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AXILLARY WEB SYNDROME AFTER SENTINEL LYMPH NODE BIOPSY (SLNB). RANDOMIZED STUDY ON THE EFFICACY OF A THERAPY PROTOCOL

*ANDREOLI C., BRANCHINI L., BASILICO V., CARNAGHI C., MIETTO R., VERONESI A., MARTINO G.**

Istituto Clinico Humanitas Castellanza (VA)

* Metis Oncology Study Centre - Training and Therapy - Milan

ABSTRACT

Obiective: Assess the efficacy of remedies, administered at an early stage in patients with breast cancer diagnose undergoing breast-conservative surgery (quadrantectomy) with sentinel lymph node biopsy (SLNB) and showing AWS or Cording of varying degree and picture.

Materials and methods: 54 women with AWS of varying degree (G0, G1, G2, G3) were randomized in two groups to assess the effectiveness of a therapy protocol consisting in three orally administered remedies with lymphokinetic, anti-inflammatory and mood-modulating effect. Patients were checked 10, 20, 30, 60 days after surgery.

Results: Based on the randomized study, the group that was administered the lymphokinetic, anti-inflammatory and mood-modulating drugs, showed fewer early postoperative outcomes (serosity, infections, limitations), 90% resolution of G0 and G1 outcomes and decreased tightness of cords in G2 and G3 cases.

Conclusions: Therapeutic protocols should be developed for the preventive and early use of medicines with lymphokinetic, anti- inflammatory and relaxing effect in order to reduce the trauma of diagnosis and surgical incision – albeit limited – as it occurs in quadrantectomy with SLNB, with the aim of improving quality of life and reducing rehabilitation costs.

Key Words: AWS, Iatrogenic outcomes after quadrantectomy and SLNB Complementary therapies, Rehabilitation.

INTRODUCTION

In Breast Unit practices, the patients' post-operative discomfort is hardly taken into consideration, since breast specialists feels satisfied with the screening for early diagnosis and the good aesthetic results of breast-conservative surgery, compared to the mutilating interventions of some time ago.

Few know that cancer diagnoses makes women's body vulnerable. This may vary as for posture, structure, constitution, physical and metabolic condition, as well as specific emotional and relational reactivity after diagnosis. Breast specialists hardly examine them before surgery in terms of biomechanical and emotional features. [1,2,3,4]

Through their studies on communication, relationship and physicality, Martino and colleagues [1,2,3,4,5] have taught us that cancer diagnosis "blends in" between motion and e-motion and that the scalpel cuts through the skin, fascia, breast and armpit affecting such vulnerability of the body: these are all intimate and meaningful parts of women.

As breast specialists of a new Breast Unit we therefore took care of: 1. conducting an accurate biomechanical and emotional examination before surgery; 2. broadening the local and systemic clinical gaze on post-conservative surgery outcomes; 3. finding appropriate and preventive therapies for physical and emotional discomfort.

More than half of the women we examined in biomechanical terms before surgery, experienced the sensorimotor alteration described by Martino et al., consisting in hypo-pendularism of the ipsilateral arm with decreased spacial representation, haptic function and therefore relational features.

Incisions in the chest and underarm areas, highly symbolic, are part of a dynamic, postural, metabolic as well as emotional and relational framework, specific to each woman. The different systemic structure can affect the local iatrogenic physical outcome.

This work starts with the examination of a local symptom which is scarcely highlighted by breast specialists, i.e. Axillary Web Syndrome, by studying its incidence rate, degree, prevention and treatment in a group of women, homogenous as for surgical operation, while inevitably different in structure, posture and emotions.

Since there are yet no dedicated therapists in our breast facilities who can handle the complex physical and emotional trauma, we had to understand if there were any complementary remedies that might affect the connective and emotional – physical components without interfering with cancer therapies.

AWS O CORDING

Incision of the skin in the chest and underarm region and opening of the clavipectoral fascia with sentinel lymph node biopsy (SLNB) may lead to post-operative development of either one or several smaller or thicker cords, that extend down, from the site of scarring, to the inner arm and forearm and sometimes continue all the way down to the wrist.

These cords lead to motion restrictions, feeling of tightness and pain. The morphology of the cords with their different pathways, tightness and size, makes etiopathogenetic interpretation difficult. Some authors talk of sclerosis of lymphatic vessels and veins with surrounding fibrosis. This manifold picture is defined as retraction, adhesion, lymphatic sclerosis and fibrosclerosis [6]. For a decade, this symptom has been generally known as "Axillary Web Syndrome (AWS) or Cording" [7, 8].

Based on literature data, AWS occurs in less than 20% of women who undergo SLNB. As already mentioned, a great number of breast specialists consider this rate overstated, since in their post-surgical visits they rarely find a picture of AWS or Cording. Immediate complications are generally not related to these outcomes, as well as the extent of glandular removal and incisions of the fascia, conditions of the tissues, the fascia, the dynamics of the shoulder, the musculoskeletal and metabolic structure and even less the sensory-motor changes caused by the trauma of diagnosis before surgery.

MATERIALS AND METHODS

Between the beginning of 2012 and the end of 2013, we studied a sample of 164 patients who had to undergo standard procedures with a single surgical team, in order to underline incidence of outcomes after quadrantectomy and SLNB [9, 10, 11, 12] in our breast unit.
Before surgery, the patients were examined as for biomechanical, metabolic, structural, postural, dynamic and emotional conditions. After 10, 20, 30 days and then after 2, 3, 6, and 12 months from surgery, they were examined paying particular attention to local outcomes, general clinical data and sensory-motor, relational and mood changes.
In the group of 164 women studied to assess post-operative outcomes, 54 showed AWS of varying degree. AWS degree was classified as follows: G0 - subclinical condition, in which case cording is reflected by the skin sliding from the shoulder towards the elbow, with no feeling of tightness and impairment.
So called stage G1 includes small superficial cords up to the elbow with slightly limited range of motion; G2 refers to one or several thick cords that extend down to the elbow and also impair elbow extension; G3 refers to cords that run down to the wrist with limited range of motion of elbow and wrist.
After assessing the outcome, women with AWS (54 patients) entered a randomized study: one group that did not take any oral medication (control group) and another group that was administered three complementary remedies with lymphokinetic, anti-inflammatory and mood-modulating effect, taken together at the beginning of the first week after surgery and for two months. The hypothesis is that these women show a fibroblast adhesion reactivity with increased reticular and collagen fibers and slower remodeling rate of the connective tissue matrix, as well as a particular fascial and postural structure and an element of stress caused by the disclosure of diagnosis.
The prescribed remedies have a lymphokinetic (Taraxacum, Calendula, Arsenicum album, Chelidonium, Leptandra, Echinacea, Phytolacca, Carduus Mariuanus, Condurango, Hydrastis, Lycopodium, Sanguinaria, drops), anti- inflammatory (Bromelina, Papaina, Tripsina, Chimotripsina, Vitamine C, D, E - tablets), and mood-balancing effect (Passiflora, Valeriana, Melissa, Avena – tablets).

RESULTS

The randomized study included 54 patients undergoing quadrantectomy and SLNB, selected from a sample of 164 women who had been studied for incidence of post-operative outcomes. They showed subclinical cording or visible thin or thick cords, differing in paths, both painful and impairing (11 Grade-0 cords, 16 Grade-1 cords, 22 Grade-2 cords and 5 Grade-3 cords). Serosity, infections, age, menopause symptoms, overweight, obesity, hypertension, metabolic diseases and structural bone or tendon restrictions occurring in 54 women with AWS did not differ in frequency from those assessed in the 110 women studied for the incidence of outcomes and not affected by AWS.
These women differed from the other 110 patients without AWS in that they showed a higher incidence of sensory- motor alterations prior to surgery. Involuntary hyperpendularism after diagnosis was assessed in 68.2% of the patients with AWS and in 37.5% of patients without AWS.
Almost all of the patients with AWS, hyperpendularism observed at the time of diagnosis was also associated with haptic hypofunction of the hand (tactile and motor exploration): signs of a lower chance to explore the world around them with the upper limb ipsilateral to the tumor.
The group of 27 women who regularly took the diluted lymphokinetic remedy, the enzymatic anti-inflammatory remedy and the mood-modulating phytotherapic compound (group A), showed an earlier improvement in symptoms compared to women of control group C, who were free to take Nsaids or painkillers (Table 1 and 2).

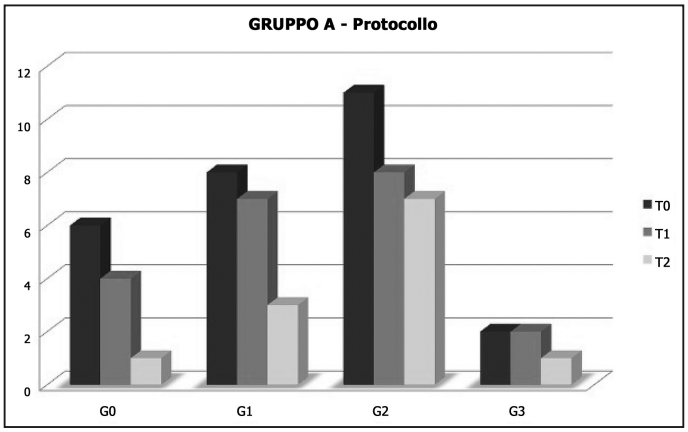

Table 1

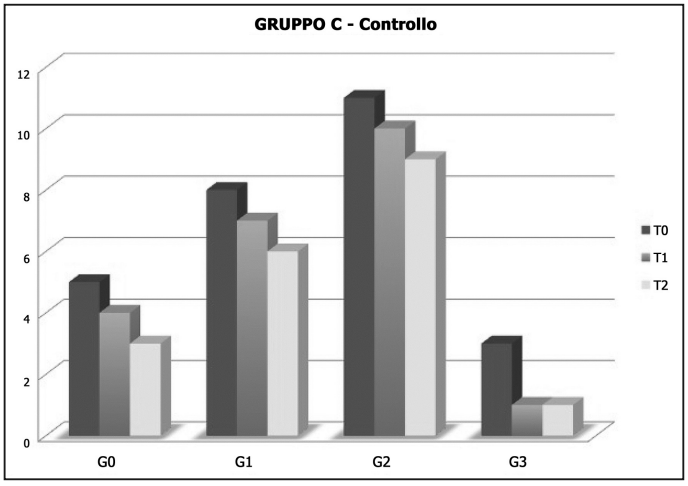

Table 2

As can be seen from the above tables, in Group A cords disappeared within two months in 90% of the patients with Grade 0 and 1 AWS; patients with G2 and G3 AWS also showed a greater reduction of symptom intensity (hypofunction, pain, tightness, cords visibility) compared to the control group.
Group A also shows reduced incidence of local inflammation, improved scar healing and faster resolution of pain compared to the control group. Regarding side effects, 30% of the women in group A complained about having a hard time taking too many drops, capsules and tablets.
After two months of close observation, patients still suffering from cording symptoms underwent manual treatments such as dissection of the scar, mobilization of the clavicle and shoulder, acupressure, laser therapy and taping [13].
We did not use the stretching movements and rupture of the cords that plastic and reconstruction surgeons implement in other breast units to decrease tension in the arm extension, since our experience shows these can lead to repercussions in fibrotic networks sometimes combined with transient lymphatic stasis.
The gentle approach of manual lymph drainage, implemented with non-standard methods (some therapists followed the Leduc method, others the Vodder method, others still a personalized method) proved more suitable compared to the traumatic manual rupture of the cords.
A psychomotor and psychological approach by dedicated therapists was required for those patients showing significant sensory-motor and haptic (tactile and exploration) weakness.
Women themselves stated that when they were diagnosed cancer, it had been a dramatic and all-involving experience.
G2 and G3 cording, still present after two months, required a cyclic motor and manual rehabilitation therapy and constant clinical follow-up, especially for patients who had undergone chemotherapy and showed moderate to severe anxiety-depression disorders.

CONCLUSIONS

Quadrantectomy and SLNB, which is considered a low invasive and side effect-free technique, often results in outcomes that might escape regular breast screening. We tend to forget that this operation affects the body of women who have been shocked by cancer diagnoses.
Incision of the skin and the fascia can indeed lead to an increase in reactivity of fibroblast adhesion, of reticular and collagen fibers and consequent hardening of cords that affect the arm and / or chest. Such incision is often made in patients showing sensory-motor and haptic changes in the upper limb.
Sensory-motor alterations caused by the trauma of diagnosis and by the symbolic value of the operation, as well as pre-surgery fascial tightness should encourage breast specialists to carry out further research and develop preventive protocols aimed at solving local, systemic and emotional traumas.
AWS in breast cancer is not a simple injury resulting from the scalpel cutting through the connective area. It involves the different vision and emotions of women about the tumor and tightness in their arm that suddenly no longer interacts with the world.
Breast specialists and rehab therapists shall have to consider carefully the deep meanings that cancer arouses in women and then assess the outcome which in turn leads to other emotional implications. They have to combine anti- inflammatory and mesenchyme-draining therapies with mood-stabilizing and anti-anxiety treatments, planning manual and perceptual-motor rehabilitation.

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ULTRASONOGRAPHY CAN HELP IN THE DIAGNOSIS OF CARPAL TUNNEL SYNDROME IN BREAST-CANCER-RELATED LYMPHOEDEMA: A PROSPECTIVE ANALYTICAL STUDY

Principal Investigator: *ESTELA MARTÍN CASTILLO* [1]
Other Investigator: *PROFESSOR ANÍBAL BÁEZ SUÁREZ* [2]
ANA BELÉN TACORONTE PÉREZ [3]
ANA ISABEL MELIÁN MARTÍNEZ [3]
MARÍA TERESA RODRÍGUEZ RODRÍGUEZ [3]
ÁNGELO SANTANA DEL PINO [4]
Thesis Director: *Professor and Doctor JUAN FRANCISCO LORO FERRER* [5]

[1] *Rehabilitation doctor. Grupo Socio-Sanitario ICOT. Doctoral Student. Las Palmas de Gran Canaria University. Spain.*
[2] *Physiotherapist. Ciudad de San Juan de Dios. Associated Professor. Las Palmas de Gran Canaria University. Medical and Surgical Science Department. Las Palmas de Gran Canaria. Spain.*
[3] *Physiotherapist. Complejo Hospitalario Universitario Insular-Materno Infantil de Las Palmas. Spain.*
[4] *Full Professor. Las Palmas de Gran Canaria University. Mathematical Department, Las Palmas de Gran Canaria, Spain.*
[5] *Full Professor. Las Palmas de Gran Canaria University. Basic Sciences Department. Thesis Director Program. Spain.*

ABSTRACT

Introduction: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. Meanwhile, breast cancer is the most common in women. Both, CTS and breast cancer are common diseases in older women and they will inevitably occur together. The gold standard test for CTS diagnosis is electromyography (EMG). Nowadays, there is scientific evidence to demonstrate the correlation between the ultrasound cross-sectional area of median nerve and EMG results. The aim of this study is to prove the efficacy of ultrasound results in patients with breast cancer related lymphoedema and CTS.

Method: Prospective, analytical and observational study. The principal investigator measured every patient with an ultrasound machine, and the valuation of the measurement of median nerve before treatment and after treatment (20 daily sessions). Clinical findings like paraesthesia, dysesthesia, Tinnel and Phalen signs, and an analogical visual scale (AVS) were also collected.

Results: 21 women with lymphoedema were recruited, with an average age of 62,45 (SD 9,615). After treatment, all of them present clinical findings of CTS in lymphoedema's arm, like paraesthesia, dysesthesia, Tinnel sign positive or Phalen sign positive. AVS before treatment 6.56 (SD1.39), AVS after treatment 5.49 (SD1.42), Cross-sectional median area before treatment 0.17mm^2 (SD 0.3), after treatment 0,15mm^2 (SD 0.15), Cross-sectional median nerve healthy arm 0.11mm2 (SD 0.21).

Conclusions: Ultrasound has to be taken into account in the diagnosis of CTS in breast-cancer-related lymphoedema patients, because it can avoid unnecessary surgical procedures in patients with increased risk of postsurgical complications. The evaluation of CTS before physiotherapy treatment is not recommended, because the improvement of the oedema can result a clinical beneficial improvement of CTS.

Key Words: Ultrasonography, Carpal Tunnel Syndrom, breast-cancer, physical therapy modality, mastectomy, rehabilitation.

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy, with an incidence of 1-3 cases per 1000 population per year. It is more frequent in 40-60 years old women [1]. Meanwhile, breast cancer is the most common in women around the world. Furthermore, CTS is a potential complication following mastectomy, with lymphoedema playing a role in their development. Both, CTS and breast cancer are common diseases in older women and they will inevitably occur together [2].
The gold standard test for CTS diagnosis is electromyography (EMG), but it is controverted because there are about 5-20% of false negative results and about 45% of false positives. Subcutaneous tissue thickness is a factor that contributes to change the EMG results and it is increased in women with lymphedema, so EMG in lymphoedema's patient could be less reliable and advisable [3].

Ultrasonography is a diagnosis imaging technique based on the application of ultrasound. Traditionally, it had been used in lymphoedema patients to discriminate lymphatic vessels and veins. Nowadays, there is scientific evidence to demonstrate the correlation between the ultrasound cross-sectional area of median nerve and EMG results, so a cross-sectional area higher than 10,8 mm^2 can cause a CTS. Ultrasound can also prove pathologic changes inside median nerve [4-11].
The aim of this study is to prove the efficacy of ultrasound results in patients with breast cancer related lymphoedema and CTS.

METHOD

This was a prospective, analytical and observational study. When 2 cm of perimeter difference in two consecutive levels were achieved, the treatment was indicated. This treatment included 20 daily sessions, from Monday to Friday, of Manual Lymphatic Drainage (MLD), pressotherapy (20min of intermittent pneumatic compression) and multilayer bandage (with 3 layer). The principal investigator measured every patient with an ultrasound machine, and the valuation of the measurement of median nerve before treatment and after treatment. The day of the evaluation, patients did not use the sleeve after the measurement.
All participants were recruited from the Lymphoedema's monographic consultation of Rehabilitation Service of the Complejo Hospitalario Universitario Insular-Materno Infantil de Las Palmas de Gran Canaria, Spain, from March 2015 and January 2016. This unit serves approximately 350 lymphoedema's patients per year. The aim and methology of the study was explained to all recruited women and voluntary participation was requested.
The inclusion criteria included: women; lymphoedema after breast cancer surgery; the need for physical therapy treatment; and literacy, including the ability to understand the study. The exclusion criteria included: bilateral oedema; primary lymphoedema; infection signs; tumour recurrence and metastasis diagnose.
The principal investigator involved in the intervention and data collection was a Rehabilitation and Physical Medicine specialist. Secondary investigators are Physiotherapists specialised in lymphatic drainage techniques for more than ten years. All of them used the same specific techniques of MLD, Vodder and Leduc methods. Both methods were used in all patients; especially Vodder method was used in fibrosis areas. Later, they had a session of pressotherapy, and finally, the multilayer bandage was placed.
A portable ultrasound machine with a lineal transducer (12MHz) was used by the principal investigator to measure cross-sectional median nerve area. The wrist was in neutral position and transducer was positioned on distal crease palmar wrist, in axial plane to take the measurement.
The principal investigator also collected clinical findings like paraesthesia, dysesthesia, Tinnel and Phalen signs, and an analogical visual scale (AVS).
Statistical study was used with SPSS program. The measurement and clinical findings results were compared to evidence the statistical signification after and before treatment. T-student and U Mann-Withney were used with quantitative variables.
Chi-Square test was used to compare qualitative variables. It was considered significant statistical levels with p value<0.05.

RESULTS

A total of 21 women with lymphoedema were recruited, with an average age of 62,45 (SD 9,615). The average value of the key variables is presented in Table 1. After treatment, there had been an improvement of 1.07 in AVS and 0.02mm^2 in cross-sectional area if median nerve. Two of the ultrasound images of median nerve are presented in Figure 1 and 2.
Before treatment, all of them present clinical findings of CTS in lymphoedema's arm, like paraesthesia, dysesthesia, Tinnel sign positive or Phalen sign positive. 9 of them (42,86%) suffered from the same symptoms in the healthy arm.

	AVS BT	AVS AT	Cross-sectional median area BT	Cross-sectional median area AT	Cross-sectional median nerve healthy arm
Average	6.56	5.49	0.17 mm^2	0.15 mm^2	0.11 mm^2
(SD)	(1.39)	(1.42)	(0.13)	(0.15)	(0.21)

Table 1 - Results of AVS and cross-sectional area before and after treatment (BT and AT).

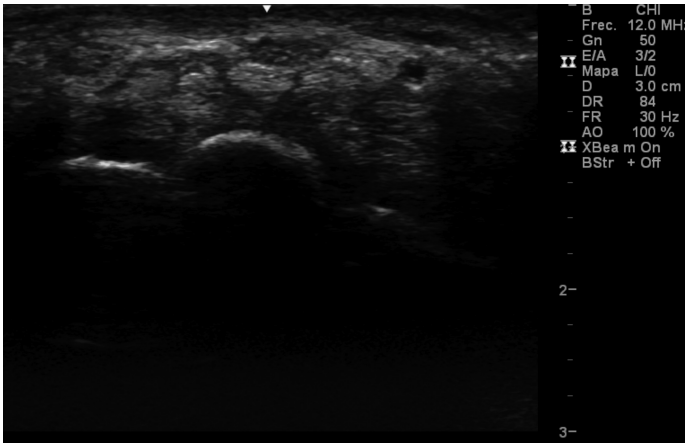

Fig. 1 - Ultrasound image of Median Nerve at the wrist of lymphoedema patient (transversal section).

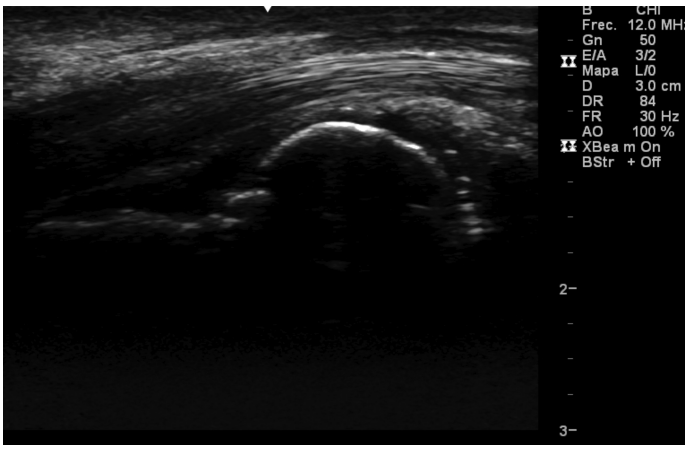

Fig. 2 - Ultrasound image of Median Nerve at the wrist of lymphoedema patient (longitudinal section).

DISCUSSION

Breast cancer and CTS are common diseases in older women and thus they will inevitably occur together. There is no evidence to conclude that lymphoedema predisposes to CTS but there is some evidence to suggest that CTS is more common after this kind of breast surgery [2]. It could be explained by the accumulation of fluid in the limb that might increase the pressure in the carpal tunnel. Our results demonstrate the increment in cross-sectional area in medial nerve in patients with clinical signs of CTS in lymphoedema arms.

Our results about cross-sectional area of median nerve are higher than the results of studies in patients without lymphoedema, in the affected limb. On the other limb they are also higher, but to a lesser extent. In all patients, after physiotherapy treatment, there was a marked improvement in clinical findings, clinical signs had disappeared or improved. Thus, in patients with lymphoedema diagnosis test of CTS should not be considered until oedema has improved.

There is a consensus that in patients with lymphoedema needle examination should not be used, but there are recent studies that found no evidence of either infection or worsening of lymphoedema after needle EMG examination [2]. Nevertheless, there is a possibility of nerve exploration with ultrasound, which is a cheap and safe option, and it could be considered after any needle examination.

Tinnel sign consist on the appearance of dysesthesias with wrist percussion. It has a level of sensitivity of 25-63% and a level of specificity of 67-87%. Meanwhile, Phalen sign consist on the appearance of dysesthesias with a wrist bilateral flexion of 90° during sixty consecutive seconds. It has a level of sensitivity of 70-89% and a level of specificity of 48% [12]. These two signs together have high diagnostic capabilities, so with the confirmation of the diagnosis with another diagnostic test, should be sufficient to confirm the diagnosis, it should not be indispensable the EMG.

EMG is the gold standard test to confirm the diagnosis of CTS, but it cannot show pathologic changes inside median nerve or pathology inside carpal tunnel associated [3]. These pathologies should be detected after a surgery treatment because the operative procedure will not resolve this situation or it will need another operative techniques [4,5,10]. Ultrasound could show these defects after surgery, so it can prevent complications during surgery.

In patients with lymphoedema is important to identify real CTS, because a surgical procedure stimulates a localized inflammatory response, thereby increasing the load on an already compromised lymphatic system. Furthermore, the sluggish flow of lymph though lymphoedematous tissues increases susceptibility to percutaneous introduction of bacteria by iatrogenic or other mechanisms, which can result in infection and lymphatic blockage [13]. For this reason, ultrasound should be included in CTS diagnose.

CONCLUSIONS

Ultrasound has to be taken into account in the diagnosis of CTS in breast-cancer-related lymphoedema patients, because it can avoid unnecessary surgical procedures in patients with increased risk of postsurgical complications.

The evaluation of CTS before physiotherapy treatment is not recommended, because the improvement of the oedema can result a clinical beneficial improvement of CTS.

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ORTHOTIC TREATMENT AS THERAPEUTIC SUPPORT FOR LYMPHOEDEMA OF THE LOWER LIMBS

MARTINELLI DORETTA [1], ACCOGLI SUSANNA [1], CAMPISI CORRADINO [2], BOCCARDO FRANCESCO [2]

[1] Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), San Martino Hospital, University of Genoa, Italy

[2] Department of Surgery, Unit of Lymphatic Surgery and Microsurgery, San Martino Hospital, University of Genoa, Italy

E-mail: francesco.boccardo@unige.it

ABSTRACT

The steady increase in the diagnosis of Lymphoedema, in both its primary and secondary forms, places this dysfunction amongst those chronic diseases that are in continual growth amongst the world's population.
It can be inferred from information published by the WHO that since 1994 the number of people affected by Lymphoedema has increased from 140 million to 300 million.
Currently in Italy an estimated 45,000 new cases are reported each year.
Medical protocols for the treatment of Lymphoedema call for the involvement of various professionals, including a Podiatrist, so as to make connections between the different aspects of the disease and alleviate the symptoms linked to its development.
To date it is still not possible to totally defeat Lymphoedema, but it is certainly possible to keep its aggravating characteristics under control thus simultaneously alleviating the symptomology. Living with this dysfunction is made tolerable with the help of early prevention, pharmacological treatments, conservative therapies and even surgery if required.
The typical development of lymphatic diseases undoubtedly brings about gradual disability in patients. When the lower limbs are affected, the gradual reduction in ability to work and in motor capacity leads to changes in interpersonal and social relationships causing a significant transformation in quality of life.
Lymphoedemas caused by orthopaedic disorders are of interest due to the frequency with which they arise, for example:

- Post-traumatic Lymphoedemas caused by a sprained ankle and/or bruising;
- acute Lymphoedemas, secondary to pulled muscles, sprains and torn ligaments. acute tendon injuries, broken bones and following operations;
- Lymphoedemas due to the use of a plaster cast or prolonged immobilisation.

When the disorder is in the lower limbs, the greatest complications encountered, other than a reduction in the immune system typically caused by lymphatic damage, are those due to reduced mobility in the limb, particularly the bending and straightening of it, caused by oedema.
In that case, the most important thing is to keep the affected limb moving.

Working on the basis that the use of foot or toe orthotics or other podiatric rehabilitation techniques impact on the positioning of the foot on the ground as well as on walking, there was the desire to establish the effectiveness of using the orthotic as a therapeutic aid which aims to improve the symptoms and functionality of people affected by lymphatic disorders.
Short-term monitoring plays a fundamental part in ascertaining the effectiveness of the device, as well as in identifying the extent of the results achieved and in ensuring they are maintained over time.
It is, however, important to point out that identifying the orthotic treatment best suited to the conditions and symptoms displayed by an individual may ensure an improvement in the current conditions but will not bring about total elimination of the symptoms.

Key Words: Orthotic Treatments of Lymphoedema, Podiatric rehabilitation, Disorder in Lower Limbs, Reduced mobility by oedema.

INTRODUCTION

The positioning of the foot on the ground when standing and gait are undoubtedly factors which impact on the posture of an individual.
Another fundamental function of the foot is linked to the upwards return of lymph as it is activated by rhythmic compression of the sole of the foot. The propulsion takes place during walking and the fluid is sent back into the blood stream at the height of the subclavian vein. [1-2]
Checking for and treating any possible alteration in the articulation of the ankles, knees or spine, as well as the muscles used for walking, is therefore a form of prevention as such conditions are detrimental to the correct functioning of the arteriovenous and Lymphatic Circulatory Systems. [3-4-5]
Static analysis and baropodometric tests allow the quality of the positioning of the foot to be analysed, focussing on fundamental factors such as:

- ✓ Weight distribution on two feet;
- ✓ The points of highest load;
- ✓ Postural and barycentric analysis;
- ✓ The transfer of body weight during the various phases of a step and the contact time of each part of the foot with the ground.

Using these methods it is possible to show the percentage contact of the ball of the foot compared to the heel and their positioning when walking.
Tests can be carried out to assess the positioning of the foot, producing a graphic record of the pressure applied on the ground, both when the patient is in a static position and when walking. Important investigations such as checking the transfer of weight, the positioning and the length and degree of load transmission are extremely useful for understanding any static or dynamic dysfunction of the foot, allowing the analysis of postural and locomotive biomechanics together with the pathological changes connected to them. [6]
During its development, Lymphoedema is affected by the impact of both any defects in posture and changes in the muscle pumps, as well as by the weight of the individual themselves, which, acts on the sole of the foot adversely compressing it. [7-8]
As the fundamental resolution offered by an orthopaedic device is to provide the patient as much relief as possible, its design and manufacture must be seen as an endeavour to alleviate the suffering of whoever is afflicted.
The orthotic device must be made to measure in order to fit comfortably between the foot and the surface the individual is standing on, responding to the force of the weight for every single shape and model.
The purpose of each orthotic therefore is not just limited to reducing some podiatric dysfunctions or deformations but it must also meet other needs: to compensate for mechanical problems making them more tolerable for the patient and thereby improving their quality of life.
Orthotics are designed to maintain the correct articulation of the feet and to respect their positioning which, during the phase of contact and propulsion, can be subjected to movements which are anomalous to the structure of the joints.
The provision of an orthotic is mainly requested in order to relieve symptoms of pain and to compensate for situations largely affecting the lower extremities following systemic diseases, for example, diabetic or rheumatic diseases, or those involving the circulatory, nervous or lymphatic apparatus.
It is possible to produce so-called corrective orthotics on the basis of functional characteristics. These are capable of acting to reduce some problems linked to development age such as in the case of infantile flat foot. An orthotic made for this purpose is aimed at changing the articulatory relationship of the feet to obtain a new morpho-structural equilibrium of the limb during the phase of contact and propulsion, when both static and dynamic.
Antalgic orthotics are, on the other hand, designed mainly to limit or eliminate the pain caused by a disease. As they provide total contact, they allow body weight to be distributed over a larger area. The pressure applied on any specific point is reduced, lowering the strain on the foot and therefore helping its anatomical structure. They are made using materials with different degrees of rigidity. In order to distribute the pressure to predetermined points, pieces with shock absorbing characteristics are selectively applied to the specific zones where there is excess pressure.
They are used for advanced arthritic conditions, deforming arthritis, gout, diabetes and generally in all situations in which the foot causes suffering.
The distinguishing characteristic of biomechanical orthotics is their ability to re-establish the correct features of the step. They are made using a more complex process which allows the identification of the characteristics of gait and the calculation of the level of daily stress the foot is placed under.
By absorbing the impact on the heel in the first phase of contact, this type of orthotic, contributes to the normalisation of the contact time of the foot on the ground, respecting the correct pronation and supination and the homogeneous transfer of body weight during the whole movement. The materials used to manufacture them can be grouped into three main categories: rigid, semi-rigid and soft. [9]

MATERIALS AND METHODOLOGY

Starting in May 2015, 33 individuals who had already been diagnosed with lymphatic diseases of the lower limbs were selected at random – 24 female and 9 male, aged between 20 and 85 years old.

Each individual was appropriately informed and in order to take part in our research, agreed to provide both their medical records and any other information deemed necessary for the research.

For each individual and without any differentiation, a medical record (see appendix) was created, made up of both a detailed medical history and the data taken at an objective podiatric examination.

The record, set out in different sections, enabled us to have a detailed understanding of physical and familial factors related to the participants.

In the final section, dedicated specifically to lymphatic disorders, all relevant information was taken from the documentation provided by the patients themselves as well as from observations made by the professionals during the assessment of the individual in question. [10 -19]

During the initial information gathering meeting, two different podiatric foot prints were taken of each individual – one using podiatric paper and another using phenolic foam to make an impression and produce a positive plaster cast.

This impression in phenolic foam was produced in two different ways depending on requirements:

a) weight-bearing, in a free orthostatic position
b) partially weight-bearing, manipulating the subtalar joint to bring it into a neutral position.

Using a baropodometric foot board a static assessment was carried out during which the individuals, temporarily without footwear, compression supports or bandages, were asked to stand for a few minutes in a natural pose on their heels, properly aligned on the footboard.

So as to get information on the dynamics of the joints, the timing of rest phase and of course the pressure value of each foot, the individuals were asked to walk along a corridor with a treadmill with a sensitised surface in the centre to carry out a dynamic analysis. [20]

To optimize the research, the orthotics were intentionally produced in two different ways in order, in addition to the main aim of

making connections to lymphatic diseases, to assess any differences in their effectiveness:

1) orthotics were made from the podiatric print and compensatory wedges added to them depending on requirements.
   Based on the end use of the orthotic, different materials are used for the base, as are different thicknesses for the compensatory materials added.
2) orthotics are obtained from the plaster cast using special materials which, having been previously heat moulded and inserted together with the mould in a vacuum pump, take on the shape of it.
   After cooling, the resulting shape is trimmed and adapted to the footwear size of the individual and the mid sole is also shaped to obtain the desired thickness.

RESULTS

During the final checks, each of the individuals participating in this research was asked some questions. The answers to those questions made it possible to compile a brief questionnaire which resulted in some interesting points for consideration.
The individuals were asked to succinctly express their opinion on their degree of satisfaction and to communicate their perceptions in relation to how quickly they tired, muscular tension and the difficulty in walking they experienced following the introduction of the orthotic.
In the questionnaire, which provided confirmation and approval, there was also room for objective assessment on the degree of compliance displayed by the patients themselves towards the orthotic proposed.

93.8% of the individuals assessed displayed a very positive degree of compliance with this research as well as with the orthotic provided, using it in the way it was intended.
Of course, over the course of this research, none of the individuals suspended their existing pharmacological therapy and physiotherapy already taking place, including any specific manual lymphatic drainage sessions and the use of compression supports.

50% of the patients expressed a sensation of increased balance when standing still and an improvement in balance when walking. In 50% a reduction in the sense of fatigue of the limbs and a perceivable reduction in the extent of hyperkeratosis were associated with the orthotics.

46.8% of individuals claimed that the perception of lower muscle strain, particularly when static, was connected to the good fit of the orthotic in their footwear.

In 40.6% of cases a perceivable, although minimal, reduction of the oedema was observed. It was not possible, however, to attribute this reduction solely to the use of the orthotic in that other factors, for example, favourable air temperature or the particularly good state of physical health of the patient, could have impacted on the measurement and contributed, even momentarily, to the reduction.

84.4% of participants expressed their sincere appreciation, happily choosing to continue to wear the orthotic after the end of the research.
The considerable quantity of information gathered made up the basis of the database from which the results and percentages needed for the research were then extrapolated.
The processing of the substantial amount of data generated many charts, which, when analysed, produced some significant statistical results.
Specifically, following the insertion of the orthotic, the following variations were recorded:

- ✓ An increase of 15.50% in the static contact surface
- ✓ An increase of 19.30% in the dynamic contact surface of the left foot
- ✓ An increase of 17.30% in the dynamic contact surface of the right foot
- • A decrease of 16.90% in the maximum dynamic pressure of the left foot
- • A decrease of 17.90% in the maximum dynamic pressure of the right foot

The research, although limited to a few individuals, suggests the extent to which an improvement in the initial conditions is perceivable through the use of orthotic devices for the treatment of lymphatic diseases.
At the same time, it draws the conclusion that one type of orthotic is not favoured over another in the treatment of lymphatic diseases.
In order to obtain positive results, the identification of an orthotic treatment must be tailored to the specific needs of the individual in question.
If an orthotic is well made, it will aid better distribution of body weight over both limbs and will compensate for the change in posture or gait which would lead to aggravation of the pre-existing malfunction of the lympho-venous system.

DISCUSSION

The aim of this study was to determine the frequency with which the use of an orthotic, through its provision of correct podiatric support, can aid in making the lymphatic disease development sustainable and improve the symptomatic and functional elements in the affected individual.[21]
As part of the same study, we wanted to identify whether one type of orthotic is favourable over another in providing adequate orthotic support and leading to a better result for the patient.
The advantages achieved by contact between the foot and the ground through the use of an orthotic were assessed using a static load.
The results obtained have shown how the presence of an orthotic allows the pressure on the foot to be redistributed in the front area, perceivably reducing the peripheral pressure, which, in many diseases, is the cause of the onset of skin lesions.
During the final examinations, which took place after differing amounts of time depending on the availability of the individuals and despite it not having been possible to ensure that the orthotics

were used constantly throughout that period, no significant positive or negative variations were observed compared to previous examinations.
On the basis of this research it has been possible to establish that, in relation to lymphatic diseases, no substantial differences were observed between the use of an orthotic heat-moulded on a plaster cast or one made up of an insole with added compensatory material.
With Lymphoedema the role of the orthotic is mainly to keep up the pumping effect, facilitating the upward return of the liquid and lympho-venous drainage, ultimately to aid the reduction of oedema.
Therefore, the identification of the most appropriate orthotic treatment, based on the specific needs of the individual and the disease they are afflicted with, will always be fundamentally based on the following specific elements:

- the pressure exerted on the ground by the foot;
- the shape and type of foot;
- areas of overload and excess contact

with the aim of improving the distribution of body weight and correcting the changes in posture or gait which aggravate the malfunction of the lympho-venous system.
The research was carried out using the same group of individuals and the information obtained and recorded before the orthotic devices were inserted as a 'control sample'.
Whilst not highlighting significant differences between the results obtained under the two scenarios, comparison of the data on a statistical basis, has definitively confirmed the effectiveness of the use of orthotics in the context of lymphatic diseases.
Having concluded this research we hope that it can be considered a pilot study and represent a sample on which to lay the foundations for a wider ranging project.
The processing of the data obtained could, in the future, easily provide the basis for another study aimed at increasing the number of case studies and providing a larger analysis of the correlation between the characteristics of lymphatic diseases and their possible interaction with appropriate orthotic devices.

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APPENDICES

PODIATRY RECORDS
(fac-simile)

SOCIAL PERSONAL DATA

name and surname: sex ☐ F ☐ M
date of birth: place of birth:
address:
weight (kg): height (cm):
phone number: mobile number:
GP: medical specialist:

FACTORS

education: profession (current or previous):
structure of family unit:

FAMILY MEDICAL HISTORY

disorders of genetic and/or hereditary transmission:
eg chromosomal abnormalities, cardiovascular, skin, blood, endocrine,
gastrointestinal, genitourinary, lymphatic, metabolic, musculoskeletal, neuropathic,
eye, oncological, respiratory, hearing

PHYSIOLOGICAL HISTORY

childbirth:
☐ first menstruation: age ____
menstrual cycle ☐ regular ☐ irregular
Menopause: onset ☐ early onset ☐ induced
bowel function: urination:
Lifestyle:
☐ diet
☐ alcohol ☐ coffee ☐ smoking
☐ sedentary lifestyle ☐ physical activity ☐ other

devices in use
☐ corrective glasses ☐ denture ☐ other

EARLY MEDICAL HISTORY

common childhood illnesses:
other childhood illnesses: ☐ whooping cough ☐ mumps ☐ other
food intolerances: skin allergies:
previous surgery:

other diseases:
autoimmune:
cardiovascular ☐ hypertension ☐ hypotension
lymphatic:
blood, endocrine, hepatic, infectious, metabolic, oncological, musculoskeletal, respiratory, serological, renal, etc.

PHARMACOLOGICAL HISTORY

☐ antiplatelet therapy ☐ anticoagulant therapy
☐ antihypertensive therapy ☐ hypoglycemic therapy
☐ hypouricemia therapy ☐ hypolipidemic therapy
☐ phlebolymphotropic therapy ☐ prescribed
☐ implemented

THERAPEUTIC MEDICAL HISTORY

☐ Conservative treatment ☐ prescribed ☐ implemented

RECENT MEDICAL HISTORY

_____

_____

OBJECTIVE TESTS:

Foot type: ☐ Egyptian ☐ Greek ☐ Roman

type of footwear: size:
degree of wear:
orthotic device in use:

skin condition:
temperature:
wrists:
changes in skin features – hairs:
changes in skin features – nails:
interdigital maceration:
hyperkeratosis:
tylosis:

MORPHOLOGICAL ASSESSMENT

anatomical completeness
changes in soft tissue
deformities of forefoot
changes in morphology

FUNCTIONAL ASSESSMENT TEST

postural alignment
abnormal twisting of limbs
structural relationship between heel and forefoot
knee
heel

MANUAL ASSESSMENT

muscle strength
joint mobility:
surface sensitivity:
- thermal
  pain sensitivity
- surface tactile sensitivity
  achiness

deep sensitivity:
- kinesthetic
- vibration perception
- pressure sensitivity

tendon reflexes:
- patellar reflex
- achilles reflex

LYMPHOLOGICAL RECORD
(fac-simile)

LYMPHOLOGICAL DIAGNOSIS

_____

_____

LOCATION OF LYMPHOEDEMA

_____

_____

LYMPHOEDEMA TYPE

☐ **PRIMARY**

☐ birth ☐ early ☐ late

☐ **SECONDARY**

☐ following oncological surgery ☐ radiotherapy
☐ tissue injury ☐ infections
☐ parasitosis ☐ post thrombosis

STAGING

RIGHT LIMB

↔ 1a ↔ 1b ↔ 2a ↔ 2b ↔ 3a ↔ 3b

LEFT LIMB

↔ 1a ↔ 1b ↔ 2a ↔ 2b ↔ 3a ↔ 3b

LYMPHATIC SYMPTOMOLOGY

	RIGHT LIMB		LEFT LIMB	
consistency oedema	☐ normal ☐ hard	☐ springy ☐ fibrous	☐ normal ☐ hard	☐ springy ☐ fibrous
venous component	☐ present	☐ absent	☐ present	☐ absent
symptoms of pain	☐ present	☐ absent	☐ present	☐ absent
syndactyly	☐ present	☐ absent	☐ present	☐ absent
stemmer	☐ present	☐ absent	☐ present	☐ absent
pitting	☐ present	☐ absent	☐ present	☐ absent
lymphorrhoea	☐ present	☐ absent	☐ present	☐ absent
lymphatic ulcers	☐ present	☐ absent	☐ present	☐ absent
lymphostatic verrucosis	☐ present	☐ absent	☐ present	☐ absent
lymphangitis	☐ present	☐ absent	☐ present	☐ absent
functional limitations	☐ present	☐ absent	☐ present	☐ absent

ANTHROPOMETRIC ASSESSMENT

	RIGHT LIMB		LEFT LIMB	
dysmetria	☐ present	cm	☐ present	cm
metatarsal circumference		cm		cm
ankle circumference		cm		cm
patellar circumference		cm		cm
circumference of subpatellar in a **distal** direction				
at 10 cm ↓		cm		cm
at 20 cm ↓		cm		cm
at 25 cm ↓		cm		cm
circumference of subpatellar in a **proximal** direction				
at 10 cm ↓		cm		cm
at 20 cm ↓		cm		cm
at 25 cm ↓		cm		cm

INSTRUMENTAL DIAGNOSIS
(fac-simile)

EXAMINATION WITH PODOSCOPE

_____

_____

BAROPODOMETRIC EXAMINATION

static analysis

_____

dynamic analysis

_____

ORTHOTIC AND ADDITIONAL COMPENSATORY WEDGES RECOMMENDED

right foot

_____

left foot

_____

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UNEXPECTED SUBSTITUTION OF LYMPHATIC PATHWAYS FOLLOWING THE DISSECTION OF THE AXILLARY NODES IN A RAT MODEL: A POTENTIAL FOR AN INNOVATIVE TREATMENT MODALITY

PASTOURET FRÉDÉRIC. MSC, PT, CARDOZO LUCIA. MLT*, LAMOTE JAN. MD, PHD**, LIEVENS PIERRE. PHD, PT**

** Vrije Universiteit Brussel, Brussels, Belgium,*
*** UZ Brussel, Brussels, Belgium.*

Address correspondence to: Drs PASTOURET Frédéric,
Department of Rehabilitation Research
Faculty of Physical Education and Physiotherapy,
Vrije Universiteit Brussel, Medical Campus, building F, Laarbeeklaan, 103
1090 Brussels, Belgium
Tel: +32 2 477 45 29 - E-mail: Frederic.Pastouret@vub.ac.be

ABSTRACT

Introduction: Axillary Nodes Dissection (AND) is the major risk factor of Breast Cancer Related Lymphoedema (BCRL). In an animal model Lymphatic Fluid Stasis (LFS) caused by AND appears to be the very first acute phase leading to primary soft tissue changes inducing a secondary lymphoedema.
The main part of physical prevention and treatment of BCRL in humans consists of external mechanical massage of the skin. Manual Lymphatic Drainage (MLD) improves the resorption of LFS and increases lymphatic flow. Other types of external mechanical skin massage as induced by a medical vibration device may induce a similar beneficial effect on the lymphatic system.

Objectives: The objectives of the presented study are double. The first objective is to appreciate the morphological effects of a complete AND on the front leg of a rat (volume) aiming at detecting LFS in the subcutaneous tissues as well as Functional Substitution Lymphatic Pathways (FSLP). The second objective is to analyse the short-term effects on accumulation of dye in the lymph nodes of mice by comparing local massage to multidirectional vibrations delivered in a horizontal position (Andullation).

Methods: Part 1: By applying an innovative posterior surgical approach, a left superficial and deep AND was performed on 30 females Wistar rats who were compared to an untreated group (10 females Wistar rats). Assessing pressure variations of water displacement during legs immersion, volume changes of the two front paws were measured preoperatively and 12 weeks after AND. The volumes were calculated in ml after plethysmometer calibration. To detect LFS and FSLP, Indocyanine Green mapping was performed before and after skin dissection.

Part 2: Ensuing injections of 20 µl Evans blue dye (EBD) in the foot-pads of 2 randomized groups of mice (total N = 15 animals), local massage for 5 minutes was applied to one group. The other group underwent 5 minutes whole body vibrations at 30 Hz in a horizontal position (Andullation). Both groups were compared to a non-treated, randomized, but similarly injected control group (N = 10 mice). Following animal euthanasia, the EBD-stained popliteal and sacral lymph nodes were carefully resected and their contained blue dye extracted. The quantity of EBD (µg) was determined using a spectrophotometric technique with a wavelength of 620 nm.

Results: Part 1: In the control group, FSLP and LFS were never detected and only normal lymphatic pathways were mapped. Volume differences (ml, mean ± sd) were found between the right (2.59 ± 0.29) and left (2.37 ± 0.42) paws but were not statistically significant after 12 weeks ($p = 0.2073$). At the level of the operated paws in the surgical groups, 43% of rats only presented a regeneration of the interrupted lymphatic pathways, 27% only showed FSLP (perforating lymph vessels), while 30% of the rats presented the two phenomena. None of all the operated and non-operated paws showed evidence of LFS. A statistical difference ($p = 0.0350$) of front paw volume (ml, mean ± sd) was found between the left operated (2.36 ± 0,31) and the right non-operated paws (2.53 ± 0,26). This indicates that there is no increase of the operated front paw volume compared to the non-operated paw volume.

Part 2: As a result of whole body vibrations in the horizontal position the quantities of EBD in the popliteal lymph nodes were statistically higher than in the control group: respectively 0.56 ± 0.26 and 0.14 ± 0.17 (mean and sd, $p<0.05$). The quantities of EBD also differed statistically from the recorded quantities following massage: respectively 0.56 ± 0.26 and 0.22 ± 0.16, mean and sd, $p<0.05$). The quantifications of EBD in sacral lymph nodes revealed strictly identical values.

Conclusions: Contrary to the predetermined hypothesis in the literature and following a period of 12 weeks, AND in a rat does

not necessarily induce LFS, although considered the first pathological event leading to secondary lymphoedema. The regeneration of lymphatic pathways and the occurrence of FLSP, especially "perforating vessels", in a rat, seem to be the key to prevent LFS and secondary lymphoedema. Consequently, it is important to stimulate the appearance of FLSP and to improve lymph flow with mechanical actions like manual lymphatic drainage or innovative technologies such as horizontal stochastic modulated vibrations (Andullation®).

Key Words: Axillary nodes dissection, substitution pathways, perforating vessels, ICG, stochastic vibrations, Andullation technology.

INTRODUCTION

In 2006 breast cancer was the most common diagnosed cancer in Europe (429.900 cases) representing 28.9% of all cancer cases in European women (Ferlay et al., 2007).
Early detection and treatment strategies of breast cancer have improved over the last years and resulted in higher survival rates. Consequently, more attention is paid to the complications of breast cancer treatment and especially Breast Cancer Related Lymphoedema (BCRL). McLaughin (2012) mentions a general BCRL incidence of 6 to 70%. Although the appearance of the BCRL is multifactorial, Axillary Node Dissection (AND) during breast cancer surgery is considered the major risk factor (Kim et al., 2013; McLaughlin, 2012; Tsai et al., 2009).
To study the effects of AND on the lymphatic system and the subcutaneous tissues at the operated side, animal models are essential (Hadamitzky and Pabst, 2008). However, standardized secondary lymphoedema animal models following axillary resection are rare. Rats appear to be the most appropriate laboratory animals to perform such evaluations (Hadamitzky and Pabst, 2008). Till now, different techniques were tested for creating an "in vivo" rat model of chronic secondary lymphoedema (Becker C, 1987), but turned out to be very difficult without additional chemical inflammatory agents (Becker C, 1987; Mendez et al., 2012) or auxiliary physical techniques such as radiotherapy (Kanter et al., 1990; Lee-Donaldson et al., 1999; Ogata et al., 2007). As a consequence, the complete anatomical and pathophysiological aspects leading to the development of secondary lymphoedema following solely AND have not been completely elucidated. In a recent mice model on AND, lymphatic fluid stasis (LFS) appeared to be the primary pathological vascular change 3 weeks following surgery leading to the appearance of markers which are associated with specific subcutaneous tissue changes occurring during chronic secondary lymphoedema in humans (Aschen et al., 2012). The present available information on the influence of AND only concerns its influence on the morphological aspect of the lymphatic system following longer post-operative periods.
In humans, the prevention and physical treatment of BCRL following axillary node dissection (AND) mainly consist in improving the lymph flow. It aims at avoiding lymphatic fluid stasis within the operated upper limb to prevent secondary lymphoedema. Manual lymphatic skin massage is the main modality of this physical treatment (Lympho, 2013) but the application of locally applied mechanical induced vibrations demonstrated positive effects on the lymphatic system. In 2007, a new technique of whole body vibration was introduced for medical applications (Germonpre et al., 2009). The innovative Andullation technology combines infrared light with stochastic modulated vibrations. The two biophysical treatment modalities are applied simultaneously to an individual in the horizontal position on a massage mattress. Massage by mechanically induced vibrations in the recumbent position is of interest as a potential additional prevention and /or treatment method in pathological conditions where vascular and/or lymphatic circulatory systems are compromised.
Two fundamental studies are presented. The objective of the first study is to evaluate the morphological effects of a total AND in the front paw of a rat (volume changes) in order to detect LFS and FSLP in the subcutaneous tissues 12 weeks following surgery.
The aim of the second study is to investigate the effect of a short exposure of multidirectional vibrations generated by Andullation technology on the lymphatic system in rats in the horizontal position.

MATERIALS AND METHODS

Part 1

The experiments were approved by the ethical committee on animal welfare of the Vrije Universiteit Brussel (VUB).
Females Wistar rats (N=40, average weight 202 ± 8 grams) were selected for this study and randomly allocated in 2 groups, an experimental group (N=30) and a control group (N=10).
At Day One, the volume of both shaved distal paws of each anesthetized animal (3 minutes induction phase: O_2 at 1l/min, Isoflurane at 5 % and maintenance phase: O_2 at 0.5 l/min, Isoflurane at 1.5-2%) was assessed with an artisanal plethysmometer based on pressure measurements (Fig. 1). The elbow of the stretched front paw was selected as reference marker. Due to the inconsistent shape of the arm and shoulder, only the volume of the paw extremity below the elbow was measured. Pressure variations were recorded with a blood pressure sensor (BP-100, World Precision Instruments, United Kingdom) connected to a data acquisition system (iWorx® AHK/214S, USA) with LabScribe3 software interface (Graph 1). The distal paw volume (ml) was calculated with the following formula [Vol (ml) = D (mmHg) / 0,1701] which was obtained after device calibration (Graph 2) based on measured pressures (mmHg) according to various known volumes (ml).

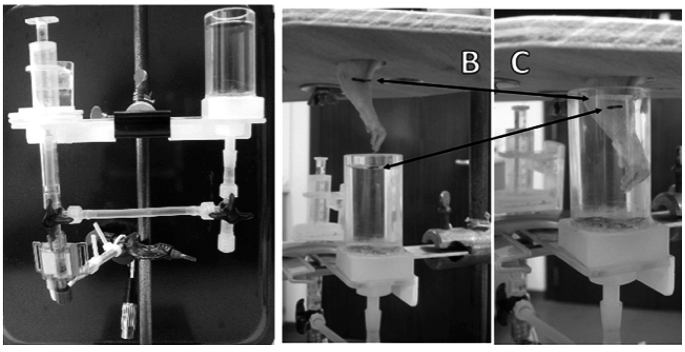
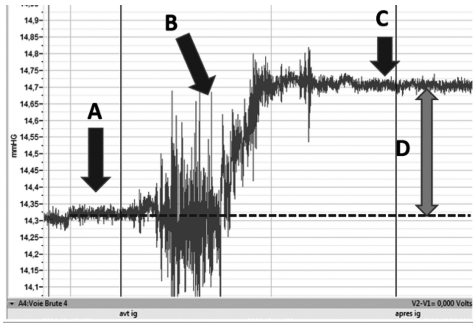
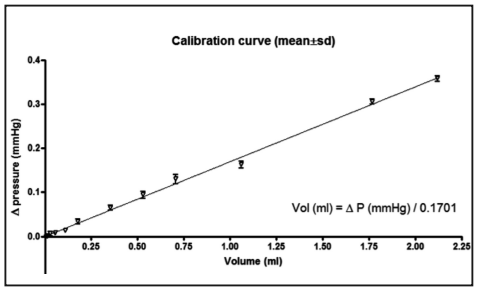


Fig. 1 - Artisanal plethysmometer (picture on the left) and paw immersion (B and C).

Graph 1: Example of a recorded pressure curve: base line period before distal paw immersion (A), immersion paw step (B), post-immersion paw period (C) and pressure difference (D).



Graph 2: Plethysmometer calibration curve (linear regression). Statistical software: GraphPad Prism 4, Goodness of the fit (Sy.x = 0.006836) and repeated pressure measures (8 times) of 12 known volumes.



In the experimental group, the rats underwent a combined left superficial dissection of the brachial nodes (Fig. 2b) and a deep dissection of the axillary nodes (Fig. 2c) by an innovative posterior surgical approach (Fig. 2a) (Pastouret et al., 2016). The technique concerns a skin incision of 1 cm length parallel to the posterior border of the triceps brachialis. The space between the interior face of the skin and the subcutaneous aponeurosis was split to assess directly the brachial nodes. Total fat tissue containing the brachial nodes was dissected followed by further dissecting and ligating the vascular pedicles and removal of the brachial nodes. Access to the axillary cavity was performed through an inter-aponeurotic passage between the cutaneous trunci and latissimi dorsi muscles. Hidden in the cavity, the axillary nodes were then delicately searched for, dissected and resected taking care that the elements of the peripheral neurovascular mass remained intact.

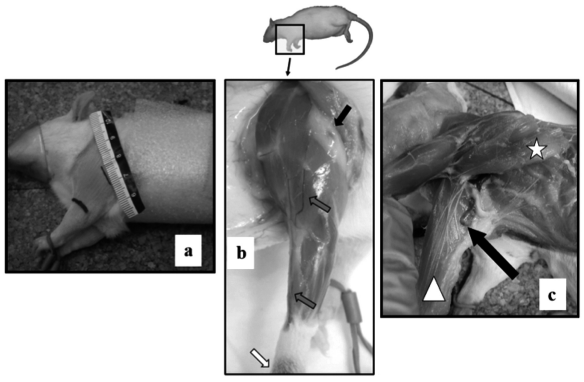


Fig. 2 - Innovative posterior surgical approach.
(a) Location of the skin incision. (b) The main superficial lymphatic pathway following skin dissection: the white arrow indicates the Evans Blue dye injection site which causes the lymphatic vessels to become visible (grey arrows). The black arrow indicates the brachial nodes in fat tissue. (c) Following cutaneous trunci muscle section (white triangle), the deep axillary nodes are located. The black arrow indicates the axillary node and the white star is positioned over the latissimus dorsi muscle.

At 12 weeks, the ultimate paw volume assessments were carried out under general anaesthesia (same protocol). Then ICG mapping was accomplished before collection of skin samples to detect LFS and after collection of skin samples to detect FLSP. Indirect lymphographies were performed following subcutaneous injection of ICG at the back side of the forefoot of each investigated front paw (0.05 ml, 5 mg/ml, Pulsion Germany). Massage at the injection site was done during 3 minutes for enhancing the absorption of tracer by the initial lymphatics and to help out its evacuation in the lymphatic collector vessels (Gashev et al., 2010; Unno et al., 2008). The ICG mappings were achieved by an artisanal near infrared camera.
The near infrared light source consisted of two parts. A 30 LED light ring (760 nm) was fixed to the camera for a general illumination of the target zone and a 30 LED mobile light module (760 nm) focused an additional illumination on a more specific part of the target. In addition, one long pass filter (Schott RG830 or Schott RG850) was placed in front of the lens of the digital camera which was connected to the near industrial camera. The choice of the filter depended on light environmental conditions. Focusing and zooming the lens could be manually adjusted. These two additional settings solved various disadvantages of the other near infrared cameras available in the medical field.
At the end of the experiment, rats were euthanized by injecting an overdose of Nembutal.

Part 2

Female N.M.R.I. (Naval Medical Research Institute, Bethesda, Maryland, USA) white mice, aged 6 to 8 weeks and weighing 28 to 30 grams, were selected for this experiment. The lymphatic vessel, popliteal and sacral lymph nodes of the posterior paw were used as lymphatic system model (Fig. 3). The investigations were approved by the local Animal Care Committee of the Vrije Universiteit Brussel.
Animal distribution was randomized in three groups of mice: 5 mice in the massage group, 10 animals in the vibration group and 10 mice in the control group. All animals were anaesthetized with urethane (2 mg/g i.p.). Hair on the posterior paws was shaved with electric clippers.
A spectrophotometric technique was chosen for the analysis of lymph node blueness to obtain quantitative values of the lymphatic functions (reabsorption and lymph flow). Having completed lymph node resections, Evans blue dye (EBD) was extravasated from the nodes according to the method used by Greco (Greco et al., 2006).

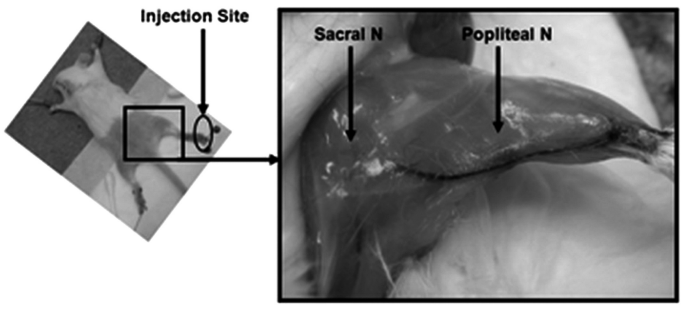


Fig. 3 - Injection site and visualisation of the lymphatic vessel, popliteal and sacral lymph nodes (coloured by Patent Blue) in the mouse posterior paw.

Experimental protocol

Following anaesthesia and shaving, the animals were placed in an identical position on a same platform allowing them to vibrate. Respecting five minutes of rest, an EBD solution (25 mg/ml, 20 µl) was injected subcutaneously at the dorsal side of the foot pad over a period of three minutes. Bilateral injections were carried out in the massage group. The choice of the first foot pad to be injected was randomized. Unilateral injections were performed in both vibration and control groups where the foot pad to be injected was randomized as well.

Each group underwent its specific treatment during five minutes. The mice in the control group only rested on the platform that was not induced to vibrate (Fig. 4). The animals in the vibration group underwent whole body vibrations at 30 Hz. The massage group received bilateral massage at the injection sites (Fig. 4). At the end of the treatment animals were euthanized by cranial dislocation. The resections of the popliteal and sacral lymph nodes were realized in a randomized order in the group of animals which only received local massage (right or left) (Fig. 4). The EBD was extracted from the removed lymph nodes during 24 hours by immersing each of these nodes in a 7:3 mixture of acetone and 0.5% aqueous sodium sulphate solution (Harada et al., 1971). Spectrophotometric analysis of EBD was performed at 620 nm.

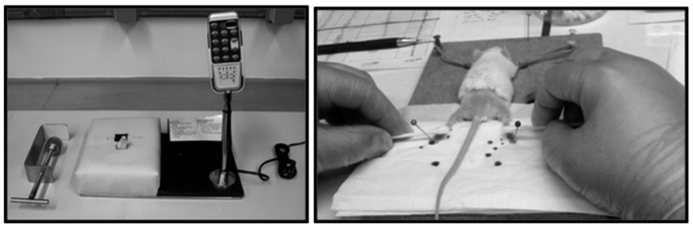


Fig. 4 - In the left picture the vibration platform is represented in which a single motor of Andullation technology was built in to generate vibrations. On the right, the same researcher is performing bilateral massage with cotton buds at the level of the injection of the dye by respecting identical direction, speed and force.

RESULTS

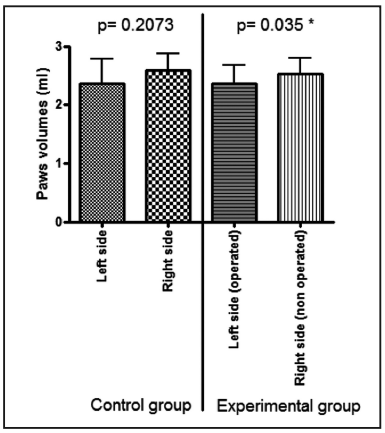
Part 1

Distal paw volumes

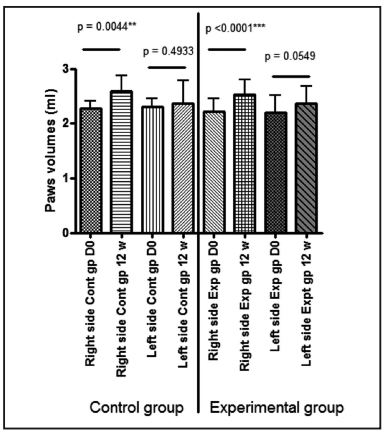
The evaluation of the distal paw volumes was performed 12 weeks following surgery. In the control group, a statistically significant paw volume difference (ml, mean ± sd) was not found between the right (2.59 ± 0.29) and left (2.37 ± 0.42) sides (p = 0.2073). In the operated group, a statistical difference (p = 0.0350) of front paw volumes was seen between the right non-operated (2.53 ± 0,26) and the left operated (2.36 ± 0,31) paws (Graph 3). This result indicates that there is no increase of the operated front paw volume compared to the non-operated paw.

The evolutions of paw volumes from day 0 to 12 weeks following surgery were further analysed in detail (Graph 4). The volume of the right paws in both control and operated groups grew in a statistically significant way during the period of 12 weeks while the growth of the left paws was not statistically significant. To explain these results, two conclusions are forwarded.

Graph 3 - Paws volumes (ml, average ± sd) 12 weeks following surgery.



Graph 4 - The evolution of the paw volumes (ml, average ± sd) from day 0 to 12 weeks following surgery.



First, in all cases the growth of the right front paws of young females rats was more important than the growth of the left front paws. Secondly, regarding the operated paws, there was no detected visible sign of secondary lymphoedema (increase of volume).

ICG mapping

In the control group, FSLP and LFS were never detected and only normal lymphatic pathways were mapped (20/20) (Fig 5). During the first ICG mapping in the operated group, LFS was never detected before the collection of skin samples (60/60).

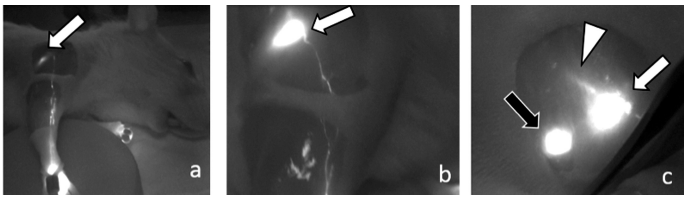


Fig. 5 - Normal lymphatic pathways in the front paw.

Global view of the right front paw after skin samples collection and the main lymphatic pathway following ICG injection in the dorsal aspect of the forefoot. The white arrow in picture (a) shows brachial nodes. The white arrow in the zoomed view of the arm and shoulder (b) illustrates the brachial nodes. Picture (c) is a close-up view of the shoulder after arm stretching. The white arrow shows the brachial nodes and the white triangle the efferent lymphatic vessel from the superficial brachial nodes to the deep axillary node (black arrow) which anatomically is located behind cutaneous trunci muscle.

Normal lymphatic pathways only were mapped on the right non-operated side (30/30). Following the collection of skin samples, a second ICG mapping of the left operated side only showed regeneration of the interrupted lymphatic pathway in 43% of rats (Fig. 6). FSLP connecting the superficial to the deep lymphatic network by a perforating lymph vessel was only seen in 27% (Fig. 7) and both phenomena were present in 30% of animals (Fig. 8).

Note that the observation of a deep lymphatic network underneath the cutaneous trunci muscle proves the existence of a connexion between the superficial and the deep lymphatic networks which might be due to lymphatic regeneration (Fig. 6), a FLSP (perforating vessel) (Fig. 7) or both phenomena (Fig. 8).

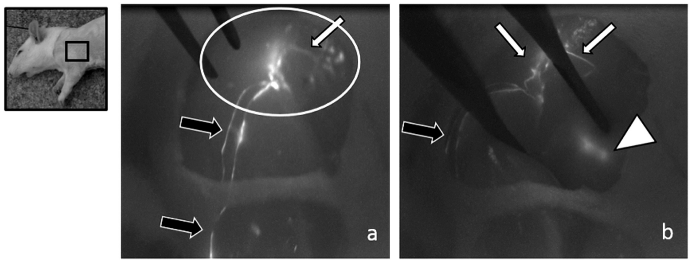


Fig. 6 - Example of regeneration of interrupted lymphatic vessels in an operated rat.

Close-up views of the left arm and shoulder. On the left (a), the black arrows indicate the main lymphatic pathway, the white circle the surgical site where brachial nodes were removed, and the arrow illustrates a regenerated lymphatic vessel. On the right (b), the black arrow indicates the main lymphatic pathway, the white triangle shows the deep lymphatic network under the cutaneous trunci muscle following stretching of the arm, and the white arrows illustrate the regenerated lymphatic vessels.

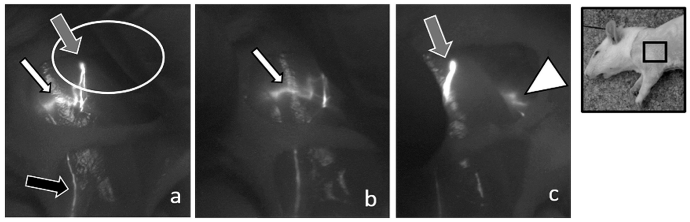


Fig. 7 - Example of FSLP (perforating vessel) in the operated rat.

Zoomed views of the left arm and shoulder. On the left side (a), the black arrow indicates the main lymphatic pathway, the white circle shows the surgical site with removed brachial nodes, the white arrow displays a perforating vessel, and the grey arrow presents a lymphatic dead-end. In the central picture (b), the white arrow shows a perforating vessel following superficial fascia stretch. On the right (c), the white triangle indicates the deep lymphatic network under the cutaneous trunci muscle following arm stretch and the grey arrow presents a lymphatic dead-end. Note that there is no evolving lymphatic regeneration process inside the surgical site.

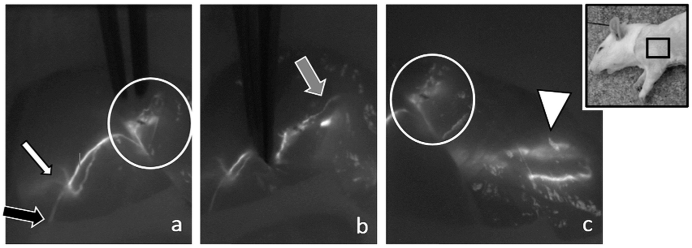


Fig. 8 - Example of lymph flow restoration by regeneration and FSLP (perforating vessel) in an operated rat.

Close-up views of the left arm and shoulder. On the left image (a), the black arrow indicates the main lymphatic pathway, the white circle shows the surgical site with removed brachial nodes, and the white arrow depicts a perforating vessel. In the central image (b), the grey arrow indicates a regenerated lymphatic vessel following fascia stretch. On the right picture (c), the white circle shows the surgical site and the white triangle presents a deep lymphatic network under the cutaneous trunci muscle after arm stretch.

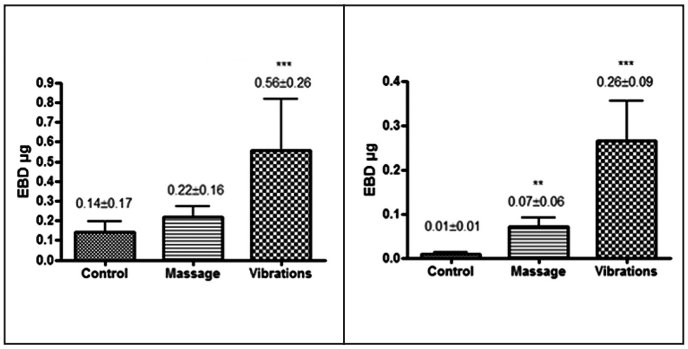
Part 2

Accumulation of EBD in the popliteal lymph node

The accumulated amount of EBD in the popliteal lymph nodes is significantly higher in the group which underwent vibration than in the control group which received no intervention (respectively, 0.56 ± 0.26 and 0.14 ± 0.17, p = 0.0005). No difference in the accumulation of EBD is observed when local massage is compared to no intervention (respectively, 0.22 ± 0.16 and 0.14 ± 0.17, p = 0.3008). However, a significant EBD accumulation in the popliteal nodes is detected when vibrations are applied rather than when local massage is applied (respectively, 0.56 ± 0.26, and 0.22 ± 0.16, p = 0.0028).

Quantities (µl) of EBD in sacral lymph nodes following vibration are higher than in the control group (respectively, 0.26 ± 0.09 and 0.01 ± 0.01, p<0.0001), which are also statistically different from those in the massage group (respectively, 0.26 ± 0.09 and 0.07 ± 0.06, p<0.0001).

Unlike the EBD quantities found in the popliteal lymph nodes and compared to control conditions, local massage increased the EBD amount in the sacral nodes (respectively, 0.07 ± 0.06 and 0.01 ± 0.01, p = 0.0029). The results are presented in graph 5.



Graph 5 - Amount of EBD (µg) accumulation in the popliteal (left) and sacral (right) lymph nodes (mean and sd).

DISCUSSION

Part1

Lymphatic Fluid Stasis (LFS) and complete AND in a rat model (innovative posterior surgical approach)

A new model of Lymphatic Fluid Stasis (LFS) on the tail of a mouse resulting from impairment of lymphatic transport by traumatic tail surgery was proposed and used to study cells and mechanisms involved in subcutaneous tissue remodelling. However, AND was not performed in this model (Zampell et al., 2012). According to their initial results, LFS seemed to induce local oedema, local presence of various markers associated with fibrosis, adipogenesis and inflammation at 3 and 6 weeks post-intervention. To confirm these findings in a more physiologically relevant model, the authors performed AND in mice (N=6). Local oedema, Lymphatic Fluid Stasis and identical specific markers in the front paws of the mice were detected as well and only 3 weeks after surgery (Aschen et al., 2012).
Theoretically, in response to the highly traumatic surgery involving dissections of skin, connective tissue and muscles, an acute postoperative inflammatory process is produced and may last for several weeks. Such a persistent inflammatory process may partially have explained the above mentioned results. However, when AND in mice is compared to a sham surgical procedure, the results seem to indicate that only AND produces LFS and is responsible for the cited subcutaneous remodeling (Aschen et al., 2012).
To corroborate with these findings, an innovative posterior surgical approach was developed by the authors realising a minimal invasive and less traumatic procedure (Pastouret et al., 2016). According to the anatomy of a laboratory rat and for reaching the deep axillary nodes by a skin incision placed across the axilla, it was essential to cut the cutaneous trunci muscle as it is attached to the pectoralis muscle. Both protect the axilla and no direct access is present between both muscles to reach that site (Fig. 9).

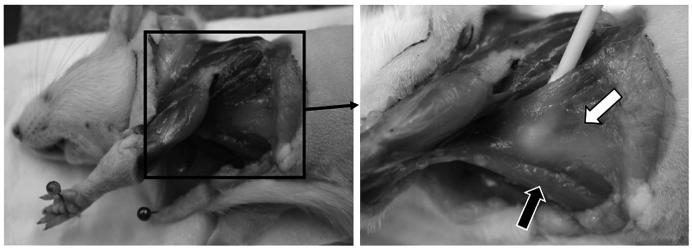


Fig. 9 - Cutaneous trunci and pectoralis muscles in a rat following skin dissection.

Lateral views of a dissected front leg (arm and shoulder). The black arrow indicates the pectoralis muscle and the white arrow shows the cutaneous trunci muscle.

In another AND rat model, an anterior surgical approach was used to induce secondary lymphoedema by adding inflammatory drugs (Becker C, 1987; Mendez et al., 2012). The posterior surgical approach allowed to realise a complete AND without muscle dissection, no nervous lesion and avoiding infection (30/30).
The extended period of time following posterior surgery and before examination is an important factor (12 weeks) to evidence if postsurgical inflammation is avoided.
An ICG mapping was selected to detect LFS and FLSP. By comparing the results in the study of Aschen (2012) to our presented findings, a difference regarding the evidence of LFS was shown. In the presented study, LFS never was detected at the operated sides 12 weeks following AND and no increase was observed in volume of the operated versus the non-operated distal front paw volume.
Skin sample collections were carried out to detect subcutaneous remodelling and sections were stained for subsequent analysis.

Regeneration process (lymphangiogenesis) and Functional Lymphatic Substitution Pathway (FLSP)

Lymphangiogenesis or the formation of new lymph vessels from pre-existing lymph vessels (Leclers et al., 2005) appears during processes of inflammation, metastasing tumours and wound healing (Tammela and Alitalo, 2010). Morphological and biochemical aspects of lymphangiogenesis during wound healing have been actively studied in the past and are topics of actual research (Lievens, 1978; Nogami et al., 2009; Pastouret et al., 2014). In the presented study, a regeneration process is the major way for lymphatic flow restoration following AND (73%), in combination with (30%) or without FLSP (43%). The FSLP found in our AND rat model is exclusively due to occurrence of lymphatic perforating vessels. During ICG mapping, functional anterior or posterior contralateral substitution lymphatic pathways were never observed. On the contrary, in another secondary lymphoedema rat model, contralateral substitution lymphatic pathways could well be observed during ICG mapping after lymphadenectomy (Takeno and Fujimoto, 2013).
In a preliminary study in a rat, lymphatic perforating vessels were observed for the first time in AND rats after Evans Blue dye injection (Fig. 10), skin and muscles dissection (Pastouret F. et al., 2016). Specific location was identified at the level of a precise point where the spinodeltoid muscles and the long and lateral portion of the triceps brachii meet (Pastouret et al., 2016). In the present study, perforating vessels were mapped in the same anatomic location during the second ICG mapping.
Perforating vessels were never observed on the non-operated sides in 50 mapped front paws in the control and experimental groups.
The authors conclude that the described lymphatic perforating vessels following AND were not functional before surgery. In our rat model the experiments do not allow to explain the origin of these vessels which probably already existed since foetal period or were formed during lymphangiogenesis in the postsurgical phase.
Our results regarding the volume change 12 weeks following surgery, seem to indicate that a regeneration process and FSLP play a primordial role to prevent LFS and secondary lymphoedema.
The change of paw volume is an important clinical sign. However, paw swelling is not sufficient to detect early secondary oedema. In the diagnosis, more attention is focussed on the presence of subclinical signs such as the significant changes in lymphatic patterns during the latent stage of lymphoedema, for example LFS, dermal back flow, without the clinical sign of swelling (Ogata et al., 2007).
In a secondary lymphoedema rat model, recovery of the lymphatic system following AND may lead to a chronic and latent lymphatic insufficiency without the clinical sign of swelling. The swelling associated with chronic lymphoedema may develop and appear

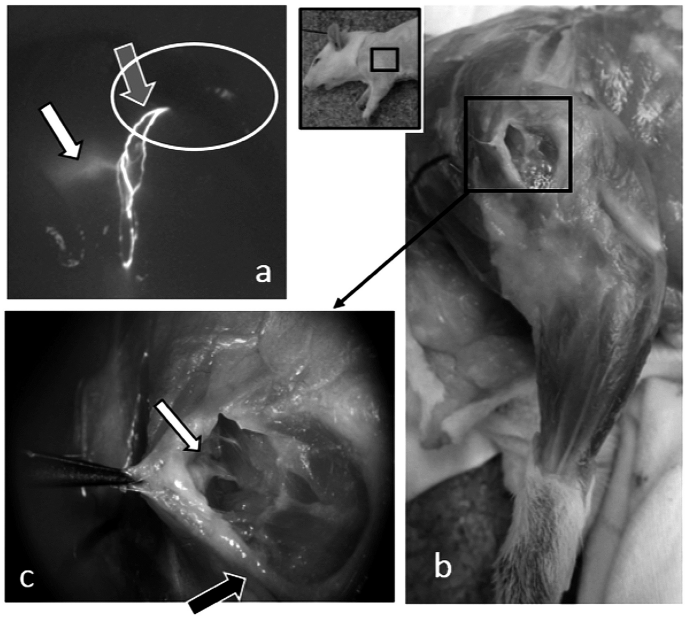


Fig. 10 - Other examples of perforating vessels in an operated rat (AND).

Zoomed view of the left arm and shoulder. In picture (a), the white circle shows the surgical site (removed brachial nodes), the white arrow indicates a perforating vessel, and the grey arrow depicts a lymphatic dead-end. In the image (b), a global view is presented of the left front paw (following skin resection), as well as the main lymphatic pathway after Evans Blue dye injection in the dorsal face of the forefoot. On the close-up view of the shoulder following muscles incisions (c), the white arrow indicates a perforating vessel and the black arrow depicts the main lymphatic pathway.

following successive tissue inflammatory processes (Mendez et al., 2012). An effective protection against external aggression leading to tissue inflammatory processes may be considered as the second key to prevent secondary lymphoedema in a rat.

Human Clinical Applications

Following breast cancer treatment in humans, ICG mappings or lymphoscintigraphies are two complementary diagnostic tools for lymphatic insufficiency detection and FSLP (Mihara et al., 2012). Functioning anterior or posterior substitution lymphatic pathways during BCRL are described in literature (Leduc et al., 1993-1994). However, a description of lymphatic perforating vessels following AND is rare. An anatomical description of both superficial and deep lymphatic system in a female cadaver who underwent an AND but presented no clinical signs of BCRL was published by Suami et al (2017). There was evidence of a more developed deep lymphatic network on the operated side compared to the non-operated side and was due to the presence of lymphatic perforating vessels at the level of the elbow. Perforating vessels substitution pathways seem to be present at birth. Poor and inconstant observations in foetuses at the levels of forearm, elbow and upper arm have been observed (Leduc et al., 1981). None seems to be functional in a normal situation, but could function in upper limb lymphatic system injuries such as AND (abnormal situation). Functional substitution lymphatic pathways as well as lymphatic perforating vessels play a major role in the therapy of lymphoedema. Physical treatment of lymphoedema consists of Manual Lymphatic Drainage (MLD) and Compression Therapy (Multilayers Bandages, Medical Elastic Compression Garments and Intermittent Compression Therapy (ICT) (Lympho, 2013)). They aim at evacuating the fluid stasis through the functional lymphatic vessels and the venous system. Lymphatic perforating vessels allow a rerouting of superficial obstructed lymph flow toward the deeper located lymphatic network. Opening and stimulating the function of lymphatic perforating vessels certainly may be influenced by local massage which induces lymph entrance and lymph flow progression inside the lymphatic perforating vessels. Till now, MLD and Multilayers bandages seem to be the best mechanical methods to take up fluid stasis. Lymph resorption and lymph flow (Lympho, 2013) is increased by local massage (MLD) (Leduc et al., 2011) or "pump local massage" during muscular contractions (Multilayers bandages) (Wilputte et al., 2005).

Part 2

Lymph node dye accumulation and effect of stochastic vibration (Andullation®)

A short time exposure to multidirectional whole body vibrations which are mechanically generated and stochastically modulated accelerates lymph reabsorption and lymph flow. The increase of dye accumulation in the lymph nodes could be deduced from the mechanical effect of vibrations on mouse skin. In the present study, mice were placed in the ventral decubitus position to obtain a maximum of contact between the EBD injection site and the platform which produced mechanical vibrations. The positional conditions allowed the whole body to vibrate and the local skin to undergo massage at the injection site. When Indocyanine Green Dye (ICG) was injected during other experiments, massage improved tracer evacuation from the injected area into the lymphatic system (Unno et al., 2008). It was demonstrated as well that massage increased the lymph flow in comparison to no manual intervention. When injected subcutaneously, EBD binds to endogenous proteins (Tsopelas and Sutton, 2002). The bound EBD-proteins as well as free EBD are absorbed by the lymphatic vessels and transported along with the lymph flow. This might explain why local massage on the injection site increases reabsorption and lymph flow of EBD and accelerates EBD accumulation in the lymph nodes as well (sacral nodes). A similar mechanism (local massage of the injection site) in addition to whole body vibration explains the more impressive quantified results.

Spectrophotometry

The spectrophotometric technique is rarely used in fundamental lymphatic research. Nevertheless, spectrophotometry is a validated technique, simple to apply, and often used as an assessment procedure in pharmacology and medicine. Regarding 'fundamental' research of the lymphatic system, the spectrophotometric

technique allows measurement of quantitative EBD-values and detection of small amounts of dye in lymph nodes. However, it remains essential to resect the dye stained lymph nodes. In fundamental studies, the spectrophotometric technique is an interesting and precise alternative procedure to other blue dye quantifying techniques such as the measurement of blue colour intensity by a digital camera (Sutton et al., 2002) .

CONCLUSION

This study primarily was carried out to detect Volume Change, Lymphatic Fluid Stasis and Functional Substitution Lymphatic Pathways in the front paw of a rat model 12 weeks following complete AND performed through an innovative posterior surgical approach.
Contrary to the hypothesis forwarded in the literature, the obtained results of the present study indicate that complete AND in a rat does not necessarily induce a LFS 12 weeks following the surgical procedure. LFS is considered the initial pathological event leading to a secondary lymphoedema. Regeneration of lymphatic pathways and FLSP, especially of "lymphatic perforating vessels", occurred following AND in the front paw of a rat model and seem to be the key in preventing LFS and secondary lymphoedema.
In humans, lymphatic perforating vessels of the upper limb have been described in the literature to rarely take place in healthy individuals and were also observed in a cadaver of a breast cancer operated woman without clinical sign of BCRL. Prevention and treatment of BCRL following breast cancer surgery aims at an earlier opening and better function of all functional lymphatic pathways and Lymphatic Substitution Lymphatic Pathways trying to improve the lymph flow with external mechanical skin massage like MLD or other types of external massage.
The authors also evaluated the effect of stochastic vibrations (Andullation®) on the lymph flow in mice by spectrophotometrically analysing dye accumulation in their popliteal and sacral nodes. The results demonstrated a significant increase in dye accumulation in the lymph nodes. Short time exposures to vibrations generated by Andullation technology improve reabsorption and lymphatic flow. The results are encouraging and provide new data regarding the value of horizontal whole body vibrations for the lymphatic circulatory system.
In addition to the validated physical techniques such as MLD, the submitted findings in both fundamental studies arouse the necessity to consider vibrations as a future potential biophysical option in the treatment of lymphatic diseases.
This original papier corresponds to the free oral communication in 2016 which was rewarded with the Isidoro Caplan price at the XXXXII ESL Congress in Mulhouse, France.

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DERMAL BACKFLOW APPEARANCE IN BREAST CANCER LYMPHOSCINTIGRAPHY: REPORT OF TWO CASES

ELAHE PIRAYESH, M.D. [1], *HAMIDREZA HASHEMIFARD, M.D.* [2]

[1] Nuclear Medicine Department, Shohada-e Tajrish Medical Center, Shahid Beheshti University of Medical Sciences

[2] Oncology Department, Vaseie Medical Center, Sabzevar University of Medical Sciences

Corresponding author: Elahe Pirayesh, M.D.
Assistant professor of nuclear medicine, Nuclear Medicine Department, Shohada-e Tajrish Medical Center, Shahid Beheshti University of Medical Sciences.

Address: Nuclear Medicine Department, Shohada-e Tajrish Medical Center, Tajrish Sq, Tehran, Iran. Tel: +982122723263; Fax: +982122723263

Email: elahe_pirayesh@yahoo.com

ABSTRACT

We report two cases of breast cancer who were referred to the nuclear medicine department for sentinel lymph node mapping before surgery. Imaging performed after intradermal injection of 99mTc-phytate in periareolar region. Unexpectedly, dermal backflow appearance was found. At final histology lymph node involvement and lymphatic vessels invasion was confirmed.

Keyword: breast cancer, sentinel node, lymphoscintigraphy

INTRODUCTION

Axillary node status is an important prognostic factor in early breast cancer. Lymphoscintigraphy has been recognized as the modality of choice for lymph node staging. After injection of radiotracer, imaging is recommended to confirm axilla and/or extra-axillary location of sentinel lymph nodes (SLN) [1]. There are several reports which explain unusual pattern of lymphatic drainage of patients with breast cancer, in which atypical location of SLNs were found. [2-4]

In the current paper, we describe two breast cancer patients who underwent preoperative lymphoscintigarphy and showed diffuse distribution of radiotracer with faint visualization of SLNs.

CASE REPORT

Case 1

A 40 year-old female known case of invasive ductal carcinoma of right breast, diagnosed by core needle biopsy, and clinically negative axillary nodes was referred to our department for sentinel nod mapping. On physical examination, in addition of palpable breast mass, the right breast was slightly denser than the left one but no evidence of erythm was noted. After intradermal injection of 0.2 ml of 1 mCi 99mTc-phytate into the peri-areolar area of the quadrant, the patient was advised to do gentle massage to the injection site for 5 minutes. Fifteen minutes after injection, anterior, lateral and oblique spot views were obtained, (3min/image, 128×128matrix) using a single head gamma camera (E.CAM Siemens), equipped with a parallel hole low energy high resolution (LEHR) collimator. Scintigarm demonstrated abnormal lymphatic transit and absence of tracer localization in the axillary lymph nodes. In addition, inversion of lymph flow and diffusion of tracer resulted in cutaneous accumulation of tracer (dermal backflow appearance) was also seen (Fig. 1). Because of non-visualization of sentinel nodes delayed images were obtained up to 2 hours and finally on the lateral view two nodes were seen. In the operating room, two sentinel nodes were found and frozen sections were in favor of metastatic involvement. The patient underwent right breast mastectomy and right axillary lymph node dissection. At final histology, two sentinel nodes as well as were metastatic.

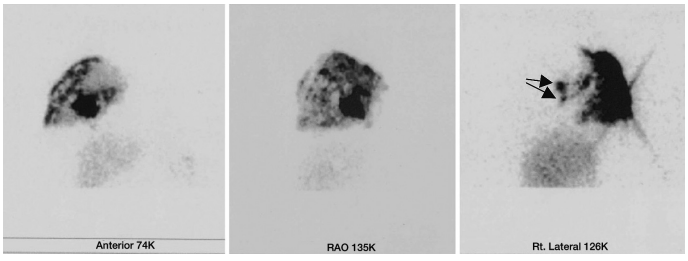

Fig. 1 - Scintigram shows dermal backflow appearance, with two faint SLNs.

Case report 2

Lymphatic mapping was performed in a 54-year-old woman who had undergone neoadjuvant chemotherapy for locally advanced invasive breast cancer, was referred to our department for lymphoscintigraphy. On the day before surgery, one dose of 0.2 mL of 37 MBq (1 mCi) 99mTc-phytate was injected interadermally in periareolar region. Because of failure of first injection, additional injection was performed on the opposite side of periareolar region. Anterior planar images were acquired after 15 minutes. Diffuse distribution of radiotracer was noted throughout the breast tissue and two faint focal hyperactivities in the axillary region was also noted (Fig. 2). During surgery, sentinel nodes were found, which were positive for lymphatic involvement.

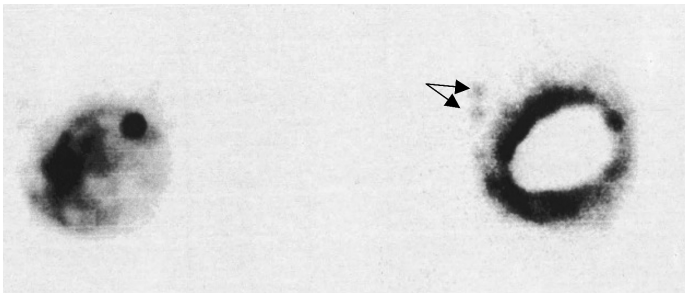

Fig. 2 - Diffuse distribution of radiotracer and two faint SLNs are seen.

DISCUSSION

After intradermal injection of radiotracer, visualization of one or more SLNs in the axillary region and sometimes lymphatic vessels is expected [1]. However, there are some reports describe unpredictable lymph pathways [2, 4, 5]. But, in our cases, diffuse distribution of radiotracer like an appearance of dermal backflow was seen, which could be suggestive of lymphatic vessels obstruction.

Lymphatic backflow might occur due to defective valves, obstruction or impaired lymphatic contractility [4, 6, 7]. Dermal backflow represents drainage through dermal lymphatic collaterals that are the final result of lymphatic obstruction [8].

Lymphatic obstruction is pathophysiology of inflammatory breast cancer (IBC) and can explain clinical course of the disease. However, regarding controversial issues, there are no definitive criteria for diagnosis of IBC. So, delayed diagnosis of these patients is a common mistake [9]. In the first patient, clinical findings were not suggestive of IBC. Maybe, the presence of denser breast was an early sign of IBC.

The second patient had undergone neoadjuant chemotherapy because of locally advanced breast cancer. Altered lymphatic drainage, fibrosis and scarring can occur after neoadjuvant chemotherapy [10], which may resulted in blockage of lymphatic pathways.

In our knowledge, this is the first report describe dermal backflow appearance in breast cancer patients and highlights the importance of imaging before surgery. Furthermore, visualization of this pattern could be suggestive of lymphatic obstruction and invasion.

Author Disclosure Statement

No competing financial interests exist.

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A RARE CLINICAL MANIFESTATION OF CONGENITAL LYMPHATIC DYSPLASIA: THE EFFICACY OF COMPLEX DECONGESTIVE THERAPY IN A YOUNG CHILD

Letter to editor

GÖKHAN ÇAĞLAYAN[1], PINAR BORMAN[1] , HÜLYA YAVUZ[1], ÖZGE SOYER[2], HÜLYA DEMIR[2]
Hacettepe University, Faculty of Medicine
[1] Department of Physical and Rehabilitation Medicine
[2] Department of Pediatrics

Corresponding author: Gökhan Çağlayan
Hacettepe University Hospital
Department of Physical and Rehabilitation Medicine
Sıhhiye, Ankara, Turkey

Fax number: +90 312 310 5769

ABSTRACT

Authors report a child of congenital lymphedema presenting with lymphedema of right face, bilateral arms and with severe intestinal lymphectasia. In this case they aimed to indicate the short term effects of manual lymphatic drainage and multilayer bandaging in the right extremity. Although the regression of abdominal distention seems to be due to the parenteral nutrition with specific diet, they believe that kinesio taping may make even a little contribution.

Keyword: Congenital Lymphatic Dysplasia, Complex Decongestive Therapy, Intestinal Lymphectasia, Parenteral Nutrition.

INTRODUCTION

Dear Sir,
We report a child of congenital lymphedema presenting with lymphedema of right face, bilateral arms and with severe intestinal lymphectasia. A sixteen- month-old female child was consulted to our department of physical and rehabilitation medicine for the swelling of right face, arms (more noticeable in the right side) and abdomen (Figure 1). She had edema from birth on her right and left hands and arms, right side of face and diffuse edema in abdominal region. Her complaints had increased for the last four months and she had diarrhea for a long time. Her family's past medical history was unremarkable. In her physical examination she had distended abdomen and tachpneic respiration besides. Her diffuse edema was non pitting type. The scintigraphic examination was revealed as; no lymphatic drainage at the right upper extremity (severe lymphatic hypoplasia or agenesia), and delayed lymphatic drainage at the left upper extremity, and normal lymphatics at the lower extremities. These findings were concordant with primary congenital lymphatic dysplasia. Also she had ascites in the abdomen and pericardial effusion in computed tomography and echocardiography. She had no cardiac or renal failure. In her upper gastrointestinal endoscopic examination there was severe intestinal lymphectasia. She had paracentesis, pericardardial drainage and was performed total patenteral nutrition, following the proper diagnosis. After her general condition was stabilized, we started complex decongestive therapy for the lymphedema in the right upper extremity which was more prominent. Manuel lymphatic drainage and multilayered banding (with relatively low tension) techniques were applied daily, for a duration of three weeks. In addition kinesiotaping was performed for the abdominal lymphedema. In the follow up period, her measurements for edema and abdominal distention were improved

Fig. 1

gradually (Figure 2.a and 2.b). In this aytpical and very rare case we aimed to report the short term relative efficacy of complex decongestive therapy in such a young child. The family was educated for the risk reduction methods for complications of lymphedema and manual lymphatic drainage as well as bandaging. They were also instructed for follow-up visits. A pressure garment was planned for the control visit, 6 months later.
Most forms of primary lymphedema are thougt to be caused by a congenital abnormality of the lymphatic system [1]. Primary lymphedema is a rare disease; prevelance ranges within 1:6.000 to 1:10.000 [2]. It is seen more in females. The most frequent clinical presentation is swelling of the leg and ankle. However upper extremity may also be affected in congenital lymphedema [3].

Complex decongestive therapy which has individual components of skin care, manual lymph drainage, compression bandages, exercise and pressure garments, is the golden standard treatment for reducing both primary and secondary lymphedema [4].
In this case we aimed to indicate the short term effects of manual lymphatic drainage and multilayer bandaging in the right extremity. Although the regression of abdominal distention seems to be due to the parenteral nutrition with specific diet, we believe that kinesio taping may make even a little contribution.

Sincerely
Gökhan Çağlayan, MD
Specialist of PRM

Fig. 2.a

Fig. 2.b

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BREAST CANCER RELATED LYMPHEDEMA: LITERATURE REVIEW ON TECHNIQUES FOR VOLUME ASSESSMENT

CAU N., PhD [1], GALLI M., Prof. [1,2], CIMOLIN V., PhD [1], CRIVELLINI M., Prof. [1], BALZARINI A., MD [3]

[1] Department of Electronics, Information and Bioengineering (DEIB), Politecnico di Milano, Milan, Italy

[2] IRCCS "San Raffaele Pisana", TOSINVEST Sanità, Rome, Italy

[3] Palliative Care, Pain Therapy and Rehabilitation DpT, IRCCS Fondazione Istituto Nazionale dei Tumori Milan, Italy

ABSTRACT

Background: Lymphedema is considered to be one of the most feared effects of the breast cancer treatment. It is a chronic and progressive condition characterized by arm swelling. An accurate measurement of the pathological arm volume is crucial for the lymphedema management (i.e. to gauge the efficacy of the treatment). Several methods of measurement have been validated and used in clinic, but literature highlights the lack of standardized methodology.

Methods: A review of specific literature was undertaken. Most important electronic databases (PubMed and ISI Web of Knowledge) were questioned for articles published between 1998 and 2013. Specific keywords have been used: Lymphedema, Volume, Water Displacement, Perometry, Circumferential, Bioimpedance and Laser Scanner 3D.

Results: More than 50 articles have been reviewed and divided into five groups based on measurement methods (Water Displacement – Perometry – Circumferential – Bioimpedance and Laser Scanner 3D). Accuracy and reliability of the different methods are compared.

Conclusions: Our analysis leads to identify the laser scanner method as the most proper technique for arm volume measuring in term of accuracy, reliability, costs and time consuming.

Key Words: Lymphedema measurement, water displacement, Laser scanning, lymphedema review, circumferential method, limb scanning, arm swelling.

INTRODUCTION

Lymphedema is a chronic and progressive condition characterized by arm or leg swelling due to an abnormal protein-rich fluid (lymph) collection in the interstitial tissue. When this fluid is chronically present in extracellular tissues, it causes an inflammatory response with fat deposition and overgrowth of connective tissue [(1)]. As a result, the arm becomes swollen and firm. A common aetiology associated with lymphedema is breast cancer and its treatments. For upper arm established risk factors include axillary dissection, radiotherapy of the breast and/or of axilla, pathological nodal status, obesity, and tumour stage [(2)]. The incidence of lymphedema is approximately 5-50% of all breast cancer patients with a risk of 15-20% after axillary dissection and 3-10% after sentinel lymph node biopsy. This wide variation depends especially on diagnostic criteria for lymphedema, differences in the studied patient group and on influence of different treatments.

Lymphedema is considered one of the most-feared side effects of breast cancer treatment and is cause of physical and psychological detriments: body image changes, anxiety, aesthetic problems, functional alteration in arm and restriction in quality of life [(3)]. As during recent years the percentage of breast cancer survivals is increasing, the attention of medical doctors and researchers to this problem is ever growing. To confirm this, in Fig. 1 the number of article published during years about the lymphedema (article find in Pubmed source using the keyword "lymphedema") is shown. More attention is mainly turned to the entity of the lymphedema as well as on treatments for its reduction.

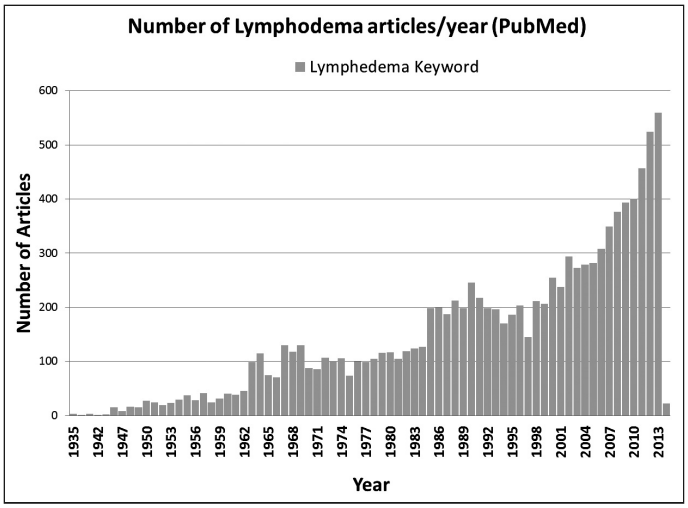

Fig. 1 - Numbers of article on the lymphedema from 1935 to 2014* – source Pubmed. (*) articles published until January 2014.

The main problem in the assessment of lymphedema entity as well as the effects of specific treatments is the measure of dimension and volume of the limb with lymphedema. The clinicians mainly use a qualitative evaluation based on circumferential measurements by tape, which is fast and simple even if not consistent and not accurate; other measures, such as volumetric measures or bioimpedence and spectroscopy measures, are

proposed in literature. This article provides a systematic review of the literature concerning the different methods and technologies used to detect the entity of the lymphedema. Aim of this work is to understand which the best method is in term of accuracy, reliability and suitability for use in clinical practice.

MATERIALS AND METHODS

The methodological approach used in this review is represented in the workflow in Fig. 2.
Some electronic databases, including Pubmed and ISI Web of Knowledge, were used.
The publications were restricted between 1998 and 2013 and the following keywords were used together with *lymphedema* term: *water displacement, circumference method, perometry, laser scanning* and *bioimpedance*.
This search yielded a total of 684 articles using Pubmed ad 469 articles using ISI Web of Knowledge (indicated below in brackets) divided as follows:

– lymphedema and water displacement method: 64 (88) papers;
– lymphedema and circumference method: 48 (123) papers;
– lymphedema and perometry: 21 (20);
– lymphedema and bioimpedance: 73 (97) papers;
– lymphedema and laser scanning: 478 (141) papers.

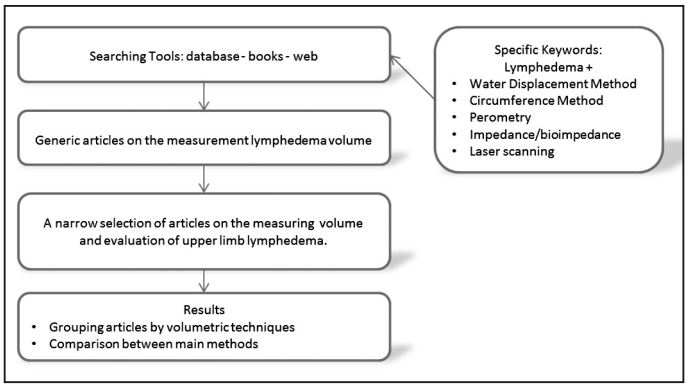

Fig. 2 - Workflow followed during the review process.

RESULTS

After a first general query, new keywords were used for limiting the research to papers on the quantitative evaluation of upper limb lymphedema volume. This search yielded to 50 papers. Further research was conducted for other references and clinical guidelines. At the end a bibliography of a 51 total of works on upper limb lymphedema volume assessment [1-51] was created.
All results were grouped according to the techniques and clustered in five groups. The results are shown in Fig. 3.
The highest percentage of the articles is on water displacement method (29%) and circumferential techniques (29%) that represent more than 50% of the total. Bioimpedance and Perometry methods are also quite good treated in literature and the percentage of article on these methods are respectively 23% and 15%; the smallest percentage is on the laser scanning (4%). Several works

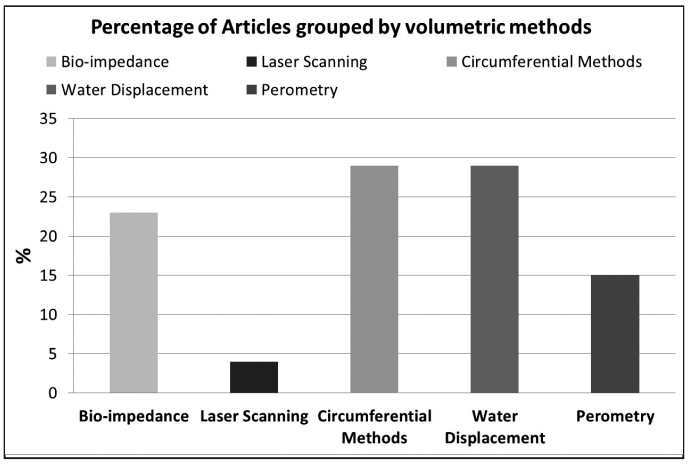

Fig. 3 - Percentage of reviewed articles grouped by volumetric method.

tackle an issue of evaluate which volumetric measure techniques can be considered most proper, simple to use and suitable for clinical requirements. The goodness of the technique is related to the quality of the measure. It is evaluated, first of all, by the accuracy and repeatability of the instrument. These parameters are compared with the gold standard, represented by water displacement method, in order to highlight vantages and disadvantages of all methods analyzed.

1. Water Displacement Method (W) [1, 6, 8, 10, 11, 15, 16, 18, 19, 23, 24, 26-31, 33, 34, 39, 40, 43, 46, 50]

A total of 16 papers on water displacement method has been reviewed. This method has been widely used to provide a direct measurement of arm and leg volumes. Water displacement is considered the gold standard for the limb volume measurement [27,31,39]. The principle is simple and easy; it is based on the well-known Archimedes principle for which the water volume moved by an object is equal to the same object volume. Thus, the affected extremity is submerged in a tank of water and its displacement is measured to determine the volume of the limb [9]. Apparatus for the measurement of arm has been described in detail in several works [1,27,39]. The main limit of this method is related to accuracy, which is strictly dependent on the size of the water tank. A small limb in a large tank will have a greater margin of error; small changes in angulation of the limb can also lead to error [29]. Beside this classical method, other authors suggest to use a variant called "inverse water volumetry". This technique has been validate by Damstra et al [39] and seems to be more suitable for hand and finger volume measurement. This technique has shown a quite good results with respect to intra and interobserver variability with an Interclass Correlation Coefficient equal to (ICC) [2,1]=0.89-0.91. However, this method has some disadvantages. First, it is laborious and difficult to use in a clinical setting; then, the water displacement method is not suitable for patients with breaks in the skin because the risk of infections [1]. Several papers reported the reliability [1,11,18,19,23,26,29,31,39,40,46], and the accuracy [1,23,26,29,39,40,46] of the method.

2. Circumferential Methods (C) [1,6,8-11,15-19,23,26-28,30,31,33,34,36,40,41,43,46]

A total of 16 papers on circumferential measuring method have been reviewed; among them, only 4 were specifically focused on the validation of this technique [9,26,27,31]. Limb volume can indirectly calculated from circumferential measurements made using a flexible tape. This technique is very popular in the clinic setting. The arm swelling is evaluated by different methods: in the first method, circumferential measures are taken at given points along the limb, and the points are measured at each reassessment [9]; in the second method the calculation of the volume is done using a geometrical approximation formulas. In this last method, the volume of each arm is calculated using two basic formulas, which are cylinder and truncated cone [frustum] formula. The limb is divided into sections, with each section representing a cylinder or cone. The final volume is determined by adding the volumes of the sections together. Several authors reported the formulas normally used to calculate the volume of whole arm [4,5,9,19,26,27,31,40,41]. Other works focused the attention on the hand volume evaluation [26,27,40]. They tackle an issue of how simplify a so complicated limb segment. They suggest different geometrical solutions and explain measure procedures. Papers on the comparison between water volumetric method and circumferential methods represent the highest percentage of the reviewed articles (60%) [6,8,16,19,23,24,26-28,30,31,33,34,40,46]. It can be explained easily if consider that the first technique is the gold standard and the second one is the most widely used method. In particular, two works focused the attention on accuracy problem in volume detection [1,29]. Accuracy depends on various factors, but the most important are the choice of the geometric formula and the spacing of the measurement. Sitzi [41] compared the cylinder and frustum formulas and stated that the frustum formula is intrinsically the most accurate. Literature about accuracy of circumferential method is here reported [1,9,15,23, 26,40,46]. Accuracy clearly depends on the spacing between and the number of measurements. In general measurement are made every 4-8 cm along the axis of the limb [4,5,23,31,40,43].
The estimation of arm volume using circumferential arm measurement is subject to several potential errors. One is related to the interobserver variation. Different degree of tensions applied to measuring tape of the limb leads to different volume estimations [46]. Reliabilities have been studied at different measure intervals and compared using different formulas. In a Sander's article [40] the Inter Class Correlation index (ICC) has been calculated using cylinder and frustum formulas in three different measure intervals – 3,6 and 9 cm. The results have shown different values of ICC to depending on anatomical segments; ICC (2,1) is equal to 0.99 for arms, while ICC (2,1) for hands is between 0.91 and 0.98. Reliability aspects are studied by several authors [1,9,11,15,18,19,23,26,40, 46].

3. Bioimpedance Method (BI) [1,10,11,13,18,20,22,32,37,38,43,48]

4. A total of 12 papers on Biompedance measuring method have been reviewed and among them, 3 papers describe in details this technique [22,37,48]. Bioimpedance measures tissue resistance to an electrical current to determine extracellular fluid volume. When a current, conventionally of 200–800 mA, is applied to the body surface through a set of cutaneous electrodes, it is transmitted through water-containing component within the tissues. The current flow through biological tissue is frequency-dependent. At low frequency, current passes through the extracellular fluid (ECF) space and does not penetrate the cell membrane. At high frequencies, however, the current passes through both the extracellular and intracellular fluid. Based on these concepts, a value for impedance can be calculated. When bioimpedance is applied to the quantitative analysis of lymphedema, the pathological accumulation of extracellular fluid is mirrored by a decrease in the measured impedance, in proportion to the degree of extracellular fluid accumulation. Thus, the impedance value can be converted into an index score, which reflects volume measurement. Since, impedance decreases while extracellular fluid volume increases. One significant advantage in bioimpedance is the ability to measure bilateral limb lymphedema [1]. The measured values of bioimpedance are conventionally expressed as the ratio of the normal limb/abnormal limb. In the absence of segmental excess fluid volume accumulation, this ratio should approximate one; as lymphedema severity increases, the measured ratio rises proportionately. Regarding to the reliability of method, the literature is in contrast: some authors affirmed bioimpedance cannot differentiate between the different types of extracellular fluid, and thus the positive results from bioimpedance resting in the first few months after the breast cancer treatment should be treated with caution [1]; on the other side some authors state that bioimpedance spectroscopy should have specific sensitivity to detect latent lymphedema, since it measures only the accumulation of extracellular fluid (ECF), of which lymph is a main component, rather that overall volume [1,11,13,18,48]. There is a lack of works on the comparison between bioimpedance and water volumetry methods in terms of errors and reliability. According to Ridner et al [37], in bioimpedance, the use of adhesive electrodes placed on fixed anatomical landmarks reduces the risk of user errors.

5. Perometry Method (P) [1,10,11,15,18,20,38,43,45]

A total of 9 papers on perometric measuring method have been reviewed. Perometry measures arm volume using infrared light. The machine has a square-shaped sliding frame, which surrounds the perimeter of the limb. This frame contains rows of infrared light emitters and sensors on opposite sides. When the arm is place inside the frame, it interrupts the emitted infrared beam on two planes. This provides two perpendicular diameter measurements of the arm segment. Thus, it is possible to estimate for each measuring point (in general with an intervals of 4.7 mm) the correspondent diameter and then to calculate the volume of the limb. This technique is considered by several authors has excellent intra and inter-observed reliability [1]. The intrarater and interrater correlation coefficient between these techniques had satisfactory value racing from 0.937 and 0.997. The infrared optoelectronic volumetry has the best reliability and is the only method that provides no difference between intrarater and interrater reliability. It means that different therapists can use it on the same patient. According to Piller [35], the accuracy of perometry can be compared to the accuracy of the water displacement

method. Perometry can discriminate at 1mm for circumferences and to the nearest 10ml for volume. Perometry is probably the most accurate method of limb volume measurement [43] but it has some disadvantages. Drawbacks include difficulty in measuring the full length of the arm right up to the shoulders because of the necessary abduction of the limb for inserting the arm into the frame. In general the measurement, performed only to a height of 40 cm, provide no information about lymphedema located above the elbow [15]. Another disadvantage is the size of the equipment, making it difficult to use in clinical context.

6. 3D Laser Scanning (3D) [11,29,47]

The literature regarding this technique is very poor. Only 3 articles on laser scanning in lymphedema volume measurement has been found [11,29,47]. 3D laser scanning is a technology that digitally captures the shape of physical objects using a line of harmless laser light. It works on the principle of triangulation. The laser probe is swept several time above the surface of the object – for example the arm of a patient. The probe projects a line of laser light onto the surface while a sensor camera continuously records the changing distance and shape of the laser line in three dimensions (XYZ) as it passes above the object. During this process, laser scanners generate "point clouds". These data are registered and merged into one 3D representation of the limb and post-processed with various software in order to obtain anthropometric information (diameters - volumes - shape). Laser scanning has been studied in term of accuracy and reproducibility and compared with the gold standard, i.e. the water displacement method. Mc Kinnon et al. [29] affirmed that laser scanner has similar accuracy and superior a reproducibility compared to the water displacement method. As accuracy in water displacement decreases with the dimension of the object, the bigger the object volume is, the lower the accuracy is [29]. According to it, the measures of a whole limb are less precise using water displacement method than laser scanning. Mc Kinnon et al. stated that a precise comparison could be made before and after treatment with laser scanning, because the scanning process produces a digitalized image of the arm. The results prove that laser scanning measure is extremely close to the real volume with very low coefficient of reproducibility – define by the British Standard Institution as twice standard deviation of the difference between two measurements.

DISCUSSION AND CONCLUSION

Aim of this study is a review on the most common techniques used to evaluate lymphedema volume. Firstly, we observed that in literature more attention is on the lymphedema problem as well as on treatments for its reduction, than on the techniques used to measure the lymphedema entity in terms of upper limb volume. Focusing the attention on methods to measure upper limb volume in presence of lymphedema, we found 51 works, which allowed identifying 5 main techniques. For all methods, after a presentation of measurement procedures and the applications on pathological state, their advantages and limitations have been discussed.

The five methods are water displacement, tape measurement, perometry, bioelectrical impedance and laser scanning technique. Water displacement represents the gold standards and is a reliable method of measuring limb volume, though its use is not very practical in a clinical setting because of water spillage and space considerations [1,23]. Perometry is very accurate but the cost of the machine limits it to specialist centres [4]. Circumferential method with tape is widely used, because of its limited cost, but the estimation of arm volume is subject to several potential errors mainly related to the interobserver variation [46]. The laser scanning procedure is painless and simply requires passing a low energy laser over the skin of the limb. It is accurate, reliable, not time consuming and its cost is quite moderate [15,29]. Another important aspect to take in considerations to evaluated the most suitable method for clinical application is the test duration. Literature underline that volumetric method is time consuming compared with tape measurements; the needed preparation and clean up add significantly to overall measurement time [9,15,26]. Circumferential method took approximately 10 minutes to perform bilateral evaluation of the upper limbs [15], as opposed to the water volumetry method which takes approximately six minutes to set up and perform. Bioimpedance procedure takes less than 1 minute [37], while perometry is the quickest method, taking only a few seconds, provides segmental information. Laser scanning is also quite fast – approximately 5-10 minutes for scanning a whole arm and to calculate the entire volume [29]. From our review, it is evident that both the wide variety of methods described in the literature and the lack of standardization make difficult for the clinician to assess the best volumetric method. According to clinical needs, the volumetric device should be easy to use, accessible, not expensive, reliable, accurate and quantifiable [1]. From our analysis, the laser scanning seems to be the most proper technique for the volume evaluation of lymphedema among the other described techniques. In comparison with other methods, laser scanning presents good accuracy and reliability together with its facility of use, leading it suitable for clinical application. However, literature on this method is very scanty. In our opinion, further researches should extend the application of this method to assess the entity of the lymphedema as well as to evaluate the effects of treatments for its reduction. In addition, the same technique could be used for the measuring the entity of lymphedema, not only of the upper limb but also of other body segments, e.g. the lower limbs.

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Contacts

PhD. Nicola Cau
email address: nicola.cau@gmail.com
telephone: (+39) 0223993359
fax: (+39) 0223993360
Address: Department of Electronic, Information and Bioengineering (DEIB) - Polytechnic of Milan
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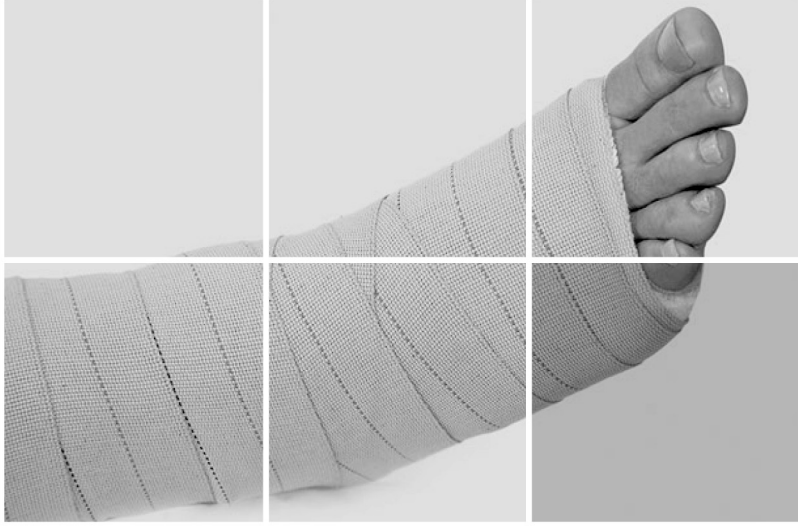

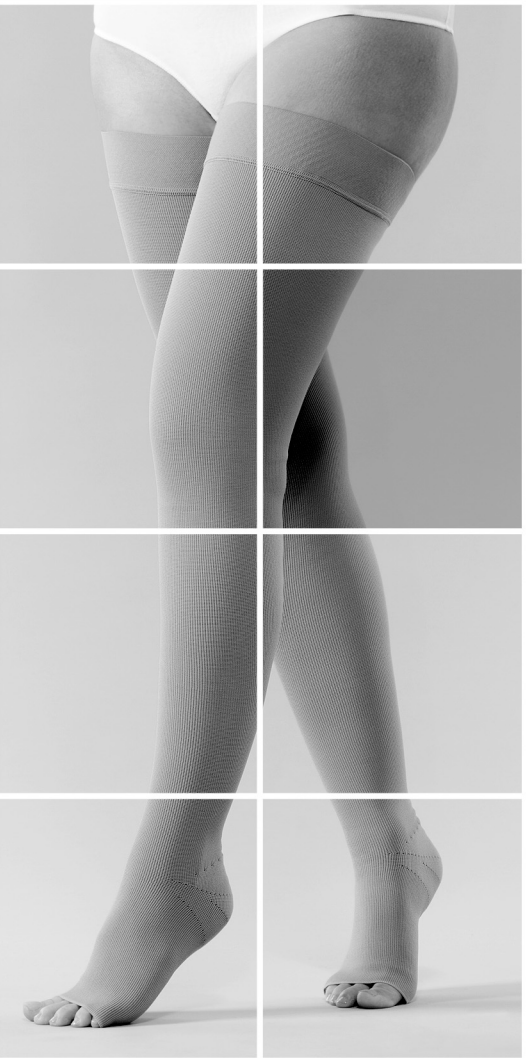

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