angiology 2010 Oct; 29(5): 454-70.
8. Lee B.B., Villavicencio J.L.: *Primary Lymphedema and Lymphatic Malformation: are they the two sides of the same coin?* Eur J Vasc Endovasc Surg, 2010; 39: 646-653.
9. Lee B.B., Kim H.H., Mattassi R., Yakes W., Loose D., Tasnadi G.: *A new approach to the congenital vascular malformation with a new concept: how the pioneer Prof. Stefan Belov enlightened us through the Seoul consensus.* Int J Angiol, 2003; 12: 248-251.
10. Lee B.B., Mattassi R., Loose D., Yakes W., Tasnadi G., Kim H.H.: *Consensus on Controversial Issues in Contemporary*

Diagnosis and Management of Congenital Vascular Malformation - Seoul Communication. Int J Angiol, 2004; 13(4): 182-192.

11. Lee B.B., Laredo J., Seo J.M., Neville R.: *Hemangiomas and Vascular Malformations.* Mattassi, Loose, Vaghi (eds) Chapter 29, Treatment of Lymphatic Malformations. Pages 231-250. Springer-Verlag Italia, 2009, Milan, Italy.
12. Lee B.B., Laredo J., Lee T.S., Huh S., Neville R.: *Terminology and classification of congenital vascular malformations.* Phlebology, 2007; 22(6): 249-52.
13. Lee B.B., Villavicencio L.: Chapter 68. General Considerations. Congenital Vascular Malformations. Section 9. Arteriovenous Anomalies. Pages 1046-1064. Rutherford's Vascular Surgery. 7th Edition. Cronenwett J.L. and Johnston K.W., Eds. Saunders Elsevier, Philadelphia, PA, USA, 2010.
14. Lee B.B., Kim Y.W., Kim D.I., Hwang J.H., Laredo J. and Neville R.: *Supplemental surgical treatment to end stage (stage IV-V) of chronic lymphedema.* Int Angiol, 2008 Oct; 27(5): 389-95.
15. Lee B.B.: Surgical Management of Lymphedema, Pages 55-63, Chapter 6, Lymphedema-Diagnosis and Treatment. Tredbar, Morgan, Lee, Simonian, Blondeau (eds) Springer-Verlag London Limited, 2008.
16. Lee B.B., Bergan J.J.: *New Clinical and Laboratory Staging Systems to Improve Management of Chronic Lymphedema.* Lymphology, 2005; 38(3):122-129.
17. Lee B.B., Do Y.S., Byun H.S., Choo I.W., Kim D.I., Huh S.H.: *Advanced management of venous malformation (VM) with ethanol sclerotherapy: mid-term results.* J Vasc Surg, 2003; 37(3): 533-8.
18. Lee B.B., Bergan J., Gloviczki P., Laredo J., Loose D.A., Mattassi R., Parsi K., Villavicencio J.L., Zamboni P.: *Diagnosis and treatment of venous malformations - Consensus Document of the International Union of Phlebology (IUP)-2009.* International Angiology, 2009 December; 28(6): 434-51.
19. Lee B.B., Laredo J., Deaton D.H., and Neville R.F.: Arteriovenous malformations: evaluation and treatment. Pages 583-593, Chapter 53, Handbook of Venous Disorders: Guidelines of the American Venous Forum, 3rd Edition; Gloviczki, P., Ed; A Hodder Arnold: London, UK, 2009.
20. Lee B.B., Lardeo J., Neville R.: *Arterio-venous malformation: how much do we know?* Phlebology, 2009; 24: 193-200.

ERRATA CORRIGE

Errata in No. 63: The current executive committee of the Society is as follows:

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HYDRAULICS OF TISSUE FLUID DURING PNEUMATIC COMPRESSION IN LYMPHEDEMA OF LOWER LIMBS

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Running title: Tissue fluid pressure and flow in lymphedema

ABSTRACT

Background: Physiotherapy of edema in cases with obstructed main lymphatics of lower limbs requires knowledge of how high external pressures should be applied manually or set in compression devices in order to generate tissue pressures high enough to move tissue fluid to the non-swollen regions and how to measure its flow rate. Methods: We measured tissue fluid pressure and flow in subcutaneous tissue of lymphedematous limbs stage II to IV at rest and during pneumatic compression under various pressures and inflation timing. An 8-chamber sequential compression device inflated to pressures 50 to 120 mmHg, for 50 sec each chamber, with no distal deflation was used. Pressures were measured using wick-in-needle and electronic manometer. Fluid flow was calculated from continuously recorded changes in limb circumference
using strain gauge plethysmography. Results: Before massage, in all stages of lymphedema, stagnant tissue fluid pressures in subcutaneous tissue ranged between –1 to +10 mmHg and did not differ from those measured in normal subjects. Pressures generated in tissue fluid by pneumatic compression reached 40 to 100 mmHg and were lower than those in inflated chambers. High pressure gradient through the skin was caused by its rigidity (fibrosis) and dissipation of applied compression force to proximal non-compressed limb regions. The calculated volumes of displaced tissue fluid ranged from 10 to 30 ml per compression cycle to reach in some cases 100 ml in the groin region. Conclusions: tissue fluid pressures generated by a pneumatic device were found lower than in the compression chambers. The obtained results point to the necessity of applying high pressures and longer compression times to generate effective tissue fluid pressures and provide enough time for moving the stagnant fluid.

Key Words: Tissue fluid, lymph, lymphedema, compression therapy.

INTRODUCTION

Pneumatic compression of tissues with lymph stasis is beside the manual massage a commonly used therapeutic modality in limb lymphedema. A number of pneumatic devices have been constructed and they are being widely used . The classification list of pneumatic compression devices includes non-segmental and segmental home models for half or full leg without or with calibrated gradient pressure [1-12]. The devices differ with respect to the number of chambers, time of inflation, deflation, regulation of inflation pressure and calibrated gradient pressure as well as garments design. Most garments are customized for limbs, however, there are also some for the trunk and hypogastrium. The diversity of devices and their function programs bear upon the results of treatment. Comparison of data is difficult because the applied compression parameters vary in different centers. This is reflected in the pertinent literature by lack of reports of comparative studies determining inflation pressure levels, inflation/deflation cycle times, total pumping times in patients grouped according to the etiology of lymphedema, its duration and staging, tissue compliance and histological changes,

lymphoscintigraphic evaluation, frequency of recurrent septic attacks (dermato-lymphangio-adenitis, DLA) and other parameters.
The technical parameters of pneumatic compression devices are usually based on blood rheological data derived from the textbooks. These are the capillary and venous blood pressure, tissue venous blood flow and capacitance, capillary filtration rate and laser-measured capillary flow. Unfortunately, there are no data on tissue fluid and lymph hydraulics. Basing on the blood pressure/flow data, the recommended compression pressures for treatment of lymphedema do not exceed 50mmHg, time of compression by a sleeve chamber remains around 5 seconds and it is followed by rapid deflation. Total compression time by an 8-chamber sleeve ranges between 20 to 40 seconds. Most devices have calibrated pressure gradients decreasing proximally by up to 20%.
Lack of consistency in results of treatment by pneumatic compression prompts investigation of the pathophysiological events and hydraulic parameters in the interstitial space of the massaged tissues and in particular the tissue fluid pressures/ flows and hydraulic conductivity in normal and edematous lower limbs. We measured tissue fluid pressures and flow under the skin of lymphedematous and control healthy lower limbs at rest and during pneumatic compression using a specially constructed, according to our design, compression device (Biocompression, Moonachie, NJ). It was made of 8 sequentially inflated chambers, with proximal gradient pressure, time of inflation sufficient for translocation of fluid from the compressed to the proximal regions and no deflation of distal chambers to prevent fluid back-flow and venous stasis. The obtained data are the first in the literature showing the hydraulic conditions created by pneumatic compression in the lymphedematous limb.

MATERIAL AND METHODS

Patients

Study was carried out on 15 patients of Polish and Indian ethnic origin, age 28-56, mean weight 65 kg (58-72), mean height of 168 cm (161-178), BMI ranged 18.5 - 25 with diagnosis of lymphedema of one lower limb, stage II to IV, duration of 2 to 15 years (Table 1). There were no obese individuals. All patients originated from large cities. They practiced daily foot washing with antiseptic soap and were wearing shoes. Seventeen patients reported small foot skin abrasions or light trauma of foot in the past followed by development of foot and calf edema disappearing after rest. Larger edema developed months to years later and in 50% of cases was complicated by 1 to 3 attacks of dermato-lymphangio-adenitis. In 3 patients edema developed without any detectable reason. Cases with acute inflammation, chronic venous insufficiency and systemic etiology of edema were excluded from the study. Five male volunteers with healthy legs served as controls.

Clinical staging

Staging was based on clinical evaluation: level of edema embracing limb from foot to groin and degree of skin keratosis and fibrosis. Briefly, in stage I pitting edema was limited to the foot, in stage II pitting edema affected foot and lower half of the calf, in stage III foot and calf were involved, with hard foot and ankle area skin, in stage IV the whole limb was edematous with foot and calf skin hyperkeratosis and papillomatosis of toes [13].

Lymphoscintigraphic staging

Evaluation of lymphatic pathways was done on lymphoscintigraphic images. They revealed in stage I spread of tracer in the foot, faint outline of superficial lymphatics and small inguinal lymph nodes. In stage II, there was spread of tracer in foot and lower part of calf, interrupted outline of a single lymphatic and few small inguinal nodes with irregular outline. In stage III no draining lymphatics were seen with some inguinal nodes of irregular outline appearing after 2 hours. Stage IV was characterized by spread of tracer in the foot and entire calf without visualization of collecting lymphatics and nodes.
The consent of patients and volunteers was obtained and the study was approved by university ethics committees and Polish-Indian intergovernmental agreement on scientific cooperation.

Pneumatic compression appliance

Pneumatic compression device met the following proposed by us conditions: multi-chamber, sequential inflation, gradient inflation

Table 1. Demographic data of patients with lymphedema of lower limb undergoing investigations of tissue fluid pressure and flow during pneumatic compression therapy

M/F	AGE	GROUP/STAGE	LEVEL OF EDEMA	SKIN CHANGES	LYMPHOSCINTIGRAPHY
2M, 3F	28-45	II	mid calf	none	foot & lower calf spread, few collectors and inguinal nodes
3M, 2F	25-52	III	knee	foot keratosis	foot & calf spread, single collector, inguinal node remnants
3M, 2F	26-48	IV	whole limb	foot, calf keratosis	foot & calf spread, no lymphatics and inguinal nodes
2M, 3F	28-52		Healty		ND

pressure, time of inflation sufficient for translocation of tissue fluid to proximal region, no deflation of distal chambers to prevent fluid back-flow and venous stasis in the superficial limb system. We used a device produced for us by Biocompression (Moonachie, NJ). It was composed of 8 segments 9 cm long each, sequentially inflated, inflation pressures were regulated from 50 to 125 mmHg, gradient pressures decreasing proximally by 20%, inflation time of each chamber was 50 sec, total inflation time equaled 400 sec., there was no deflation of distal chambers, deflation time of all chambers was 50 sec at the end of each cycle. The inflation pressures were measured in chambers and compared with those on pumping device manometers. The differences ranged between 2 and 5 mmHg.

Tissue fluid pressure measurement

The wick-in-needle technique was used. Calf and thigh skin were disinfected with isopropyl alcohol. One ml of 2% xylocaine with 5 ∝g/ml adrenaline was injected intradermally and subcutaneously at 6 points of calf and thigh (Fig.1). Adrenaline constricted arterioles and small veins preventing blood leakage at the tip of the wick. An 8 gauge injection needle with a polyethylene tubing (OD 1.34mm) containing glass-wool wick protruding 5 mm from the tubing tip was introduced under the skin at the depth of 5-8 mm at the level of chambers 3 to 8. The needle was withdrawn, whereas the wick-in-tubing remained in situ. A drop of antibiotic ointment was placed at the site of tubing entry to seal off channel made by the needle. The outer part of tubing was fixed to the skin by adhesive tape. It was led out through an opening in the compression sleeve, then connected to the pressure transducer (Honeywell, Elblinger, Poland). Recording was done using a 3 channel device, pressure range -20 to +150 mmHg (Telsoft, Warsaw, Poland) and LabView software (National Instruments, Austin, TX, USA). Calibration of pressure was done with use of electronic device (National Instruments, Austin, TX, USA) and mercury and water manometers. Position of the transducer was zeroed putting it exactly at the level of the subcutaneously located wick using a light beam device. Pressure recording was started 1 min before inflation of the sleeve and continued over the entire sequential

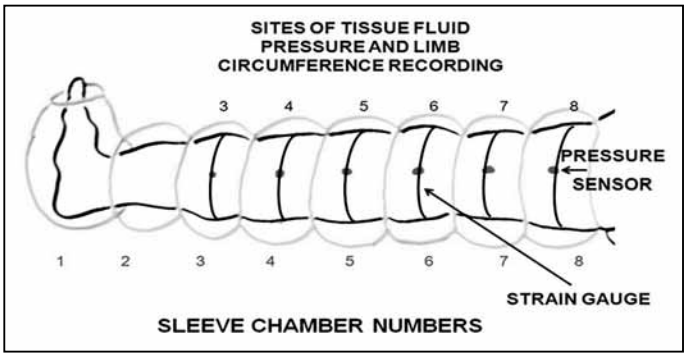

Figure 1: Schematic presentation of lower limb in a pneumatic sleeve with 8 chambers 9cm wide each. Tissue fluid pressure was measured at 6 points indicated by large dots. The lowest point in the calf was at chamber 3 level, then at levels 4 and 5. In the thigh, pressures were measured at chamber levels 6, 7 and 8. The lines encircling calf and thigh show the site of strain gauge placement for continuous measuring of circumference changes during compression.

inflation of 8 chambers. The data were collected using Microsoft Excel program and were presented graphically on a pressure/time scale.

Continuous limb circumference measurement

Strain gauge plethysmography was used to measure circumference changes in the calf and thigh segments corresponding to the sequentially inflated chambers (Fig.1). The obtained data served calculation of volume changes of limb, brought about by the proximally moved tissue fluid. Briefly, a plethysmograph (Hokanson, Bellevue, WA, type EC6) in a recording vein mode was applied. Six mercury strain gauges of a length of 22 cm to 53 cm were put around limb at chamber levels 3 to 8. Elongation of the gauge was read off on the recorder graph scale in mm. It reflected the change in consecutive segments' circumference when inflation of chambers propelled mobile tissue fluid in the proximal direction. The obtained numerical data were used for calculation of volume by multiplying the cross area of limb segments by 90 mm (length of the compressing chamber). Subtracting the volume value obtained before compression from that during compression provided data on the proximally transferred fluid volume.

RESULTS

Resting limb tissue fluid pressures

Tissue fluid pressure measured under the skin in lymphedematous calf subcutis in a horizontal position without movements ranged between –1.5 and 10 mmHg (mean 2.5±3.0 SD) and in controls between –1.8 and 3.0 mmHg (mean 0.8±1.2 SD). There were no statistically significant differences between the groups although in some advanced lymphedema cases pressures were slightly above the mean value.

Tissue fluid pressures and flow during pneumatic massage

Tissue fluid pressures during the first inflation of each sleeve chamber were in all patients lower than those in the chambers. This was observed both in the normal and edematous limbs (Fig. 2 A, B and 3). Summarized data of 15 patients and 5 normal subjects are presented on Fig. 4. The high gradient across skin was most likely caused by skin rigidity (fibrosis) and dispersion of the applied force to the proximal non-compressed regions. Unexpectedly, there was little tissue fluid pressure transmission from the compressed to the non compressed proximal segments for a distance of 9 cm (width of the chamber) in normal as well lymphedematous limbs. For example, inflation of chamber 1 and 2 in the calf did not increase pressure at level 3. Interestingly, there was building up of pressure in the distal parts of the limb during sequential inflations of proximal chambers (Fig. 2 A, B). This was presumably due to flow obstruction at the inguinal level what could be depicted on lymphoscintigrams. Another finding was that in the popliteal and upper thigh tissue fluid pressures were reaching lower levels than in other limb regions. These two regions contain loose connective tissue, are usually less swollen and accumulate fluid translocated during sequential massage.

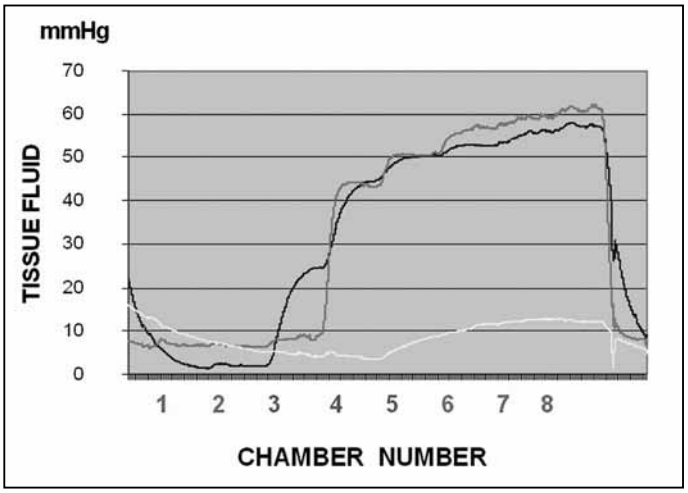

Figure 2A: Tissue fluid (TF) pressure recordings in the NORMAL CALF subcutaneous tissue (stage III) during pneumatic compression of 50 mmHg. Pressures recorded at chamber, level 3, above ankle (first ascending line), 4, mid-calf (second ascending line) and 5, below knee (third ascending line). Note that TF pressures during first inflation of chambers at level 3, 4 and 5 were lower than those in the chambers. Inflation of chamber 3 produced at level 3 pressure of 25mmHg (first ascending line), stepwise rising during inflation of consecutive chambers to 55mmHg. Inflation of chamber 4 (second ascending line) produced tissue fluid pressure rise at level 3 and 4 to 45mmHg to increase during inflation of consecutive chambers to 60 mmHg. Third ascending flat line represents pressure in the medial aspect of calf just below the knee (level 5) usually with less edema and low flow resistance.

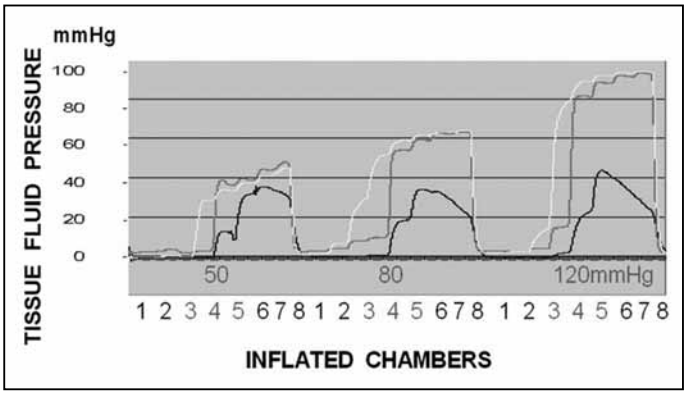

Figure 3: Tissue fluid (TF) pressure recording in a LYMPHEDEMATOUS CALF subcutaneous tissue at the level of sleeve chambers 3, 4 and 5. Inflation pressures were 50, 80 and 120 mmHg. Inflation time of each chamber was 55 sec, there was no deflation of distal chambers. Number 1 to 8 denote consecutive sleeve chambers. Pressures recorded under chambers 3 (first ascending line), 4 (second ascending line) and 5 (third ascending line). Note that TF pressures during first inflation were at all levels lower than those in chambers. Inflation of chamber 3 increased TF pressure at level 3 to 30 mmHg but not at level 4. Inflation of chamber 4 produced pressure at level 4 to 40 mmHg and at level 5 to 12 mmHg. Similar shape of pressure curves were observed during inflation to 80 and 120mmHg. Note that at level 5 (third ascending line) close to the knee with soft popliteal tissue, the TF pressures were much lower than in chamber 5. This could be explained by low resistance to flow in the popliteal fossa. However, the most important observation was lack of transmission of pressure from the compressed level to the proximal next.

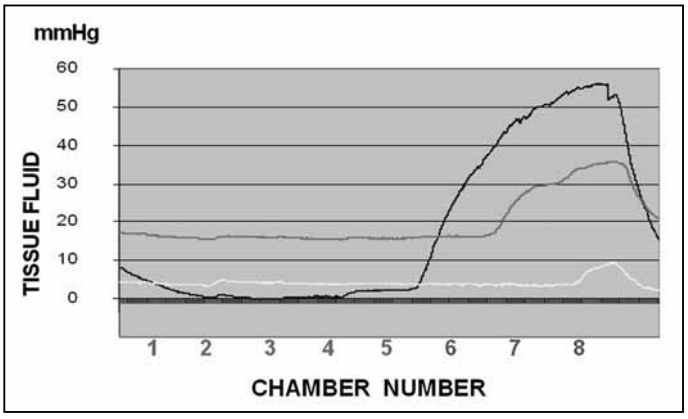

Figure 2B: Tissue fluid (TF) pressure in the NORMAL THIGH subcutaneous tissue stage IV during pneumatic compression of 50 mmHg. Pressures recorded at chamber, level 6, above knee (first ascending line), 7, mid-thigh (second ascending line) and 8, upper thigh (third ascending line). Note that, as in the calf, tissue fluid pressures during first inflation of all chambers were lower than those in the chambers. Inflation of chambers 1 to 5 to 50mmHg did not generate pressures at level 6. Inflation of chamber 6 produced at level 6 pressure of 35 mmHg (second ascending line), stepwise rising during inflation of consecutive chambers to 55 mmHg. Inflation of chamber 7 produced tissue fluid pressure rise at level 6 to 50 mmHg and at level 7 to 30 mmHg to increase during inflation of consecutive chambers to 55 and 35 mmHg, respectively. Third ascending flat line represents pressure at level 8 close to the groin usually with less edema and low flow resistance.

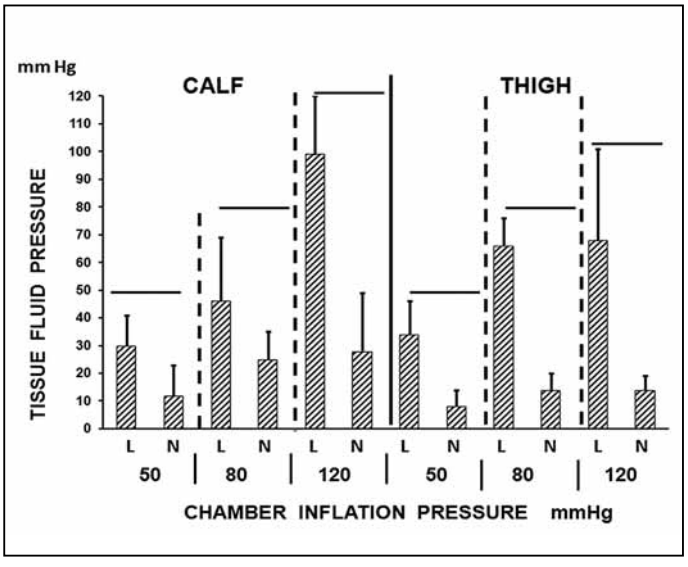

Figure 4: Tissue fluid pressures in calf (level 4)and thigh (level 7) subcutaneous tissue in patients with lymphedema (n=15) and normal subjects (n=5) during the first inflation of pneumatic sleeve to 50, 80 and 120 mmHg. L- lymphedema, N- normal, horizontal line denotes pressure in the sleeve chambers, mean values in mmHg ± SD. Note that TF pressure was in all cases lower than in the sleeve both in the lymphedema cases and healthy subjects (for explanation see text). There were also evident differences between lymphedema and control cases.

Circumference (volume) changes during pneumatic massage

Continuous recording of circumference changes during sequential compression gave indirect insight into the volumes of fluid translocated from the compressed to the proximal segments. Following inflation of a chamber, increase of limb circumference occurred proximally to this chamber due to transfer of mobile fluid . Sequential inflations of chambers from 1 to 8 resulted in stepwise increase of circumference in the consecutive segments of the limb (Fig. 5). The increase in circumference at each level was recalculated into volume. Summarized data of 15 patients are presented on Fig. 6. The transferred volume was evident in the calf, but even much more in the thigh containing larger volumes subcutaneous tissue with fluid and fat.

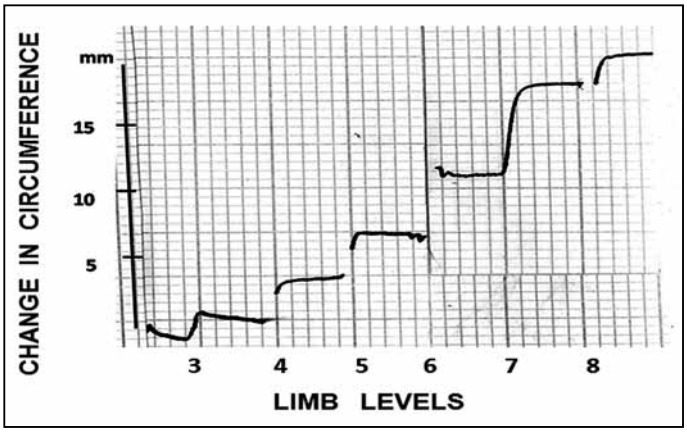

Figure 5: Changes of limb circumference during pneumatic massage of a patient with lymphedema stage III at levels corresponding to compression chamber positions (3,4,5 - calf; 6,7,8 - thigh) (in mm). The measuring device was placed at 3,4,5,6,7 and 8 level. Sequential inflation of sleeve chambers brought about consecutive increase in circumference, eventually reaching at level 8 value of 20 mm. Changes in circumference served calculation of changes in volume (sq cross area x length of chamber 9 cm). There was no backflow of proximally pushed fluid.

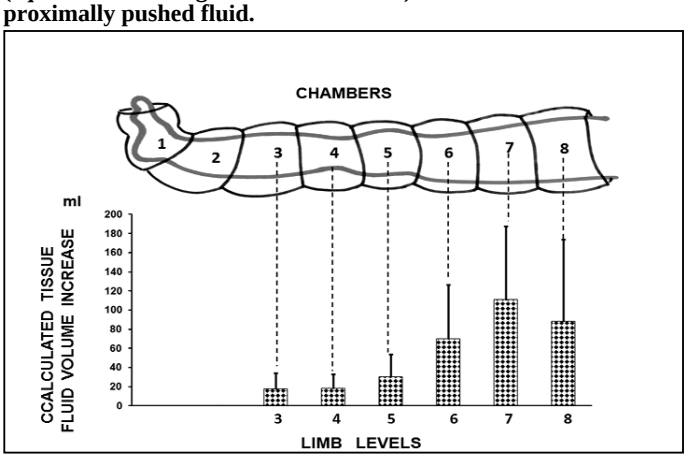

Figure 6: Calculated volumes of tissue fluid (TF) moved sequentially from distal parts of lymphedematous limb (stage II, III and IV) toward the groin by pneumatic compression of chambers 1 to 7. The volume increases in consecutive limb segments to reach highest values in the mid-thigh. Note that although edema is clinically most visible above the ankle level, bulk of the fluid is moved from the thigh. Values are means ± SD, n=15. Note high SD caused by differences in accumulation of TF in individual patients.

DISCUSSION

The knowledge of the subcutaneous tissue hydraulic properties is scarce, whereas the pneumatic compression therapy needs information on the hydraulic conditions in the massaged tissues. This is indispensable for setting the massaging devices at effective pressures in order to propel the accumulated fluid toward the root of the extremity. So far, no consistent data on pressure and flow in the swollen extremities can be found in the literature. There have been some reports on pressures generated at the sleeve-skin interface, however, they give no insight into the intra-tissue physical events.

There is a general notion, so far not supported by any objective evidence, that the tissue fluid pressure in lymphedema is high. In this study we showed that pressures were low, ranging between –1.5 to +10mmHg. Moreover, we found that there were no statistically significant differences with normal limbs, although there was a slight tendency for higher pressures in lymphedema. The obtained data corroborate our previous clinical and experimental findings of low tissue fluid pressures in lymphedema [14, 15]. The mechanism of low pressure can easily be explained by high skin compliance in the early stages of edema formation allowing its stretching and expansion of the subcutaneous space accumulating excess of capillary filtrate not drained away by lymphatics. Accumulation of soluble proteins causes, in accordance with Starling's law, causes rise in oncotic pressure, this in turn to attraction of water and further expansion of the tissue space.

The pneumatic compression is applied in order to raise tissue fluid pressure and create a gradient between the compressed and proximal non-compressed tissues in order to generate physical condition for fluid flow. The generally applied compression pressures usually range between 50 and 120 mmHg. An open question remains whether the externally applied pressures generate tissue fluid pressures of the same level as in the sleeve encompassing the limb. In our studies, pneumatic compression produced tissue fluid pressures were lower than those in the inflated sleeve. The created gradient was most likely created by low skin compliance (rigidity) caused by fibrotic process routinely ongoing in lymphedema. Another factor responsible for low pressures could be dispersion of the applied compression force in the subcutaneous tissue to the proximal non-compressed regions. Another interesting finding was a limited tissue fluid lateral pressure transmission to the non-compressed proximal segments. This could be accounted for by physiologically low hydraulic conductivity of the subcutaneous tissue both in lymphedema and normal conditions.

We also observed building up of tissue fluid pressures in the distal parts of the limb during inflation of proximal chambers. This could be explained by slow tissue fluid flow from the compressed tissues caused by low tissue hydraulic conductivity and in addition by flow obstruction at the inguinal level, seen on lymphoscintigrams. This last is a consequence of the ongoing fibrotic process in the groin lymphatics and nodes.

Even high generated tissue fluid pressures may remain ineffective in propelling fluid, especially in advanced stage of lymphedema. This is why beside of recording tissue fluid pressures, we simultaneously measured fluid flow. For this purpose strain gauge was put around the limb at six levels corresponding to level of

sleeve chambers and connected to a recording device. It provided data on the continuous changes of circumference during sequential compression and allowed to calculate the approximate volume of displaced fluid by each inflated chamber. The calculated volumes ranged from 10 to 40 ml per inflated chamber. They were low in the calf to increase in the thigh, reaching at groin level the total volume for the entire extremity of more than 100 ml. The displaced volume was certainly of tissue fluid but not venous blood, as there was no resistance to blood flow and blood did not accumulate in the proximal segments of the limb.

Taken together, this is the first published study presenting hydraulic parameters of the massaged skin and subcutaneous tissue in lymphedema. It showed that in lymphedema the resting tissue fluid pressures are low only slightly above zero. The tissue fluid pressures generated by compression devices are lower than those in the inflated chambers. This may be due to low skin compliance, low physiological hydraulic conductivity of the subcutaneous tissue and resistance to flow at the groin level, factors hindering tissue fluid flow to the non-swollen tissues. Our observations point to the necessity of applying high pressures and long compression times to generate effective tissue fluid pressures and provide enough time for moving the stagnant fluid to the root of the extremity. The obtained data should be useful for physiotherapy allowing to set the parameters of compression devices at levels corresponding to those in the in-tissue conditions.

REFERENCES

1. *Special report: comparative efficacy of different types of pneumatic compression pumps for the treatment of lymphedema.* Technologica MAP Suppl. 1998: 42-3.
2. Centers for Medicare and Medicaid Services (CMS): *National Coverage Determination for Pneumatic Compression Devices.* Publication number 100-3, Manual section number 280.6.
3. Rockson S.G., Miller L.T., Senie R. et al.: American Cancer Society Lymphedema workshop. Workgroup III: *Diagnosis and management of lymphedema.* Cancer, 1998; 83: 2882-5.
4. Wilburn O., Wilburn P., Rockson S.G.: *A pilot, prospective evaluation of a novel alternative for maintenance therapy of breast cancer-associated lymphedema.* BMC Cancer, 2006; 6: 84.
5. Blue Cross and Blue Shield Association Technology Assessment Program (TEC). *Special report: Comparative efficacy of different types of pneumatic compression pumps for the treatment of lymphedema.* 1998 (2).
6. Centers for Medicare and Medicaid Services (CMS). *National Coverage Determination for Pneumatic Compression Devices.* Publication number 100-3, Manual section number 280.6. Retrieved from http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=280.6&ncd_version=1&basket=ncd%3A280%2E6%3A1%3APneumatic+Compression+Devices.
7. Palmetto GBA-Statistical Analysis Durable Medical Equipment Carrier (SADMERC). Durable Medical Equipment Coding System (DMECS) Product Search for HCPCS codes E0650, E0651, E0652. Retrieved from http://www3.palmettogba.com/dmecs/do/productsearch.
8. National Lymphedema Network (NLN): *Position statement of the national lymphedema network.* Treatment. 2006. Retrieved from http://www.lymphnet.org/pdf Docs/nlntreatment.
9. Harvey N. Mayrovitz: *Interface Pressures Produced by Two Different Types of Lymphedema Therapy Devices*. Phys.Therapy 2007; 87: 1379-1388.
10. Cohen S.R., Payne D.K., Tunkel R.S.: *Lymphedema: strategies for management.* Cancer, 2001; 15: 92 (4 Suppl): 980-7.
11. Rockson S.G.: *Lymphedema.* Curr Treat Options Cardiovasc Med., 2006; 8: 129-36.
12. Belgrado J.P., Bourgeois P., Röh N., Moraine J.J.: *Intermittent pneumatic compression in the treatment of lymphedema: current state of knowledge.* European Journal of Lymphology and Related Problems, 2007; 17: 4-10.
13. Olszewski W.L.: *Atlas of Lymphology.* Servier, Paris, 2001.
14. Olszewski W.L.: *On the pathomechanism of devolopment of postsurgical lymphedema.* Lymphology, 1973; 6: 35-39.
15. Olszewski W.L., Engeset A.: *Intrinsic contractility of leg lymphatics in man. Preliminary communication.* Lymphology, 1979; 12: 81-84.

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A PROSPECTIVE ANALYSIS OF THE INCIDENCE OF BREAST CANCER RELATED LYMPHEDEMA OF THE ARM AFTER SURGERY AND AXILLARY LYMPH NODE DISSECTION IN EARLY BREAST CANCER PATIENTS TREATED WITH CONCOMITANT IRRADIATION AND ANTHRACYCLINES FOLLOWED BY PACLITAXEL

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ABSTRACT

Background: Breast Cancer Related Lymphedema of the arm (BCRL), a debilitating complication after axillary lymph node dissection and irradiation, is caused by the accumulation of interstitial fluid of the affected arm due to a blockage or a malfunction of the lymphatic system. The incidence of BCRL varies between 6% and 62.5% due to various measurement methods and diagnostic criteria and different patient and treatment risk factors.(1) A prospective analysis of the incidence of BCRL in 52 early breast cancer (BC) patients receiving radiotherapy concomitant with adjuvant anthracyclines and paclitaxel has been done and compared with the incidence in a control group, consisting of 48 patients receiving concurrent irradiation and anthracyclines only. *Methods:* All patients have been treated with breast surgery and axillary lymph node dissection followed by concurrent postoperative irradiation (50 Gy on the chest wall and regional lymph nodes) and chemotherapy, consisting of 4*FEC (500/75/600 mg/m^2) followed by 12*weekly paclitaxel (80 mg/m^2) or 6 cycles of FEC only. The circumferences of both arms have been measured by tape every three weeks during the adjuvant chemotherapy, every three months during the first year and every 6 months during the second year postoperatively. A difference of ≥ 2 cm in limb girth between the two arms has been considered as the clinical diagnosis of BCRL. *Results:* Fifty two patients were enrolled prospectively in the paclitaxel group. At 1 to 2 years post diagnosis, there was a BCRL incidence of 40% in the paclitaxel group. In most of the patients the BCRL occurred early during the

adjuvant therapy with paclitaxel, suggesting a possible causal relationship with the use of taxanes. The incidence measured retrospectively in the control group was 3 times lower.
Conclusions: This is the first prospective analysis of the incidence of BCRL in early BC pts treated with concomitant post operative irradiation and anthracyclines followed by taxanes comparing with a control group treated with concurrent irradiation and anthracyclines only. The early onset during adjuvant taxane treatment suggests that capillary leakage, together with the previous concomitant chemo-irradiation, is a potential mechanism that contributes to the occurrence of BCRL. In a second prospective study our research group is investigating whether and how the onset of BCRL during paclitaxel can be monitored, prevented or blunted.

Key words: early breast cancer; concurrent chemo-irradiation; axillary lymph node dissection; breast cancer related lymphedema; taxanes; capillary leak syndrome; manual lymph drainage

INTRODUCTION

The standard of treatment for early breast cancer with positive lymph nodes is breast surgery with axillary lymph node dissection (ALND), followed by post operative irradiation and systemic therapies, including chemotherapy, hormonotherapy and trastuzumab depending on the histopathology and stage of the resected primary tumor. There is no consensus in the literature about the optimal strategy of combining the post operative chemotherapy and irradiation. In clinical practice, chemotherapy and irradiation are most frequently used sequentially due to the increased skin and hematological toxicity caused by the concomitant combination. Our department has 30 years of experience with the concomitant use of post operative irradiation and anthracyclines in early BC patients with positive lymph nodes, resulting in a significant better survival when compared with the patients in the SEER database.[2] Also in other solid tumors, concomitant use of irradiation and chemotherapy has proven to be more efficacious than either modality alone or sequencing both approaches.[3,4,5] With the introduction of taxanes in adjuvant settings of the early BC population three years ago, an increased incidence of BCRL has been observed in our patient group treated with breast surgery and ALND, followed by concurrent irradiation and anthracyclines followed by taxanes. Both taxanes, docetaxel and paclitaxel, are derived semisynthetically from the needles of the European yew called Taxus baccata. They exert their antitumor activity by stabilizing the microtubules against depolymerisation, which leads to the blockage of cells in the metaphase of the cell cycle. Both drugs are applied in different solid cancers with high response rates not only in BC, but also in ovarian-, head and neck-, prostate-, bladder- and non small lung cancer. In the early clinical trials, a development of progressive peripheral edema of both legs and nonmalignant pleural effusions has been observed most frequently with cumulative doses of at least 400mg/m^2 docetaxel.[6, 7]
A small prospective pilot study has been set up to verify the first clinical experience of an increased BCRL incidence in BC patients, treated with adjuvant taxanes. The circumferences of both arms have been measured in fifty two early BC patients, treated with breast surgery and ALND followed by concurrent irradiation and systemic therapy consisting of anthracyclines followed by weekly paclitaxel. The results have been compared with a control group of forty eight early breast cancer patients, treated between 2005 and 2007 with concomitant irradiation and anthracyclines only.

MATERIALS AND METHODS

In total one hundred early BC pts with stage IB through IIIC disease, who needed breast surgery and ALND have been recruited between 01/01/2005 and 01/11/2009 in the Oncology Department of the University Hospital of Brussels. Information including age, body mass index, professional status, type of surgery, number of lymph nodes removed, and incidence of seroma and wound infection has been collected for all these patients.
One month postoperatively fifty two patients in the prospective pilot study received immediate irradiation and concurrent systemic therapy consisting of 4 cycles of 5-fluoro-uracil at a dose of 500mg/m^2, in combination with epirubicine at 75 mg/m^2 and cyclophosphamide at 600mg/m^2 (FEC scheme), followed by 12 cycles of weekly paclitaxel at 80g/m^2 according to the Sparano regimen.[8] Forty eight early BC patients, treated with breast surgery and ALND followed by post operative concurrent irradiation and the same FEC combination have been included in the control group. Data of these patients have been retrospectively reviewed from the clinical files between 2005 and 2007. Patients with bilateral or inflammatory BC, sentinel procedure only, systemic or local recurrence or lymphangitis of the breast or the arm have been excluded.
All patients received conventional post surgery irradiation of the breast and supra- and infraclavicular and axillary nodes with two opposing tangential fields. They have completed 25 daily fractions of 2 Gy in five weeks. The radiation area was located between the mid-sternal line, the mid-axillary line, 2 cm cranio caudal from the papable breast or 5 cm from the scar in case of total mastectomy. In case of breast conserving surgery, an additional boost of 8 fractions of 2 Gy was delivered at the operation area, resulting in a total dose of 66 Gy in 7 weeks.
During treatment, every patient received preventive manual lymph drainage and shoulder mobility exercises for the levator scapulae muscle, upper trapezius muscle, pectoralis maior muscle, medial and lateral rotator cuff muscles in conjunction with functional activities and proprioceptive neuromuscular facilitation exercises without resistance.
Our main objective was to detect prospectively the incidence of lymphedema of the affected arm in the patients treated with postoperative combined chemo radiation consisting of 4 times FEC followed by weekly paclitaxel and to compare with a control group, treated with concomitant irradiation and 6 cycles of FEC. Therefore arm measurements have been performed every three weeks during the adjuvant treatment, every three months during the first year postoperative and every six months during the second year. An oral consent was obtained from all the patients included in the study group.
The diagnosis of BCRL has been set following the most common used diagnostic criteria: ≥ 2 cm increase in the circumference of any two adjacent points compared with measurements in the other

arm [9, 10] It has been reported as a valid and reliable method for accurately quantifying and diagnosing secondary lymphedema.[11, 12] A standard flexible, narrow tape measure with an accuracy of 1 mm has been used to measure the circumferences of the arms, at 5cm intervals along both arms using the elbow fold as the starting point. The measurements have been taken only once, bilaterally with the arms stretched, by the same therapist.
The patient characteristics and the incidence of BCRL in both groups have been recorded. We used the T-Test to compare means between groups and the Pearson χ^2 test to compare proportions between the two groups.
Comparison of the incidence rate between the two groups was made using the Pearson χ^2 test.

RESULTS

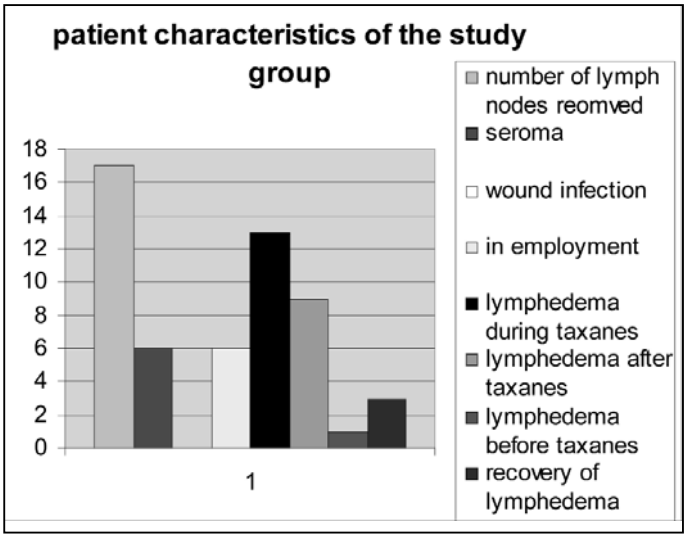
Patient characteristics *(Table 1)*

Fifty two patients, with a mean age of 54 yrs (SD 10.6) and a mean BMI of 27.9 (SD 7.8) have been included in the paclitaxel group. Most of them are treated with a total mastectomy and ALND with a mean number of seventeen lymph nodes removed. None of them developed a wound infection and only six had an occurrence of seroma formation. All patients received standard physical therapy two to three times a week and one quarter of the patients returned to their professional live at the end of the adjuvant therapy.
Forty eight patients, with a mean age of 52 years (SD 9.9) and a mean BMI of 25.3 (SD 5.31) have been included in the control group. Six patients developed a seroma. Two thirds of the patients underwent mastectomy with a mean of 17 lymph nodes removed. In the control group, no one developed a local infection and only six did show a seroma.
Results of the T-test indicate that patients of the two groups were not significantly different in age (p-value=0.2653), BMI (p-value=0.431) or in number of removed lymph nodes (p-value=0.1375).

Table 1. Patient characteristics

	Study group (%)	Control group (%)
Number	52(100)	48(100)
Mean age	54 yrs	52 yrs
Mean BMI	27,9	25,3
Stage I	2	3
Stage II	38	34
Stage III	12	11
Mastectomy	29(56)	32(66.6)
Breast conserving surgery	23(44)	16(33.3)
Mean number of removed LN	17.6(SD 5.4)	17.2(SD 6.7)
Seroma	6(11,5)	6(12,5)
BCRL	23(44)	7(14)

Results of the Pearson χ^2 test indicate that no significant difference in proportion of mastectomy (p-value=0.3623), breast conserving surgery (p-value=0.3623), seroma (p-value=0.8728) or stage (p-value=0.858) was found between the two groups.
Over forty percent of the paclitaxel group developed BCRL, of whom ninety six percent during or after the treatment with taxanes (Figure 1). Sixty one percent of the patients with BCRL demonstrated a circumference difference of 2 to 2.5 cm between both arms. In three cases a complete resolution of the BCRL occurred after one to two years post operation. In the control group, only fourteen and a half percent of the patients developed BCRL. In only one patient the BCRL was presented after the chemotherapy, with a follow-up of three years. The Pearson χ^2 test (χ^2=9.08, df=1, p-value=0.003) indicates that a significant higher proportion of BCRL is found in the paclitaxel group (44.23%) compared to the control group (14.58%).



DISCUSSION AND CONCLUSION

This is the first report on BCRL occurring after concomitant irradiation and anthracyclines followed by taxanes for the adjuvant therapy of early breast cancer patients treated with breast surgery and ALND. In the literature, only two reports on concurrent paclitaxel and radiation therapy for unresectable locally advanced BC have been published. They observed an incidence of G 1 or more BCRL in 43%.[13, 14] One of the plausible explanations for the development of BCRL, could be the capillary leakage of proteins and fluid in the extra cellular space, a well known side effect of docetaxel, and first described by Semb Karin *et al.*[7] By measuring the colloid osmotic pressure of the plasma and interstitium and the interstitial hydrostatic pressure before and after total doses of docetaxel of 200 and 500mg/m^2, the authors observed a decrease in the colloid osmotic gradient caused by an increase in plasma volume, leading to an enhanced fluid retention in the interstitium. After five courses of docetaxel a stabilization of the interstitial colloid osmotic pressure occurred together with

an increased interstitial volume, as indicated by weight gain and edema formation, which implies a capillary leakage of proteins. BEHÀR *et al.* have performed a capillaroscopy and capillary filtration tests by using 99mTc albumin in a group of patients receiving docetaxel. They concluded that there is an abnormality in the permeability of the capillaries as well as a progressive accumulation of proteins in the interstitial space.[15, 16] One could also argue that large doses of steroids may be the underlying mechanism of fluid retention. However in this study only 10 mg of dexamethasone has been administered intravenously before the weekly infusion of the first doses of paclitaxel to prevent hypersensitivity reactions. If the patients did not develop any allergic reaction, a dose reduction of dexametasone to 5 or even 2.5 mg weekly was decided. Furthermore dexamethasone reduces the vascular permeability and maintains normal vascular responsiveness to circulating vasoconstrictor factors, reducing the risk of capillary leak syndrome.[17] Another possible explanation for the occurrence of peripheral BCRL in this study population could be the development of axillary fibrosis, due to the concurrent use of irradiation and anthracyclines followed by taxanes. The combination of an interruption in the lymphatic flow at the irradiated axilla and the capillary leak syndrome, due to the implementation of taxanes in an adjuvant setting, is the most reliable explanation of our observation. Further research is needed to confirm the first study conclusions. Of course we must admit there are shortcomings in this study. Comparison of a non randomized pilot study with data retrospectively collected could have biased the results. Other limitations are the missing data of the baseline preoperative measurement of the arm circumferences and the small number of patients. In healthy subjects, the volume of the dominant arm is bigger than the non dominant arm. If the non dominant side is operated, the degree of BCRL needs to be higher before diagnostic criteria can be reached. JOHANSSON *et al.* describe a difference in arm volume between the dominant and the non dominant side in healthy subjects of 1.4-1.6%, while SAKORAFAS *et al.* report a difference of 2.5%. WARD *et al.* found the highest difference of 3.6% between the dominant and the non dominant arm in healthy subjects.[18, 19, 20] Also MCLAUGHLIN *et al.* and RIDNER *et al.* have found a significant difference in arm volume between the dominant and the non dominant arm.[21, 22] It is important to use a correction factor according to the dominance of the arm, when using diagnostic criteria for BCRL. The most correct method is to measure both arms at baseline, before surgery and to take this volume difference into account after surgery when evaluating BCRL. So we can conclude that the mechanism responsible for the BCRL could be the concurrent administration of adjuvant anthracyclines and irradiation followed by taxanes in early breast cancer patients. To confirm these preliminary results, the breast lymphology research group is now conducting a prospective randomized clinical trial, comparing the incidence of BCRL in early breast cancer patients, treated with postoperative anthracyclines concurrent with irradiation, or treated with postoperative anthracyclines and irradiation followed by taxanes. The results of this study will be correlated with the changes in skin and subcutis thickness measured by ultrasonography and with changes in quality of life, measured with the ULL-27, a standardized, validated questionnaire, concerning self reported symptoms of the swollen arm.

REFERENCES

1. Passik S.D., McDonald M.V. (1998): *Psychosocial aspects of upper extremity lymphedema in women treated for breast carcinoma.* Cancer, 83: 2817-20.
2. Voordeckers M., Vinh-Hung V., Lamote J. (2009): *Survival benefit with radiation therapy in node-positive breast carcinoma patients.* Strahlentherapie und Onkologie, 185: 656-62.
3. O'Rourke N., Roqué I., Figuls M. (2010): *Concurrent chemoradiotherapy in non-small cell lung cancer.* Cochrane Database Syst Rev, 16: CD002140.
4. Pignon J.P., le Maître A., Maillard E. (2009): *Meta-analysis of chemotherapy in head and neck cancer MACH-NC: an update on 93 randomized trials and 17,346 patients.* Radiother Oncol, 92: 4-14.
5. Chemotherapy for cervical cancer meta-analysis collaboration. (2008): *Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systemic review and meta-analysis of individual patient data from 18 randomized trials.* J Clin Oncol, 10: 5802-12.
6. Capri G., Tarenzi E., Fulfaro F. (1996): *The role of taxanes in the treatment of breast cancer.* Semin Oncol, 23: 68-75.
7. Semb K.A., Aamdal S., Oian P. (1998): *Capillary protein leak syndrome appears to explain fluid retention in cancer patients who receive docetaxel treatment.* J Clin Oncol, 16: 3426-32.
8. Sparano J.A., Wang M., Martino S. (2008): *Weekly paclitaxel in the adjuvant treatment of breast cancer.* N Engl J Med, 358: 1663-67.
9. Lacomba M.T., Yuste Sanchez M.J., Goni Z.A. (2010): *Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial.* BMJ, 340
10. Armer J.M., Stewart B.R. (2005): *Comparison of four criteria for lymphedema in a post-breast cancer population.* Lymphat Res Biol, 3: 208-217.
11. Karges J., Mark B., Stikeleather S.: *Concurrent validity of upper extremity volume estimates: comparison of calculated volume derived from girth measurements and water displacement.*
12. Taylor R., Jayasingue U., Koelmeyer L. (2006): *J. Reliability and validity of arm volume measurements for assessment of lymphedem.* Phys Ther, 86: 205-214.
13. Kao J., Conzen S.D., Jaskowiak N.T. (2005): *Concomitant radiation therapy and paclitaxel for unresectable locally advanced breast cancer: results from two consecutive phase I/II trials.* Int J Rad Oncol Biol Phys, 61: 1045-1053.
14. Bellon J.R., Lindsey L.K., Ellis K.G. (2000): *Concurrent radiation therapy and paclitaxel or docetaxel chemotherapy in high-risk breast cancer.* Int J Rad Oncol Biol Phys, 48: 393-397.
15. Behàr A., Pujade-Lauraine E., Maruel A. (1997): *The pathophysiological mechanism of fluid retention in advanced cancer patients treated with docetaxel, but not receiving corticosteroid comedication.* Br J Clin Pharmacol, 43: 653-658.

16. Oulid Aissa D., Behàr A., Spielmann M. (1994): *Management of fluid retention syndrome in patients treated with Taxotere (docetaxel): Effect of premedication.* Proc Am Soc Clin Oncol, 13: 465 (abstract 1614)

17. O'Sullivan B.T., Cutler D.J., Hunt G.E. (1997): *Pharmacokinetics of dexamethasone and its relationship to dexamethasone suppression test outcome in depressed patients and healthy control subjects.* Biol Psychiatry, 41: 574-584.

18. Johansson K., Branje E. (2010): *Arm lymphoedema in a cohort of breast cancer survivors 10 years after diagnosis.* Acta Oncologica, 49: 166-173.

19. Sakorafas G.H., Peros G., Cataliotti L., Vlastos G. (2006): *Lymphedema following axillary lymph node dissection for breast cancer.* Surgical Oncology, 15: 153-165.

20. Ward L.C., Czeniec S., Kilbreath S.L. (2009): *Operational Equivalence of Bioimpedance Indices and Perometry for the Assessement of Unilateral Arm Lymphedema.* Lymphatic Research and Biology, 7: 81-85.

21. McLaughlin S.A., Wright M.J., Morris K.T., Giron G.L., Sampson M.R., Brockway J.P., Hurley K.E., Riedel E.R., Van Zee K.J. (2008): *Prevalence of Lymphedema in Women With Breast Cancer 5 Years After Sentinel Lymph Node Biopsy or Axillary Dissection: Objective Measurements.* Journal of Clinical Oncology, 26: 5213-5219.

22. Ridner S.H., Montgomery L.D., Hepworth J.T., Stewart B.R., Armer J.M. (2007): *Comparison of upper limb volume measurement techniques and arm symptoms between healthy volunteers and individuals with known lymphedema.* Lymphology, 40: 35-46.

Addendum:
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MULTILAYER BANDAGING IN HOSPICE PATIENTS WITH MALIGNANT LYMPHOEDEMA

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ABSTRACT

The aim of the study was to evaluate indication and efficacy of multilayer bandaging in patients with advanced cancer related lymphoedema. The study was carried out on 14 patients with malignant lower limb oedema during hospitalisation at Hospice Unit of a comprehensive cancer center. The patients submitted every day to multilayer bandaging with short-stretch monoelastic bandages and exercise programme until discharge or exitus. Results was assessed as percentage reduction in limb size between beginning and end of treatments. In 28.5% lymphoedema reduced by 1.0-3.0 cm, in 28.6% reduction was of 3.0-6.0 cm and in 42.9% of 8.0 cm. The median of reduction was of 6.6%. We also observed regression of lymphorrhea and improvement of skin status, consistency, painful sensation, range of motion, walking.

Key words: advanced cancer, malignant lymphoedema, hospice patients, multilayer bandaging.

INTRODUCTION

Limb lymphoedema is a frequently observed complication in patients with advanced cancer. In particular, breast, prostate, bladder, colon metastatic cancers, as well as lymphomas and sarcomas may lead to malignant lymphoedema, which can be very severe and particularly difficult to be treated. Many factors are involved in the development of lymphoedema, such as lymph flow obstructions secondary to cancer infiltration to locoregional lymph nodes and cutaneous and subcutaneous lymph vessels, venous obstructions due to the presence of neoplastic thrombosis or migrating thrombophlebitis, extrinsic lymphatic or venous compressions, caused by neoplastic or lymph node masses, or either superior or inferior vena cava compressions [(1)]. Besides these causes, other general factors (hypoproteinemia, immobility, severe hyposthenia, long lasting bed rest, the use of non-steroidal anti-inflammatory drugs (NSAIDs), calcioantagonists and corticosteroids) may either favour the development of lymphoedema or worsen it. Malignant lymphoedema is typically acute, it progresses quite rapidly within a few weeks and it is often accompanied or preceded by pain and/or neurological symptoms. The affected limb is characterized by tense, thin and translucid skin. Skin colour is usually normal/waxy or erythematous/subcianotic in case of venous vessel involvement. Lymphatic blisters may also be present, as well as skin fissures or lymphorrhea, which may sometimes be very abundant and cause significant discomfort. Oedema has usually a soft consistency, with marked and persistent fovea, due to an elevated water content of limb soft tissues.
Pain is almost a constant symptom; it is often neuropathic, due to the infiltration to brachial and lumbosacral plexus or to the compression by neoplastic masses or metastatic adenopathies.
In some patients it is associated with hyposthenia of the affected limb, paresthesia, allodinia or functional impairment.
Malignant lymphoedema may easily be diagnosed, especially after an extensive clinical evaluation has been carried out, and the most characteristic symptoms (pain, skin colour, marked fovea, rapid

progression, hyposthenia) have carefully been investigated.
When the underlying disease is refractory to antineoplastic interventions, treatment of malignant lymphoedema is palliative and it mainly aims at relieving accompanying symptoms (pain and lymphorrhea), as well as at preventing further limb size increase and both preserving and improving the function of the involved limb [2]. Kind and duration of treatment should always be determined based on the local conditions of the affected limb and on patient's general conditions. Among the currently available treatment options, manual lymphatic drainage is indicated, although it may be not feasible, as it requires limb elevation over a long period of time, as well as forced prolonged positions for patients, sequential compression is to be avoided, as it tends to obstruct limb root, especially in those cases in which flow obstruction is already present [3-4]. By contrast, multilayer bandaging can stimulate both lymphatic and venous flow, by improving muscle efficiency in bed-bound patients, especially if it is associated with exercises [5].
In the light of the above we carried out a observational prospective study on the efficacy of bandaging and exercises in lower limb lymphoedema in hospice patients with advanced cancer.

MATERIALS AND METHODS

The present study was carried out at the Hospice Unit of the Palliative Care, Pain Therapy and Rehabilitation Department at the Fondazione IRCCS "Istituto Nazionale dei Tumori" in Milan, from May 2008 to August 2009. Fourteen consecutive patients (10 females and 4 males) were enrolled, who presented, at admission with lower limb lymphoedema secondary to lymph node relapses and/or cancer relapses in the abdominopelvic area (Table 1).
Patients' age ranged from 28 to 84 years (average 56 years). All patients experienced lymphoedema in the months immediately preceding hospitalization. In 8 of them both lower extremities were affected, while in the remaining 6 patients lymphoedema was unilateral. In all cases lymphoedema was characterized by a soft consistency, with a marked persistent swelling; skin was thin, translucid, with a normal to waxy colour.
All the patients were undergoing diuretic therapy with furosemide and/or antithrombotic therapy with low-molecular-weight heparin (LMWH): 4 patients received only LMWH, 7 received only diuretic therapy, and 2 patients were submitted to both treatments, whereas 1 patient did not receive any drug therapy.
When starting treatment 5 patients were bed-bound because of fatigue, pain or lymphoedema. Of the remaining 9 patients, 3 were capable of autonomous walking, while 6 could only walk short distances within their room with the help of either a family member or a therapist.
Before starting treatment all the patients were submitted to clinical evaluation and to measurement of both limbs. This latter exam was performed at 8-cm intervals from the base of the heel with foot flexed to 90°, up to the popliteal cavity. Due to the unfeasibility to assess the extent of lymphoedema based on centimetric measurements in bilateral lymphoedema, ankle circumference was taken as main reference, thus defining as severe those lymphoedema with a circumference ranging between 30 cm and 38 cm and moderate those with a circumference ranging between 23 cm and 29 cm.
Clinical evaluation also included the assessment of all the following features: colour, consistency, fovea, skin status, joint function, muscle tone/trophism, pain, load and walking capability, subjective symptoms. All these data were reported in an individual assessment record properly pre-arranged. Both the clinical evaluation and the centimetric measurement were repeated with the same modalities at the end of treatment.
The bandaging was arranged by applying short-stretch monoelastic bandages, as part of a multi-layered system, the number of bandages depending on the size of oedema and the length of the limb (from a minimum of 3 to a maximum of 6 layers).
In order to avoid too large bulky bandage, fingers were not bandaged and no padding were used (undercast padding or low density foam). A cotton tubular bandage was only employed in case of lymphorrhea, in order to absorb exudation.
Bandaging was applied daily and always by the same operator, by using 8 and 10 cm bandages, wrapped with reverse spiral technique ("figure of eight") and 50% overlap, both for bed-bound patients and partially or totally autonomous patients.
All patients started a proper rehabilitation program including active and active/assisted exercises for lower limbs; in autonomous patients load and walking were increased.
Bandaging and exercise programme were performed until patient discharge (12 patients) or patient exitus (2 patients).
Response to treatment was assessed as the percentage reduction in the size of the limb or limbs from the beginning to the end of treatment. For unilateral oedema limb size was calculated as the sum of the circumferences of the oedematous limb and the normal one. The decrease was assessed based on the median difference of limbs between therapy beginning and treatment completion.
In bilateral cases limb sizes were, instead, calculated as median of the sum of the circumferences of both limbs.
In this latter case, lymphoedema reduction was assessed as the difference of median size as calculated at the beginning and at the end of therapy.

Table 1. Cancer sites in patients with lymphoedema

	Patients
Breast	4
Lung	2
Gastrointestinal tract	5
Kidney	1
Sarcomas	2

RESULTS

Compression therapy was regularly administered to all the enrolled patients. No case of treatment withdrawal was reported due to side effects (dermatitis, infection, skin lesions) or due to any increase in lymphoedema. At the time of hospital admission of the 14 enrolled patients, 6 presented with severe lymphoedema (ankle circumference 30-38 cm), whereas 8 had moderate

lymphoedema (ankle circumference 23-29 cm). Average treatment duration was 10 days (from a minimum of 7 days to a maximum of 15 days). Patients wore the bandages for a daily median of 9 hours: removal of the bandages before night rest was suggested to all patients. At weekend bandaging was arranged by either a patient's family member or by properly instructed nurse staff.
In all cases there was a favourable response to compression therapy, with a median reduction of 6.6%.
Data relating to centimetric reduction of lymphoedema are reported in Figure 1, as observed at the end of treatment. In 4 (28.5 %) patients lymphoedema was reduced by 1.0-3.0 cm, in 4 patients (28.6) reduction was from 3.0 to 6.0 cm, whereas in the remaining 6 patients (42.9%) reduction exceeded 8.0 cm.
The evaluation of the results obtained in patients with moderate lymphoedema (Table 2) and in severe cases (Table 3) showed that in the former group limb size reduction was 2.2 cm and in the latter group it was 5.4 cm.
In 10 patients severe lymphoedema resulted into moderate lymphoedema and in 4 cases it turned into mild lymphoedema. In all cases painful skin tension was improved, as well as skin status.
Regression of lymphorrhea was observed in all the 5 patients presenting this symptom before treatment.
In both bed-bound and autonomous patients compression resulted into an improvement of range of motion of the ankle and knee joint. Walking was also significantly improved in terms of duration and fluidity of movement.

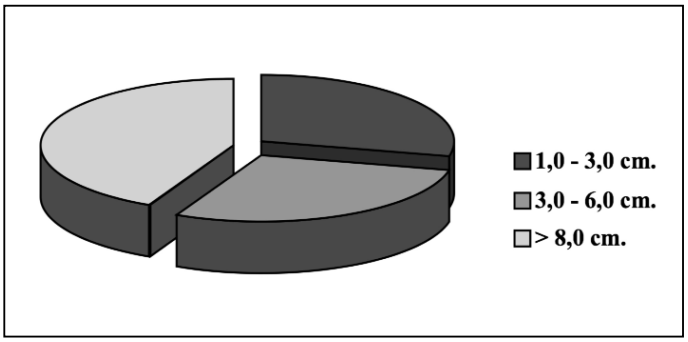

Fig. 1 - Results at the end of treatment: percentage and centimetric reduction.

Table 2. Results in moderate lymphoedema patients

Patients	Start treatment (cm)	End treatment (cm)	Average difference (cm)
Pt 1	206.5	196	1.7
Pt 2	204.5	191.5	2.2
Pt 3	387	370.5	2.7
Pt 4	333.5	314.5	3.2
Pt 5	191	187.5	1.0
Pt 6	356	349	1.2
Pt 7	358	354	1.0
Pt 8	368.5	341	4.5

Table 3. Results in severe lymphoedema patients

Patients	Start treatment (cm)	End treatment (cm)	Average difference (cm)
Pt 1	366	326	6.6
Pt 2	247.5	239	1.4
Pt 3	214	200	2.0
Pt 4	393	363	5.0
Pt 5	230	210.5	3.2
Pt 6	396	309	14.5

CONCLUSION

Although the series in the present study was a small one, it can be concluded that bandaging in combination with exercise programme does represent a valid treatment option in the management of malignant lymphoedema in palliative care patients.
Treatment proved effective, well tolerated and accepted by patients. It can easily be applied and it can be repeated more than once a day, even by well instructed non medical or paramedical staff or family members. It is a valid alternative to compression garments, which are contra-indicated in some cases, such as in the presence of lymphorrhea, fragile skin, skin folds, and more.
Even in case of bilateral lower limb lymphoedema, patients submitted to bandaging of both limbs did not experience any remarkable discomfort.
Multilayer bandaging represents, therefore, an important therapeutic option for malignant lymphoedema and should be undergoing further validation study to be evaluated as the treatment of choice in the management of lymphorrhea, as it favours reduction of both extra lymphatic and intra lymphatic hypertension.

REFERENCES

1. Keeley V.: *Oedema in advanced cancer.* In: Twycross R., Jenns K., Todd J. (eds.), " Lymphoedema". Oxon: Redcliffe Medical Press, 2000: 338-58.
2. Gray R.C.: *The management of limb oedema in advanced cancer.* Nurs. Times., 1987; 73(10): 504-06.
3. Casley-Smith J.R., Casley-Smith J.R.: *Venous disease, ulcers, palliative and geriatric care and acute injuries in modern treatment of lymphoedema.* The Lymphoedema Association of Australia, 1997.
4. Földi E., Földi M.: *Lymphostatic diseases.* In: Földi M., Földi E. (eds.), Foldi's "Textbook of Lymphology", 2nd ed., Munich: Elsevier, 2006: 223-319.
5. Strossenreuther R.H.K.: *About materials used for compression bandages.* In: Földi M., Földi E. (eds.), Foldi's "Textbook of Lymphology", 2nd ed., Munich: Elsevier, 2006: 595-627.

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GENOA (ITALY), DECEMBER 1-3, 2011

Under the Auspices of:
INTERNATIONAL UNION OF ANGIOLOGY

XXI MLAVS 2011

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XXI MLAVS 2011
Genoa (Italy), December 1-3, 2011

PROGRAM AT A GLANCE

	Thursday December 1st, 2011		Friday December 2nd, 2011		Saturday December 3rd, 2011	
Room A	Morning	*REGISTRATION*	Morning	JOINT SYMPOSIUM **"Translational Lymphology"**	Morning	JOINT SYMPOSIUM **"New Horizons in CardioVascular Medicine"**
	Afternoon	ROUND TABLE **"What's New in Aortic Surgery?"** **WELCOME ADDRESS and OPENING CEREMONY** Key-Note Introductory Lectures *P. Balas (Greece), N. Angelides (Cyprus), C. Campisi (Italy).*	Afternoon	JOINT SYMPOSIUM **"CEAP Classification: What about the Role of Lymphatics in Chronic Venous Insufficiency?"** ROUND TABLE **"What's New in Carotid and Peripheral Arterial Diseases?"**	Afternoon	**CLOSING REMARKS and CONCLUSIONS**
Room B	Morning		Morning		Morning	PAPER AND POSTER SESSIONS **(Miscellaneous)**
	Afternoon	FORUM LECTURES AND PAPER SESSIONS **(Angiology/CardioVascular Medicine, Vascular and Endo-Vascular Surgery, Lymphology and Phlebology)**	Afternoon	FORUM LECTURES AND PAPER SESSIONS **(Angiology/CardioVascular Medicine, Vascular and Endo-Vascular Surgery, Lymphology and Phlebology)**	Afternoon	
Room C/D	Morning		Morning	TECHNICAL SYMPOSIA	Morning	TECHNICAL SYMPOSIA
	Afternoon	PAPER AND POSTER SESSIONS **(Miscellaneous)**	Afternoon	PAPER AND POSTER SESSIONS **(Miscellaneous)**	Afternoon	

23rd International Congress of Lymphology

September 19-23 2011
Malmö, Sweden

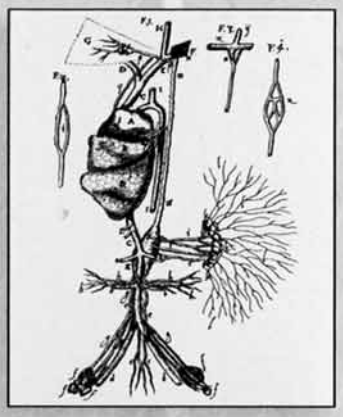
23rd International Congress of Lymphology

Welcome to Sweden and the 23rd International Congress of Lymphology!

Dear Colleagues and Lymphologists!

The Department of Plastic and Reconstructive Surgery at Malmö University Hospital, Sweden, is honoured to organize the 23rd International Congress of Lymphology in cooperation with the Faculty of Medicine at Lund University, and the Swedish Lymphology Association. Problems related to the lymphatic system are central issues for us, and one of our main focuses is the development of surgical techniques related to lymphology.

Olof Rudbeck (1630-1702), a Swedish scientist, published his first treatise *De Circulatione Sanguinis* in 1652, at the age of 22 years only, and he actually became the first one to describe the delineation and function of the lymphatic system in *Nova Exercitatio Anatomica*, which he published one year later. With this historical perspective in mind, we are enthusiastic about hosting the 23rd International Congress of Lymphology in Sweden. We are also proud of being entrusted with the task of arranging the prestigious congress in the city of Malmö. In fact, Malmö connects on to another pioneering scientific work in the field of lymphology performed by Thomas Bartholin (1616-1680), who was active in the nearby capital of Denmark, Copenhagen.



In 2011, from September 19 to 23, the most renowned scientists from all over the world will gather in Malmö to present and debate their front line knowledge and experiences in the various fields of lymphology. This will assure for an interdisciplinary and all-round illumination of the lymphatic system, its pathophysiology, and the state-of-the-art of different treatment regimes. Moreover, at the end of the summer but before fall, September is an excellent time of the year to visit Sweden.

We look forward to seeing you all in Malmö on this very special occasion. Please contact us for any additional information or suggestions that can make your stay even more pleasant in our dynamic and beautiful city.

Turning Torso, a 190 m tall building for residents. Photo: Pierre Mens

On behalf of the Organizing Committee,

Håkan Brorson

Håkan Brorson, MD, PhD
Congress President

www.lymphology2011.com

23rd International Congress of Lymphology

Program outline

Monday September 19
Registration opens

Tuesday September 20
Welcome reception

Wednesday September 21
Optional social evening,
Tivoli Gardens in Copenhagen

Thursday September 22
Congress dinner

Friday September 23
Congress ends at noon

Tivoli Amusement Park in Copenhagen. Photo: Tivoli

Life in the Viking village

Malmö Opera House Photo: Charlotte Strömwall

Topics will include:

- Anatomy of lymphatic system
- Physiology of lymphatic system (lymphatic endothelial cells, lymphatics and lymph nodes)
- Physiopathology of lymph stasis and related disorders (infection, fibrosis, adipose tissue)
- Prevention
- New frontiers in lymphatic research (genetics, lymphangiogenesis, lymphatic dysplasias)
- Lymphatic imaging
- Cancer and lymphedema (oncolymphology & sentinel node)
- Filariasis and lymphedema
- Clinic on lymphedema (diagnosis, staging, classification)
- Treatment (surgery, complex decongestive therapy, rehabilitation, alternative therapy, new approaches)
- Phlebolymphology

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