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BREAST EDEMA FOLLOWING BREAST CONSERVING SURGERY AND RADIOTHERAPY

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ABSTRACT

Introduction: Breast edema following cancer treatment is very rarely documented.

The aim of this study was to investigate tissue water content in skin and upper subcutis in women treated for breast cancer with breast conserving surgery and radiotherapy (RT) to the breast and compare the changes with the healthy breast.

Material and methods: One hundred eighteen patients were measured prior to, during and 2 and 4 weeks after end of RT. Local edema in the four quadrants of both breasts was measured with MoistereMeterD (Delfin Technologies Ltd, Finland). A parameter, tissue dielectric constant (TDC), directly proportional to tissue water content to the effective depth of 2.5 mm, was calculated. Breast edema was defined as a TDC ratio exceeding 1.40 (mean + 2SD) between the irradiated and healthy breast.

Results: Difference in TDC ratio ($p < 0.001$) between the operated and healthy breast was found at each measurement time-point. The incidence of breast edema was 31.4% before start of the RT treatment, increasing during RT and was 62.6% at 4 weeks after completion of RT. The mean pre-RT TDC ratio 1.30 ± 0.29 increased during the first week of therapy to 1.43 ± 0.33 and stayed elevated through the observation period ($p < 0.001$). Pre-RT patients with scar in quadrant 4 showed higher TDC ratio ($p = 0.02$) ($n = 71$, TDC ratio 1.36 ± 0.31) than patients with no scar tissue in quadrant 4 ($n = 46$, a TDC ratio 1.20 ± 0.23).

Conclusion: The healthy breast can act as a control to provide a ratio between the breasts. Based on the evaluation of the mean TDC ratio, the incidence of breast edema was found to be high (> 30%). The TDC values illustrating edema in the operated breast were higher compared to the healthy breast at all measurement time-points, also pre-RT, suggesting a high influence of surgery on breast edema. However, axillary surgery did not seem to increase breast edema more than sentinel lymph node biopsy. It was also shown that patients with scar in the fourth quadrant are more likely to have a higher TDC ratio. The higher weekly doses in the hypofractionated RT seem to induce more edema than conventional fractionation.

Keywords: Breast cancer, breast edema, breast surgery, radiotherapy, tissue dielectric constant

INTRODUCTION

It is well-known among clinicians that breast edema may occur after breast cancer treatment, still it is often an overlooked side effect. Breast edema is very rarely documented and only in a few studies the incidence has been estimated. Rönkä et al. [(1)] found subcutaneous edema of the breast, measured with ultrasound one year after surgery and radiotherapy (RT) to the breast, in 70% of the patients with axillary node dissection and in 28% with sentinel node biopsy. Goffman et al. [(2)] found an incidence of breast edema only in about 10% of the patients in a similar material but more than 2 years after cancer treatment using clinical signs like erythema and changes similar to peau d'orange of the breast and the patients complains about swelling, heaviness, redness, and pain as criterion of breast edema. It was also argued that these symptoms are distinctly different from the minor swelling often seen during RT(2). Constantine et al. [(3)] clinically scored breast edema on a 10-point scale and found that 17% of the patients treated for ductal carcinoma in situ experienced breast edema during and within 90 days of RT. Nuutinen et al. [(4)] using dielectric technique observed that skin tissue water content in irradiated and contralateral breasts decreased during RT. These observations were associated with the radiation-associated obstruction of skin capillaries. Previously, Papp et al have noticed using the same technique with experimental burn injuries in landrace pigs that a superficial burn injury damaging skin vasculature induces edema in subcutis [(5)].

Wide differences in the incidence of breast edema are most likely due to the method and phase where the edema has been evaluated. Breast edema may also consist of several edemas of different origin. Radiation-induced edema during RT and at 3-6 months post-RT during delayed acute reaction originating mostly from failure to microvasculature may be impossible to distinguish from lymphedema resulting in damage to lymphatic vessels. Therefore, in the following we use the term breast edema to describe edema which may have different origin.

Recently, a new device, MoistereMeterD, with a technique based on electromagnetic waves measuring tissue water content, has been introduced showing potential to measure breast edema [(6)]. Since the MoistereMeterD enables the measurement of different quadrants of the breast, the technique may lead to improvement in conservative treatment of breast edema. In the present investigation we examined tissue water content in skin and upper subcutis in women treated for breast cancer with breast conserving surgery and RT to the breast, prior to, during and 2 and 4 weeks after RT treatment and compared to changes with healthy breast.

MATERIALS AND METHODS

Patients

Two hundred sixty breast cancer patients treated with breast conserving surgery and sentinel lymph node biopsy (SNLB) or axillary lymph node dissection (ALND) and RT to the breast at the

Department of Oncology at Skåne University Hospital, Sweden, were included in the study.
Patients with preoperative chemotherapy, recurrent cancer, concurrent diseases that may interfere with measurement of lymphedema and difficulties in participating in the study, for example dementia, were excluded.

Measurements

Local tissue water was measured with the TDC technique (MoistureMeterD, Delfin Technologies Ltd, Finland). The device transmits a very high frequency electromagnetic (EM) wave of 300 MHz into an open-ended coaxial probe in contact with the skin. A major part of the EM energy is absorbed by tissue water while the rest is reflected back to the coaxial line and an electrical parameter, tissue dielectric constant (TDC), directly proportional to tissue water content in skin and upper subcutis, is calculated [7].
With the TDC technique local tissue water of both breasts was measured to the effective depth of 2.5 mm. The effective depth illustrates the depth where the EM field has attenuated to 37% of the value at the skin surface.The TDC scale ranges from 1 to 78 based on the percentage of fluid of the measurement site where the TDC value 1 illustrates that the object has no water and 78 that object has 100% of water.
Body Mass Index as calculated by the individual's body weight divided by the square of their height expressed in kg/m^2.

Design

Measurements of local tissue water with the TDC technique were made within a week before start of RT and at the end of each week with RT treatment (lasting for 3 or 5 weeks) and 2 and 4 weeks post-RT.

Procedure

Adjuvant chemotherapy was in general given to patients with axillary node metastasis, in 6 cycles within three weeks starting approximately four weeks after surgery. For these patients RT was started after completion of chemotherapy and for patients without chemotherapy RT started approximately eight weeks after surgery. Prescribed dose of radiotherapy was 42.5 Gy in 16 fractions during 22 days (later called the hypofractionated three weeks schedule) to patients ≥ 40 years without node metastasis [8]. Patients younger than 40 years received conventional fractionation up to 50 Gy in 25 fractions during 5 weeks and one patient an additional boost of 16 Gy in 8 fractions to the pre-operative tumor volume with adequate margins for microscopic disease, movements, set-up uncertainties and beam specificities. All patients with more than 2 node metastasis, a T3 or Grade 3 tumor received 50 Gy in 25 fractions during 5 weeks.
To determine the normal variation of the TDC values, both breasts in fifteen healthy women (57.1 ± 4.7 years, BMI 24.2 ± 2.9 kg/m^2) were measured. The TDC threshold ratio for breast edema was defined as a value that equals or exceeds the mean TDC ratio of these 15 healthy right and left breasts plus 2SD. Based on the measurements the TDC threshold ratio ≥ 1.40 was then determined. In practice, a TDC ratio 1.40 illustrates that the tissue water in the affected breast skin and upper subcutis is 40% higher than that in the contralateral side.
Affected and contralateral breast TDC values were measured with the patient in a supine position. The probe was placed in the middle of each quadrant of the breast with the edge of the probe 10 mm from the areola. Three repeated measurements were made in each quadrant. The mean TDC value for the total breast (4 quadrants) was then calculated. However, quadrant(s) with scar tissue were excluded. To eliminate individual differences in tissue water content the TDC ratio between the affected and healthy breast for each patient was calculated.
Height was measured at the first visit and body weight at each measurement occasion to calculate changes of body mass index (BMI) during the follow-up period.

Statistics

Paired sample t-test was used for the study group to detect differences at different time-points. Independent sample t-test was used for comparison between groups. No imputation was used for missing data. A level of significance was set at 0.05 and two tailed p-values are reported. All statistical analyses were performed using IBM SPSS Statistics 21.

RESULTS

Patients

Of the two hundred sixty patients recruited to the study 138 patients declined to participate and four patients dropped out after the pre-RT measurement. Finally, 118 patients were included (Table 1).

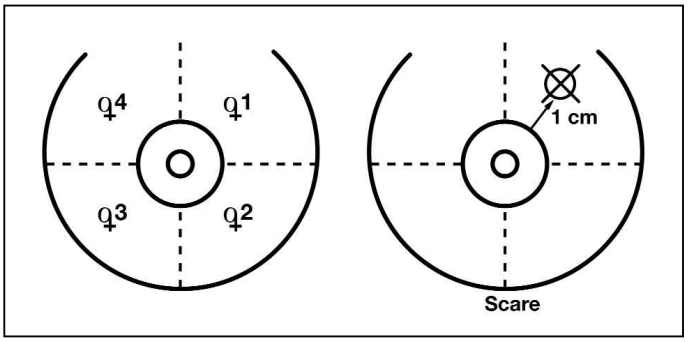
Table 1 - Characteristics of the breast cancer treated patients (n = 118) taking part in the study.

Age (years)*	61.3 ± 8.4
Affected site, left/right, n (%)	57(48.3) / 61 (51.7)
Sentinel node/Axillary dissection, n (%)	96 (81.4) / 22 (18.6)
Tumor size (mm) $^{\alpha}$	14.7 ± 7.2
Scar in quadrant, n (%)	
No 1/2/3/4	8 (6.8) / 5 (4.2) / 11 (9.3) / 20 (16.9)
1+2/2+3/3+4/1+4	1 (0.8) / 4 (3.4) / 6 (5.1) / 44 (37.3)
1+2+4/1+3+4/2+3+4	1 (0.8) / 1 (0.8) / 1 (0.8)
0, $^{\beta}$	16 (13.6)
Radiotherapy	
Total dose 42.5 Gy/50 Gy/66 Gy, n (%)	96 (81.4) / 21 (17.8) / 1 (0.8)
Chemotherapy, yes/no, n (%)	16 (13.6) / 102 (86.4)
BMI (kg/m^2)*	27.0 ± 4.4

(α) With multifocal tumors in 15 patients the size of each tumor were added up to a total sum.
(β) Surgery considered to be performed in 0 quadrants are illustrated in Figure 1.
(*) Mean ± 1SD.

The majority (81.4%) of the patients had surgery with SLNB and related hypofractionated radiotherapy to breast up to 42.5 Gy. The rest (18.6%) had ALND and RT to breast and axilla to 50.0 Gy. Scar tissue in the breast was most frequent (36%) in quadrants 1 and 4 followed by quadrant 4 (17%) only (Table 1). A scar that did not interfere with any quadrant was frequent (14%) (Figure 1).

Figure 1 - The 4 quadrants of the breasts were marked before the TDC probe was placed in the middle of each quadrant of the breast with the edge of the probe 10 mm from the areola.



BMI was 27.0 ± 4.4 at start and 27.3 ± 5.3 kg/m^2 at end of the study with no significant change.
In order to determine that the healthy group was representative for the study group a matching was made. At start of the study the women in the study group and healthy group of fifteen women were similar by age (57.6 vs 57.1 years) and BMI (24.2 vs 24.2 kg/m^2). The mean TDC values (30.0 vs 29.6) in the healthy breast of the study group and corresponding breast in the healthy group, also indicated no difference between the groups.

TDC values

In the study group there was a higher TDC value in the operated breast compared to the non-operated breast at all measurement occasions ($p < 0.001$) (Table 2). The TDC value increased during the first week of RT in the operated breast and stayed elevated throughout the observation period ($p < 0.001$). An increased TDC value was also found in the healthy breast at 4 weeks post-RT ($p < 0.05$) (Table 2).

Breast edema incidence and TDC ratio

Due to the individual variation of TDC values in the healthy group (ranging from 19.8 to 39.4) the absolute TDC value is not useful to determine the incidence of breast edema. Therefore, a TDC ratio between the right and left breasts was calculated. Despite minor increase of TDC values in the non-operated breast at 4 weeks post RT (Table 2) the TDC ratio was determined as a ratio between operated and non-operated breast at each time-point. Accordingly, there was a significant difference in TDC ratio ($p < 0.001$) between the operated and healthy breast at each measurement time-point. The incidence of breast edema was 31.4% before start of the RT treatment, increasing during RT and was 62.6% at 4 weeks after completion of RT. The mean pre-RT TDC ratio increased during the first week of radiotherapy to 1.43 and stayed elevated through the observation period ($p < 0.001$) (Table 3). Although the mean TDC ratio was lower in the sentinel node biopsy group than in the axillary node dissection group during the whole observation period the difference was not significant. Therefore, the groups are not stratified for surgery and the data presented in Table 3 include all patients.

Comparison between the SLNB and the ALND groups

Although the ALND group had a higher TDC ratio (n = 24, 1.36 ± 0.25) than the SLNB group (n = 95, 1.29±0.30) before RT the difference was not significant.
When comparing patients with scar tissue in quadrat 4 (n = 71, TDC ratio 1.36 ± 0.31) to patients with no scar tissue in quadrant 4 (n = 46, a TDC ratio 1.20 ± 0.23) a significant difference between the groups was found before RT ($p = 0.02$).

Comparison between conventional and hypofractionated RT

For patients receiving conventional fractionation to 50 Gy (n = 22) the measurements were made also at 4 and 5 weeks during radiotherapy (Table 4). The TDC ratio of the hypofractionated group (n = 96) was higher at all time points compared with pre-RT ($p < 0.001$) but in the group of conventional fractionation only at the end of the five week schedule ($p < 0.01$). The difference between the groups was significant only at end of the third week ($p = 0.01$), i.e. at the end of the three weeks schedule (Table 4).

Table 2 - TDC values (mean ± 1SD) in the healthy and operated breast prior to and during radiotherapy treatment and 2 and 4 weeks after RT.

	n	Healthy	Operated
Pre RT	118	27.8 ± 4.8	36.0 ± 9.5 *
End of 1st week of RT	112	27.7 ± 4.7	39.2 ± 9.9 */**
End of 2nd week of RT	112	27.8 ± 5.0	39.1 ± 9.8 */**
End of 3rd week of RT	111	27.5 ± 4.5	39.1 ± 9.8 */**
2 weeks after RT	99	28.3 ± 4.4	39.1 ± 9.9 */**
4 weeks after RT	101	28.3 ± 4.2 ***	39.8 ± 9.0 */**

(*) Significant ($p < 0.001$) increase in compared to healthy breast.
(**) Significant ($p < 0.001$) increase compared to pre RT for operated breast.
(***) Significant ($p < 0.01$) increase compared to pre RT for healthy breast.

Table 3 - Incidence of edema (TDC ratio ≥ 1.4 between the breasts), TDC ratio mean±SD values and range in the breast prior to and during radiotherapy treatment and 2 and 4 weeks after.

		Edema	TDC ratio	
	n	n (%)	mean±SD	range
Pre RT	118	37 (31.4)	1.30±0.29	0.91-2.13
End of 1st week RT	112	53 (47.3)	1.43±0.33*	0.88-2.28
End of 2nd week RT	112	53 (47.3)	1.44±0.35*	0.77-2.37
End of 3rd week RT	111	51 (45.9)	1.44±0.37*	0.75-2.50
2 weeks after RT	98	45 (45.9)	1.44±0.36*	0.74-2.39
4 weeks after RT	101	53 (62.6)	1.47±0.35*	0.79-2.47

(*) Significant (p = 0.001) increase compared to pre RT.

Table 4 - Comparison of TDC ratios (mean ± 1SD) of the breasts between patients treated with breast conserving surgery with adjuvant radiotherapy to 42.5 Gy in 3 weeks or 50.0 Gy in 5 weeks.

	RT 42,5 Gy		RT 50,0 Gy		RT 42,5 Gy/50,0 Gy
	n	mean±SD	n	mean±SD	p-value
Pre RT	96	1.32 ± 0.29	22	1.23 ± 0.28	= 0.232
End of 1st week RT	91	1.45 ± 0.29*	22	1.31 ± 0.30	= 0.067
End of 2nd week RT	91	1.44 ± 0.33*	22	1.31 ± 0.33	= 0.088
End of 3rd week RT	91	1.47 ± 0.32*	20	1.26 ± 0.31	= 0.011**
End of 4th week RT	–	–	21	1.29 ± 0.31	
End of 5th week RT	–	–	20	1.34 ± 0.30**	
2 weeks after RT	80	1.41 ± 0.32*	18	1.29 ± 0.33	= 0.780
4 weeks after RT	83	1.43 ± 0.31*	19	1.30 ± 0.23	= 0.101

(*) Significant (p < 0.001) increase compared to pre RT.
(**) Significant (p < 0.01) increase compared to pre RT.
(***) Significant difference in comparison between 42.5 Gy and 50 Gy treatment schedule.

DISCUSSION

The incidence of breast edema cannot be assessed based on the results in this study since the reference measurements were not performed before the breast operation. However, matching of the study group with the healthy group indicates that the TDC values of the contralateral healthy breast in the study group did not differ from those of a healthy population. The healthy breast in the study group could thus act as control to provide a reference ratio between the breasts. Similar assumption is made when arms of healthy and operated side are compared with breast cancer treatment related arm lymphedema [9, 10].

The slight increase of the TDC values found in the healthy breast in the study group 4 weeks post-RT may be explained by the fact that the lymph collaterals between the breasts have opened up. Normally there is an anatomical lymphatic midline in the thoracic part of the body where lymph transportation is directed into the axilla of each side [11]. However, the midline is richly provided with collaterals between the two sides. When the irradiated side can no longer be emptied sufficiently through the normal passage, lymph fluid will instead find new pathways through the collaterals into the healthy side.

A significantly higher mean TDC value was found in the operated breast compared to the healthy breast at all measurement occasions and also pre-RT. Also the incidence of breast edema, based on the evaluation of the mean TDC ratio, was found to be high (> 30%). The duration between breast surgery and start of radiotherapy treatment was rather short, about 8 weeks with almost all patients. Therefore, the high incidence of breast edema may be explained by a post-surgery wound healing including an inflammatory process. However, 16 patients (14%) had chemotherapy delaying the start of radiotherapy with 4 to 5 months. Still, the chemotherapy group had an equally high TDC value before RT (1.27 ± 0.28). Although the patients receiving chemotherapy had a much longer period of recovery after surgery than the non-chemotherapy group, the finding suggest that the surgery has a more extensive and long-lasting influence on the drainage of edema from the breast.

The influence of surgery on the edema/lymphedema drainage from the breast becomes even clearer when looking at the fact that patients having surgery to the 4th quadrant also had significant higher TDC values than those with no surgery to quadrant 4. The influence of scar tissue in the breast seems to be even more important for edema formation than axillary dissection as we noticed that seven patients (6%) that had the TDC ratio >1.80 (indicating 80% edema compared with contralateral healthy breast) all were found among patients with SLNB surgery. In this group the most frequent quadrant with scare tissue was quadrant 4.

Quadrant 4 is the quadrant situated closest to the axilla and through this quadrant runs most of the lymph drainage from the breast (except for quadrant 1) [12]. Thus lymph nodes from this region as well as the scar tissue cause more edema than injury to other parts of the breast.
During 3 weeks of RT a significant increase (11.4%) of TDC ratio was found in the hypofractionated group receiving 42.5 Gy ($p < 0.001$). However, respective increase was 8.9% until the fifth week in patients with conventional fractionation up to 50 Gy. Although the difference is small the higher weekly doses in the hypofractionated RT seem to induce more edema, most likely due to the inflammatory process related to RT [13, 14]. This finding is in contrast with the UK START trial where standard fractionation induced more edema than hypofractionated RT [15]. The reason for the difference may be related to the assessment of edema which in the START trial was clinical evaluation of the whole breast while in the present investigation our quantitative approach was based on superficial edema measurements. Also timing of the edema evaluation may influence the results since the START trail provide results from a 10-year follow-up.

CONCLUSION

The healthy breast can act as control to provide a reference TDC ratio between the breasts. Based on the evaluation of the mean TDC ratio, the incidence of breast edema was found to be high (> 30%). The TDC values in the operated breast were higher compared to the healthy breast at all measurement time-points, also pre-RT, suggesting a high effect of surgery on breast edema. However, axillary surgery did not seem to increase breast edema more than sentinel lymph node biopsy. It was also shown that patients with scare in the fourth quadrant are more likely to have higher TDC ratio, i.e. edema of the breast. The higher weekly doses in the hypofractionated RT seem to induce more edema than the conventionally fractionated RT.

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HOMEOSTATIC INFLAMMATION IN LYMPHEDEMA

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ABSTRACT

In metabolic syndrome saturated fatty acid with the help of alarm signals causes inflam-
mation activating Toll-like receptor 4 and releasing inflammatory cytokines such as TNFα.
It is called homeostatic inflammation.It is sure that lympedema is associated with inflam- mation, because adhesion molecules (1), interleukin-6 (2), CRP (3) and ESR (4) are high in lymphedema. Histological examination of unilateral lymphedema shows lymphocytic (T cell) (4) infiltration in the lymphedematous extremity. Some fatty acids* including saturated are increased and free fatty acid* is also high in lymphedema. Acid phosphatase and lysozyme- positive macrophages are infiltrating (5) and partial tissue oxygen pressure is low (6) in lymphedema. Lymphedema is most likely to be associated with homeostatic inflammation
Oral EPA(IPA) with or without physiotherapy by sequential compression and magnetic fields, vibration & hyperthermia (7) has been tried in the lymphedema patients to inhibit this homeostatic inflammation*. It is not so effective if only oral EPA is given. But it works in some unsevere cases, specially if it is combined with the physiotherapy and given for longer period*. A perfect healing of lymphedema has been reported (8, 9). In order to gain this permanent healing, management of this inflammation is very important. No one has ever mentioned homeostatic inflammation in lymphedema.

(*) *Presentented by the author in 24th International Congress of Lymphology, Rome, 2013.*

LIPID AND LYMPHATIC SYSTEM

The fat is not only energy source and constitutional component of the membrane but also an important organ which secretes cytokines and adipocaines. Prox-1 (which regulates lymphatic sprouting from the vein) knocked out mouse developes obase adult (10). High fat diet induces abnormal fatty acids in blood from which abnormally functioning lymphatics with an increased permeability develop (11). Thus fat deposit in the fat cell ocurrs (11). What is deposited in the tissue in metabolic syndrome is not fat but fluid, although the fat cell is gigantic. Main cause of weight gain is not by fat but fluid deposit in the body (12). Fluid is deposited in the subcutis ln lymphedema (13). and the fat cell can easily produces saturated fatty acid as well as inflammatory cytokine such as TNFα causing inflammation. Liposuction works for the treatment of lymphedema (14) and there is rarely recurrence after the treatment. Fat is considered to be closely associated with lymphedema.

HOMEOSTATIC INFLAMMATION

In metabolic syndrome the fat cells are large (120- 140m μ) (Table 1). However the oxygen penetration is up to 100 m μ deep. Thus the fat cell has always oxygen deficit. To compen- sate this, an inflammation is induced by the help of alarm signals such as saturated fatty acid, M1 macrophage, ER stress, hypooxidative stress, $\alpha 5$, $\beta 1$ integrin, angiopoietin-like protein 2, etc (damage-associated molecular patterns) activating Toll-like receptor 4. This inflammation stimulates macrophages to produce inflammatory cytokine such as TNFα as well as to destroy fat cells (necrosis & necrotosis) producing more saturated fatty acid which results in a so-called vicious cycle. Thus blood circulation and vascular oxygen permeability become increased offering more oxygen to the fat cell. This inflammation is called homeostatic inflammation (15), (Fig. 1). The question is whether or not the lymphedema is associated with this homeostatic inflammation.

INFLAMMATION IN LYMPHEDEMA

The lymphedema shows elevated ESR(erythrocyte sedimentation rate) (4), CRP (3), inter-leukin –6 (2) and adhesion molecules (1). Acid phosphatase and lysozyme positive macro- phages are infiltrating in the histology (5) and the lymphedematous skin of the unilateral lymphedema of the extremity shows lymphocytic infiltration (T cell) (4) which is variable after the location but in average more marked whereas the uninvolved skin reveals the less severe infiltration (4). And the lymphedematous skin shows lysozyme positive M1 macrophages (5). TNFα and its receptor control proliferation and cell death of the fat cell. And the dead fat cell releases plenty of fatty acids including saturated fatty acid which activates macrophage to produce TLR4. This reaction leads to homeostatic inflammation resulting in a so-called vicious cycle. TNFα is not elevated in the lymphedematous patients (the authors'own observation). This contradicting result may come

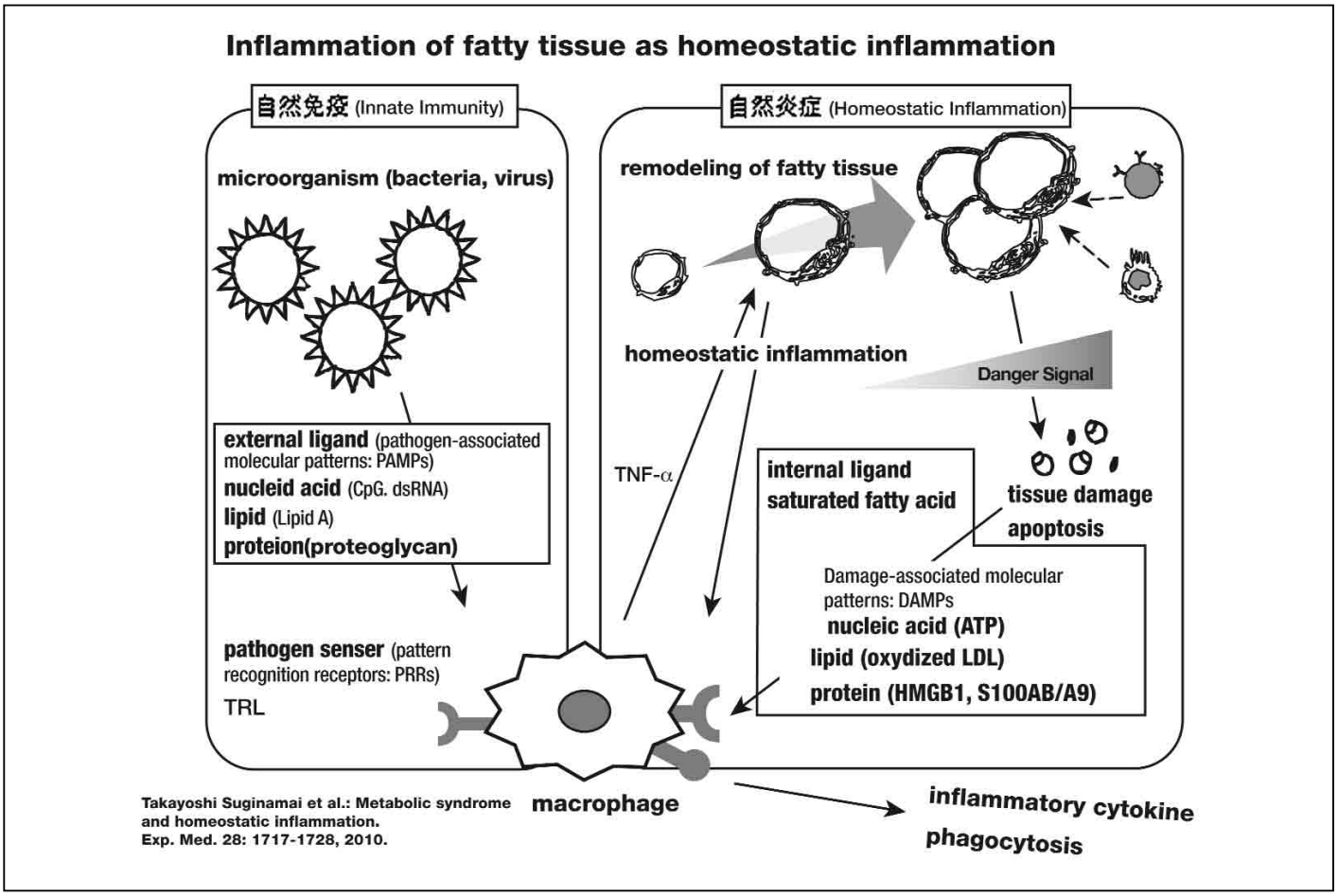

Fig. 1 - Inflammation caused by pathogen associated molecular patterns and by damage associatd molecular pattern. Saturated fatty acid with alarm signals induces the latter: taken from Suganuma's papers [15].

from the following fact that half life of TNFα is short (a few hours) and to detect its rise is difficult in lymphedema patient, Interleukin-1 is not raised either in blood in lymphedema [16], whereas Olszewski et al shows presence of interleukin-1 in human lymph [17] and its increase in bacterial complication.This discrepancy can be explained by the following fact that over 90% of Il-1 is inactivated after it passes through the lung. The unilateral lymphedema shows a lower partial tissue oxygen pressure in the lymphedematous extremity [6]. Thus the lymphedema is surely associated with inflammation.

HOMEOSTATIC INFLAMMATION IN LYMPHEDEMA

Acid phosphatase and lysozyme positive macrophages are infiltrating [5] and partial tissue oxygen pressure is low [6]. Free fatty acid (including saturated fatty acid) is high (*) and so are some unsaturated fatty acids (Fig. 2) [18] in lymphedema patients (*). High free fatty acid and fatty acids in lymphedema are characteristic for lymphedema because they become decreased except EPA and DHA after physiotherapy of lymphedema (authors' own observation). Oral EPA (IPA) with or without physiotherapy by sequential compression and magnetic fields, vibration & hyperthermia [7] is effective in the treatment of lymphedema (*). EPA is thought to be effective because its end products are resorbin E1 and E2 which are antiinflammatory substances by resisting agaistst TLR4 (Fig. 3), [18]. About 40% of all primary and secondary lymphedema have past history of bacterial complication. This bacterial complication is known to worsen lymphedema. However the rest 60% of the complication free patients are still getting worse & worse, although it goes slowly. Summering up these data, the lymphedema is most likely to be associateed with homeostatic inflammation.

(*) *Presented by the author in 24th International Congress of Lymphology, Rome, 2013.*

DISCUSSION

Obesity, metabolic sndrome and lymphedema are associated with each other (Table 1), although the obesity is differeent from non obesity (Table 2). Thus Lipids are closely associated with lymphatic system and lymphedema. Non bacterial inflammation called homeostatic inflammation ocuurs in metabolic syndrome caused by saturated fatty acids helped by damage-associated molecular pattern (Fig. 1) [15]. The lymphedema shows elevated ESR, CRP, Il-6 and adhesion molecules and its histology shows lymphocytic infiltration. It has a chronic inflammation in the skin. The skin's partial oxygen pressure is low, lysozyme positive macrophages are infiltrating in the tissue. Free fatty acid and some fatty acids including saturated are increased in the lymphedema. The lymphedema is said to be an incurable disease. Olzweski reported even if the edema disappears its pathological condions remain unchanged for at least 3 months [20]. In the same way in the lymphedema, by manual massage, edema may go away but reappears easily. Thus the lymphedema is not healed perfectly. After the physiotherapy [21] performed by the authors the immunity

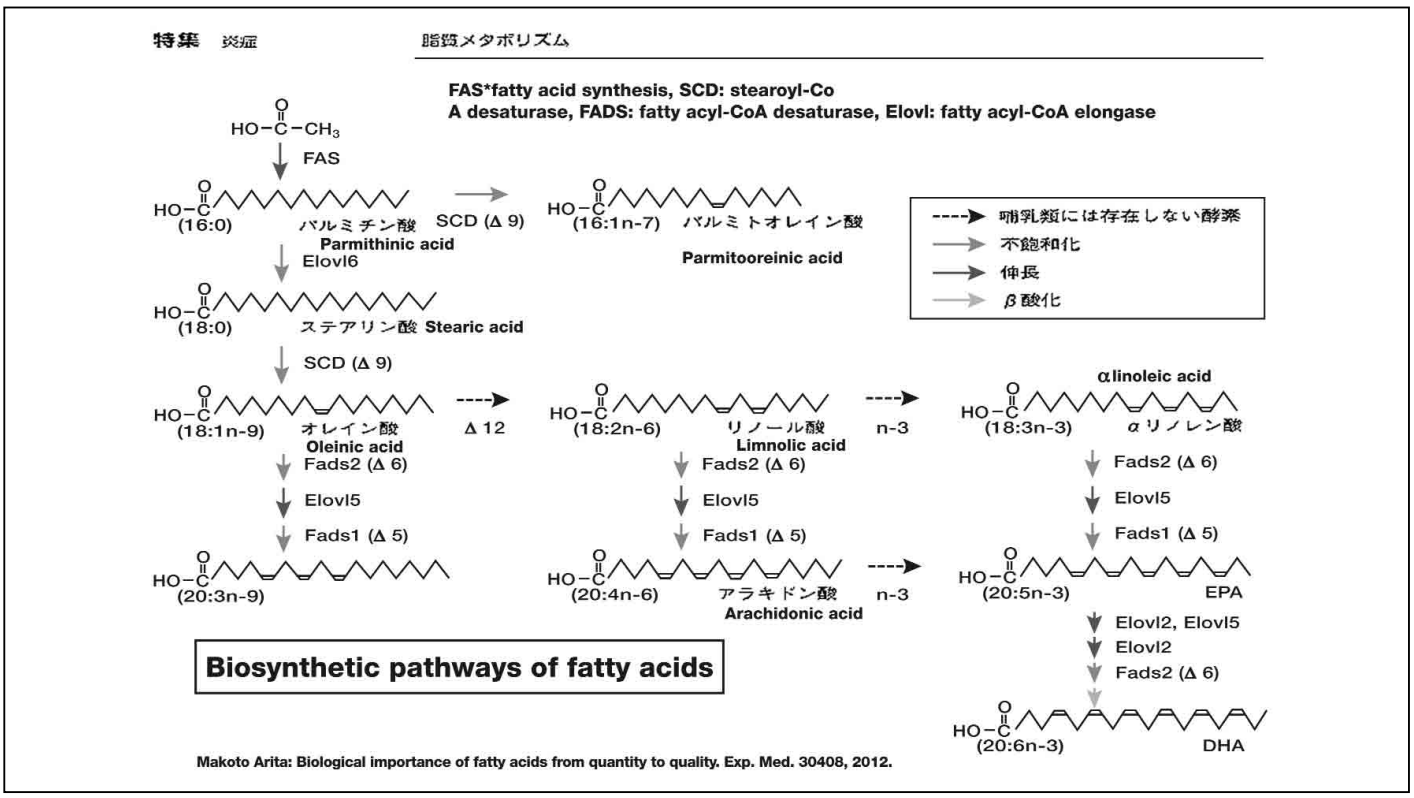

Fig. 2 - Various saturated and unsaturated fatty acids. Some n-3 series fatty acid (ex. EPA or DHA) are not produced in mammalian body: taken from Arita's papers [18].

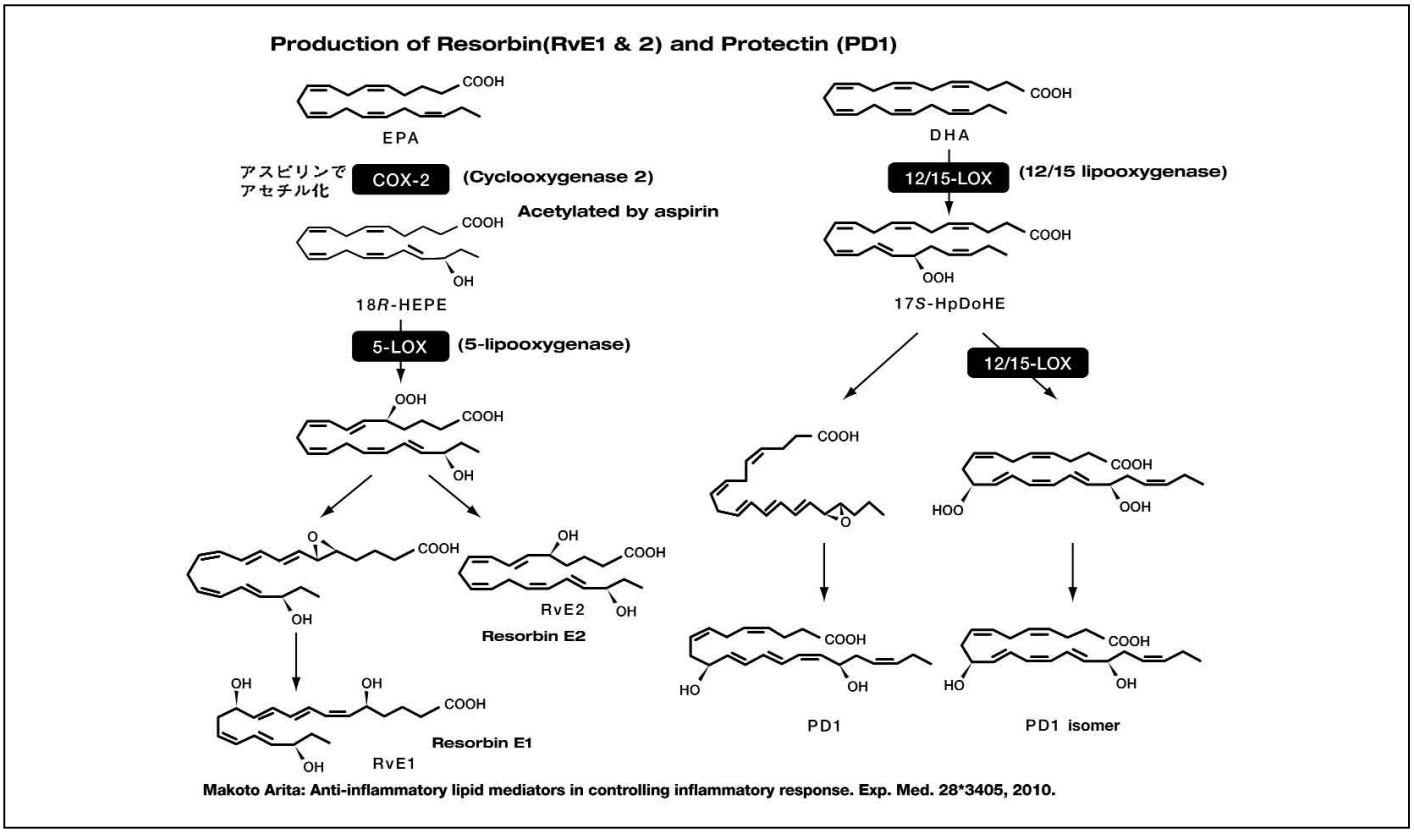

Fig. 3 - Resorbin E1 an 2 are endoproducts of EPA which show antiinflammatory effect: taken from Arita's papeers [18].

Table 1 - Differential Diagnosis of Obesty, Metabolic Syndrome, Lipiedema and Lymphedema.

Definition	Obesity BMI > 25*	Metabolic syndrome**	Lipiedema	Lymphedema
Etiology & pathogenesis	Genetic diet	Genetic diet, fatty acid alarm signals	Genetic	Genetic (primary) disturbed lymph flow (secondary)
Edema		+	++	++ ~ +++
Fatty tissue	Thick	Thick	Thick	Thick (3rd stage)
Fat cell	Big	Gigantic		Swollen
Fat distribution	Whole body	Internal organs	Thigh, buttock, lower trunk	
Oxygen deficit	+	++		+
Homeostatic inflammation	+	++	?	+
ER stress***	+	+		?
Macrophage	M1/M2 ↑	M1/M2 ↑		+
Free fatty acid	↑	↑		↑
TNFα	↑	↑		↑?
Monocyte taxis, or MCP-1****	↑	↑		
Agplp 2 *****	↑	↑		?
CRP	↑	↑		↑
Insulin sensitibity	↑	↑		Normal
Leptin	↑	↑		?
Adipocain	↑	↑		?
Adiponectin	↓	↓		Partly ↓

* Effective for Japanese adult.
** Abdominal circumference > 85 cm (male), 90 cm (female) with more than 2 of the following; triglyceride > 130 mg/dl, HDL < 49 mg/dl, FBS < 110 mg/dl, BP > 150 mmHg, systolic, > 80 mmHg diastolic.
*** Unfolded protein response.
**** Monocyte chemoattractant protein.
***** Angiopoietin like protein 2.

Table 2 - Difference between Obesity and Non Obesity.

	Obesity	Non Obesity
Inflammation	More in internal organ's fat	
Macrophage	M1	M2
Increased cells	Lymphocyte, mast cell, fat cell, fibroblast	
Remodeling	Vascular	
Extracellular matrix	↑	
Cytokine	TNF α, Il–6, MCP–1	Il–10
Nitrous oxide	↑	↓
Th1/Th2 ratio	↑	
PPAR γ *	+	
ATF3**	+	
NFκ B***		Working
EPA, DHA	Inhibit inflammation	inhibit inflammation

* PPAR γ: peroxisome proliferators activated receptor γ.
** Active transcription factor 3.
*** Nuclear factor κ B.

becomes stronger [22] and the inflammation becomes decreased [21]. Thus many lymphedema patients have been perfectly healed [22]. If we can handle this fat problems properly, we may have more number of perfectly healed lymphedema patients.The edema caused by a temporal inflammation, for example post inflammatory edema after hysterectomy which subsides spontaneously in a few month or postinflammatory face and genital edema due to contact dermatitis which go away in days do not produce a chronic edema because the lymphatic flow is restored spontaneously. The lesion of urticaria do not stay long because the lymphatic function is working well. Inflammation accompanied by impaired lymphatic function produces chronic edema. Thus lymphedema is most likely to be associated with homeostatic inflammation which is similar to metabolic syndrome. If this inflammation in lymphedema is well managed, a perfect healing of lymphedema may be posssible.

CONCLUSION

Lymphedema is most likely to be asscociated with homeostatic inflammation which is similar to what is seen in metabolic syndrome.

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ECHO-COLOUR-DOPPLER DIAGNOSTICS IN PRIMARY PREVENTION AFTER BREAST CANCER SURGERY: METHOD REVIEW

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SUMMARY

It is known that when lymphatic vessels are in difficulty, veins do not remain indifferent because, similar to a kind of twinning between them, an increase of the calibre and the flow velocity is noted.
With this awareness in the previous study, after bilateral venous system evaluation to exclude venous flow abnormalities, it was decided to analyze the venous system behaviour in subclinical stage after monolateral breast cancer surgery and lymphadenectomy: during this evaluation an asymmetrical calibre of cephalic veins, due to the increase of the homolateral side, was noticed in most cases and consequently it was decided to focus the attention on this measurement and compare it to the lymphoscintigraphy exam in order to investigate an eventual correlation.
With this method, homolateral increase of calibre of cephalic vein corresponded to slower radiotracer flow in 100% of the cases.
In the current study, modifying the position of the probe, placed parallel along the tendon of the lateral site of pectoralis minor, the results have highlighted, as in the previous study, how the increase of the calibre of homolateral cephalic vein has a positive correlation with the result of the lymphoscintigraphy: the homolateral increase of the calibre of the cephalic vein always corresponded to slower radiotracer flow.

INTRODUTION

In the previous study it was decided to analyze the venous system behaviour by Echo-Colour-Doppler, in subclinical stage after monolateral breast cancer surgery: during this evaluation an asymmetrical calibre of cephalic veins, due to the increase of the homolateral side, was noticed in most cases, and consequently it was decided to focus the attention on these measurements and to compare them to the lymphoscintigraphy exam previously carried out, in order to investigate an eventual correlation.
With this method, the homolateral increase of the calibre of the cephalic vein always corresponds to slower radiotracer flow (100% of the cases).

In the current study it was decided to review the previous method modifying the position of the probe: it placed parallel along the tendon of the lateral site of pectoralis minor including a piece of it on the recorded images in order to demonstrate the reproducibility of probe placement. With the new method the results were the same: the homolateral increase of the calibre of the cephalic vein corresponded to slower radiotracer flow in 100% of the cases.

MATERIALS AND METHODS

In the previous study with the patient supine on the bed (back at 30°), with upper limbs alongside the body, the physiotherapist measured and marked the compared upper limbs and the lymphologist measured the compared calibre of superficial and deep veins by Echo-Colour-Doppler (Sonoline Antares 7.5 MHz probe) at the end of expiration.
During this investigation the following results were noted:

– sometimes a symmetry of all superficial and deep veins,
– sometimes an asymmetry of cephalic veins, due to homolateral increase, and at the same time the symmetry or asymmetry of basilica veins and the symmetry of deep veins.

Following this preliminary evaluation, the attention of the lymphologist was focused on the calibre of the cephalic vein, due to its behaviour, symmetrical or asymmetrical due to homolateral increase, and as it resulted very easy to follow in all its course above all in the arm, it was decided to measure and analyse the calibre of the compared cephalic veins.
Furthermore, these measurements were compared to the lymphoscintigraphy exam (bilateral subcutaneous injections of 99mTc nanosized colloids in interdigital space - 185 MBq) carried out in all patients, by the same nuclear doctor, in order to search for possible correlation between them: the increase of the calibre of the homolateral cephalic vein had a positive correlation with the result of the lymphoscintigraphy (homolateral increase of the calibre of the cephalic vein always corresponded to slower radiotracer flow).
In this study it was decided to review the previous method.
The current study has been carried out on 43 patients, 15

monolateral sentinel node biopsy and 28 monolateral axillary lymphadenectomy, all subclinical stage, female aged 25-60 years, who had undergone on surgery 3-18 months before lymphological examination.
The lymphologist carries out Echo-Colour-Doppler exam with the patient sitting on the chair and arms comfortably pending along the body without movement, and measures the calibre of the compared cephalic veins, at the end of expiration, by probe parallel along the lateral side of the tendon of pectoralis minor including a piece of it on the recorded images in order to demonstrate the reproducibility of probe placement. (Photo 1)
In the cases of sentinel biopsy a symmetry in 73% and asymmetry in 27% of patients was noted, while in the cases of lymphadenectomy symmetry in 32% and asymmetry 68% of cases was noted.
As in the previous study the measurements of the calibre of the compared cephalic veins were then compared to the lymphoscintigraphy exam, carried out by the same nuclear doctor using the same method of the previous study, the results of which were: no slower radiotracer flow or homolateral slower radiotracer flow. Lymphoscintigraphy exam was evaluated only after venous measurement.

RESULTS

Sentinel lymph node biopsy (Photo 2)

– The symmetry of the cephalic veins (73%) corresponded to normal exam in 64% of the cases and a slower radiotracer flow in 36% of the cases (75% slowing - 25% stops);
– The asymmetry (27%) due to homolateral increase, corresponded to slower radiotracer flow in 100% of the cases.

On comparing the surgical side it was noted:

– In the cases of symmetry, right side in 50% of the cases and left side in 50% of the cases; all patients were right-handed,
– In the cases of asymmetry due to homolateral increase, right side in 50% of the cases and left side in 50% of the cases; all patients were right-handed.

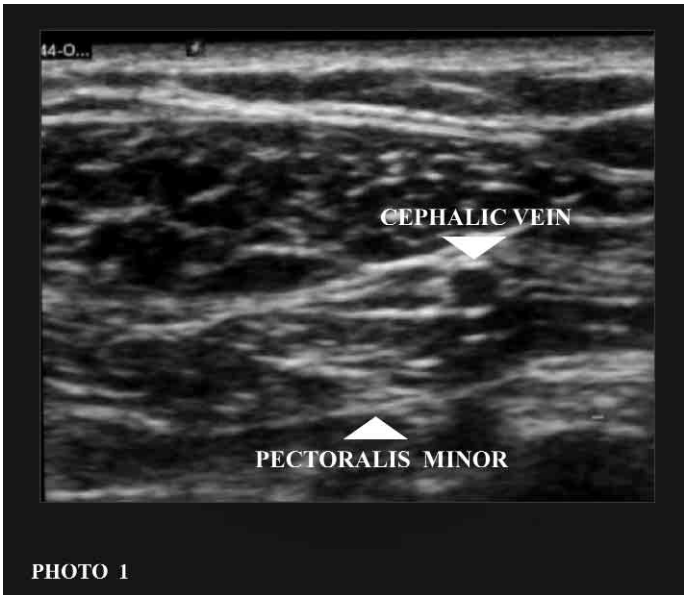

PHOTO 1

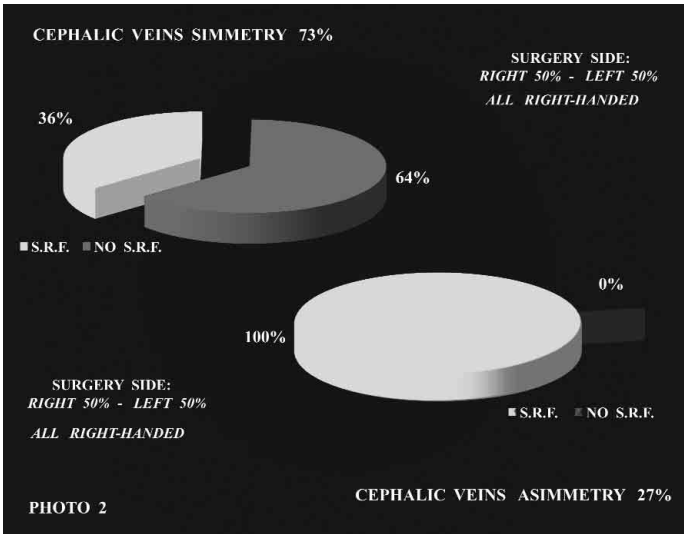

PHOTO 2

Lymphadenectomy (Photo 3)

– The symmetry (32%) corresponded to normal exam in 56% of the cases and slower radiotracer flow in 44% of the cases (slowing 25%, stops 25%, initial dermal back flow 25% and stops-initial dermal back flow 25% of the cases); furthermore in the cases of initial dermal back flow and stops-initial dermal back flow, a controlateral slower radiotracer flow was noted (slowing in 80% and stops in 20% of the cases);
– The asymmetry (68%) due to homolateral increased size, correspond to a slower radiotracer flow in 100% of the cases

On comparing the surgical side it was noted:

– in the cases of symmetry, right side in 33% of the cases and left 67% of the cases; 1 patient was left-handed,
– in the case of asymmetry due to homolateral increase, right side in 36% and left side in 64% of the cases; all patients were right-handed.

The results carried out with this new method highlighted, as in the previous study, how the increase of the calibre of homolateral cephalic vein have a positive correlation with the result of the lymphoscintigraphy in sentinel lymph node biopsy and

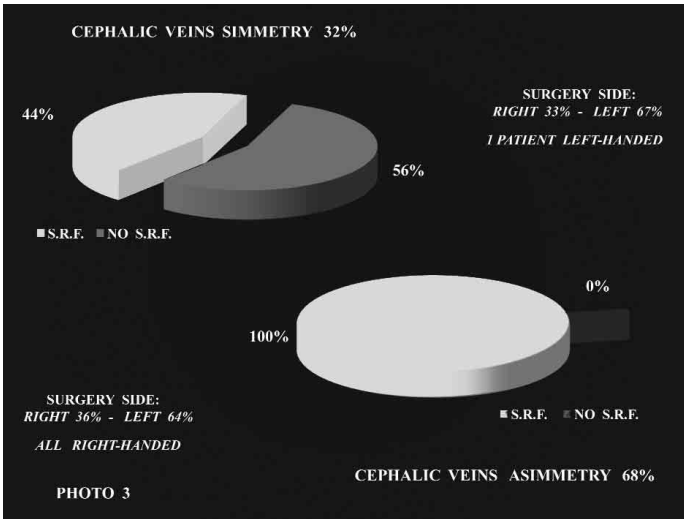

PHOTO 3

lymphadenectomy: the homolateral increase of the calibre of the cephalic vein always corresponded to slower radiotracer flow (100% of the cases).
In this study the side of surgery (right or left) was not relevant. Furthermore no sports were carried out by the patients.

CONCLUSIONS

In the current study the calibre of the compared cephalic veins has been measured by Echo-Colour-Doppler, modifying the position of the probe placed parallel along the tendon of the lateral site of pectoralis minor and including a piece of it on the recorded images in order to demonstrate the reproducibility of probe placement.
In this study symmetry or asymmetry, due to the homolateral increase, was found and these results were compared to the lymphoscintigraphy exam.
The results, carried out with the new method highlighted, as in the previous study, how the increase of the calibre of the homolateral cephalic vein has a positive correlation with the result of the lymphoscintigraphy in sentinel lymph node biopsy as well as in the lymphadenectomy: the homolateral increase of the calibre of the cephalic vein always corresponds to slower radiotracer flow.
The rehabilitation team knows that further investigation is required in order to understand the meaning of changes in the calibre of the cephalic vein size by Echo-Colour-Doppler exam, very easily repeatable, relatively inexpensive and fast, but the confirm of the hypothesis that the increase of the homolateral cephalic vein always corresponds to a slower radiotracer flow, would be very interesting in the ambit of primary prevention: it could allow the rehabilitation team to include patients at risk of edema onset in the early treatment, inform them on preventive behavioural measures, through individual settings, and include them in a follow-up.

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SURGICAL TREATMENT OF CONGENITAL LYMPHEDEMA

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SUMMARY

Lymphedema is a pathologic condition that results from a disturbance of the lymphatic system, with localized fluid retention and tissue swelling. Primary lymphedema is a congenital disorder, due to a malformation of lymph vessels and/or nodes (hypotrophic or hypertrophic).
Major progress has been achieved in the radiological diagnosis of the lymphedema-affected patients. Magnetic Resonance Lymphography (MRL), with T2 weighted imaging, allows clear visualization of the lymphatic system anatomy and its malformations, without the need of any injection.
The ideal treatment of the affected limb should restore both function and cosmetic appearance. Surgical treatment is an alternative method of controlling chronic lymphedema. Free lymph nodes autologous transplantation is a new approach for lymphatic reconstruction in hypoplasic forms of primary lymphedema. The transfered nodes will pump the extracellular liquid out of the affected limb and contain germinative cells that will improve the immune functions. Human lymph nodes express high levels of VEGF-c, a growing hormone responsible for stimulating lymphangiogenesis.
Hyperplasic forms and abnormal lymphatic duct forms can be treated with lymphovenous anastomosis, relieving the higher pressure into the venous system.

Key words: lymphedema, magnetic resonance lymphography, lymphnodes transplantation, microsurgery, VGEF-c, lymphangiogenesis.

INTRODUCTION

The ideal treatment for lymphedema of the limbs must restore both function and normal cosmetic appearance. Physiotherapy (manual drainages, pressotherapy, compression, bandages) is the usual treatment for chronic lymphedema and is considered by many as the only treatment for long-term management. It is not a curative therapy, but helps to control the evolution of the disease. Chronic lymphedema is a progressive condition, characterized by a degenerative and inflammatory process resulting in diffuse, irreversible tissue fibrosis. Surgical treatment is an alternative method of controlling chronic lymphedema [1].
Precise diagnosis of lymphedema has done major progress: lymphangiography with oil and lymphoscintigraphy were once very useful, but these exams have important drawbacks (infection, pulmonary embolism...). Magnetic Resonance Lymphangiography (MRL) with T2 weighted imaging has greater sensitivity, and allows complete visualization of the lymphatic system, without any injection [2].
Free autologous lymph nodes transplantation in hypoplasic forms of lymphedema is a new approach for lymphatic reconstruction; a more anatomical strategy compared with the multiple lymphovenous anastomoses. Recent findings on the growing hormones produced by the lymph nodes permit further understanding on the efficacy of these procedures. Three lymph nodes flaps can be used, depending on the affected segment and available donor sites. These flaps are located on the inguinal, thoracic or cervical area. The transplanted nodes will pump the extracellular liquid, responsible for the lymphedema formation, and contain germinative cells that will improve the immune functions.
Recent findings on the growing hormones produced by the lymph nodes permit further understanding on the efficacy of these procedures. Human lymph nodes express high levels of the lymphatic vessel growth factor VEGF-c. This growing hormone is responsible for stimulating lymphangiogenesis in the treated limb. Saaristo *et al*. compared the production of this growing factor by different tissues of the immune and hematopoietic systems. Lymph nodes expressed the highest levels of VEGF-c among the tissues tested [3].
Each living node contains a plexus between the lymphatic and venous systems. The transplanted lymph nodes probably work as biological lymphovenous anastomosis also.

Clinical presentation [4]

Alterations of lymph drainage induce stasis of the lymph and progressive tissue changes with enlargement of the subcutaneous tissue and thickening of the skin. Secondary infections, immune disorders, cosmetic and psychosocial impairment can severely affect lymphedema patients.

Diagnosis of lymphedema is done mainly by clinical assessment. A detailed history, clinical evaluation and physical examination are necessary. Age of inset, episodes of infections and inflammatory attacks, previous medical treatments, and visits to tropical countries with endemic filariasis should be recorded. Transitory edema of the affected limb and a family history of limb edema should be questioned. Lymphedema is usually painless, but a sensation of heaviness of the affected limb is a common complain. Acute inset or worsening of the lymphedema can produce pain, due to the distention of the aponevrosis around the deep lymphatic system.
In the lower limbs, lymphedema is usually unilateral, and if it is bilateral, it is generally asymmetric. In young adults the lymphedema interesting the lower limb, is unilateral in 70% of the cases, and bilateral in the other 30%. The lower body, upper extremities (unilateral or bilateral), the abdomen, genital area, and trunk can be involved. The skin folds at the base of the toes and fingers are broadened. This is due to excessive skin thickness, fluid accumulation with tissue overgrowth (Stemmer's sign).
Skin changes include pinky-red discoloration, hyperkeratosis, papillomatosis, and lymph vesicles. Inter-digital mycosis must be treated to prevent secondary infections. Associated venous insufficiency may cause ulcerations of the skin.
Elephantiasis can be observed in hypoplasic and hyperplasic forms, but the disorders of the skin and the multiple folds are very difficult to treat. Evolution into lymphangiosarcoma is rare, but can occur if elephantiasis is not treated.
Perimetry of the limb is an indirect assessment of its volume. It is a traditional tool to evaluate limb changes. Measurements are made at the level of the two distal major joints (knee and ankle in the lower limb), 10 and 20 cm proximal to them.

Associated Diseases

Primary lymphedema can be associated with other organs malformations and genetic disorders. Cancer and diseases in the central nervous system, lungs, heart, kidneys and other organs can accompany lymphedema of sudden onset. The most prevalent hereditary disorders associated with lymphedema are Milroy's syndrome, Meige syndrome, lymphedema-distichiasis and yellow nail syndrome.

Milroy's syndrome: mutation of the VEGFR-c encoding gene, located at the 5q35.3 region. This syndrome is associated with lower and sometimes upper limb edemas. Genital lymphedema can be observed. This hereditary familial lymphedema doesn't present a macrostructural defect of the lymphatic system. The lymphatic collecting vessels are present, but there is an impairment of absorption of the lymph, reflecting as a functional defect.

Meige syndrome: affects lower limbs and appears during puberty. It is a hereditary form of lymphedema, but the genetic mutation is still unknown.

Lymphedema-distichiadis: associated with cardiac malformation, cleft palate, ptosis, double eyelashes. In this syndrome, lymphatic collectors lack intraluminal valves, resulting in lymph reflux. The genetic mutation has been identified at the locus q24-3 on the chromosome 16.

Yellow nail syndrome: rare syndrome in which lymphedema due to lymphatic hypoplasia is associated with pleural effusions, and yellow distrophic nail.
Lymphedema may accompany complex vascular malformations, as seen in Proteus and Klippel-Trenaunay syndromes. In Turner's syndrome, it is often present, with a characteristic distribution (distal and symmetric, with lymphangiomas).

Complementary Investigations

Today, radiological evaluation of lymphedema patients can be done thru lymphoscintigraphy, MRL or PDE (Photodynamic eye, Hamamatsu, Japan). Other exams have historical value or a very specific use during surgery.
PDE is useful to access the superficial lymphatic system anatomy thru fluoresceine intake from an injection distally to the limb.
Lymphoscintigraphy is a good functional exam that studies the ability of the lymphatic system to transport to regional lymph nodes a radioactive marker injected at the toes.
Magnetic Resonance Lymphography (MRL), with T2 weighted imaging allows visualization of the lymphatic system anatomy with greater sensitivity than lymphoscintigraphy, without need of any injection[2] (Fig. 1, 2).

Fig. 1

Fig. 2

SURGICAL TREATMENT BY AUTOLOGOUS LYMPH NODE TRANSPLANTATION [5,6,7]

Patients with hypoplasic forms of lymphedema on the MRL are the preferred candidates for the procedure. For some of these patients, long-term physiotherapy, hospitalizations, bandages, compression garments and other treatments are insufficient to prevent lymphedema. These patients can benefit from autologous lymph node transplantation: the high concentration of lymphatic growing hormone induces the neoformation of lymphatic vessels improving uptake of lymph by the local lymphatic system.
In the hyperplasic cases, the high pressure on the lymphatic system can be deviated by lymphovenous bypass. This is the case for

patients diagnosed with blockage or absence of the thoracic duct. In elephantiasis, combination of various techniques is necessary: excisions of the folds, nodes transplantations and liposuction at a further stage to excise the remaining lipoedema (hypertrophy of the subcutaneous fat in chronic lymphedema).

Operative technique

In patients presenting with lymphedema on the entire limb, the flap should be transplanted to the proximal insertion of the limb (axila or inguinal region). In socket-pattern lymphedemas, the flap can be placed at the level of the knee. MRL can help establishing the level of the hipoplasy. Large lymphedemas might require 2 different flaps (inguinal and knee region).
The surgery starts at recipient site. In the inguinal region, the incision is performed in the inguinal crease. Deeply, just at the level of the inguinal ligament, the circumflex iliac vessels are individualized and prepared for the micro anastomosis. A little pocket is created to receive the transplant, at the depth of the deep lymphatic system (Fig. 3, 4, 5). At the knee region, an incision of approximately 7cm is performed at the medial aspect, just above the knee. At the superior medial side of the adductor muscle, the saphenous vessels will be the recipient pedicle.

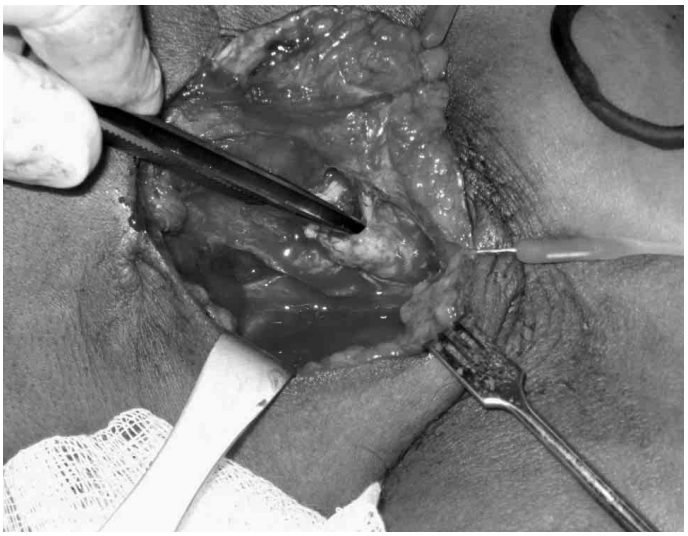
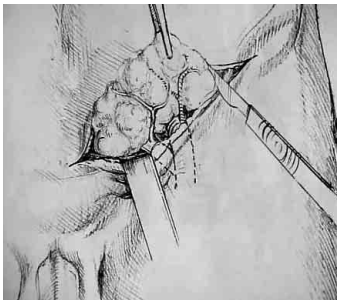


Fig. 3 - Axillary dissection, old seroma sometimes to be dissected. The flap will be iserted in the region of the adenectomy.



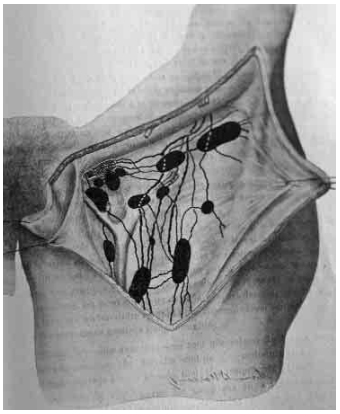


Fig. 4, 5 - Harvesting the flap in the inguinal crest, never go in the thight to avoid lymphedema of the donor site.

The lymph node flap is usually taken at the thoracic region. An incision of 5 cm is performed in the low axillary region, laterally to the nipple. The lateral edge of the dorsalis muscle is identified and the vessels on its anterior aspect are dissected. The fat tissue located deeply on the lateral thoracic wall and anterior to these vessels contains functional lymph nodes. It can be dissected as a lymph node flap based on small branches of the lateral thoracic vessels or the toracodorsal system. The vessels are prepared with microvascular clamps for identification on the recipient site.
The cervical flap is based on the transverse cervical artery. Incision is performed on the internal part of the clavicle, over the sternocleidomastoidus, which is reflected. The flap is raised as a free-style flap, in the same manner as the thoracic region.
The flap is transferred with microsurgical techniques, under microscope magnification and 10-0 nylon sutures. Skin is closed with multi-layer absorbable sutures.
Local excisions of excessive tissue and deep folds are performed on demand. This helps with the prevention of fungal and/or bacterial infections and allows for optimal physiotherapy post-operatively [8] (Figures 6, 7, 8, 9, 10, 11).

Fig. 6, 7 - Donor site: thoracic flap. 4 nodes depending from the distal branches of the thoracodorsal artery or the external mamary vessels. Not axillar flap, region near axillar vein never touched!!!

Fig. 8 - Cervical flap dependant of the cervical transverse artery.

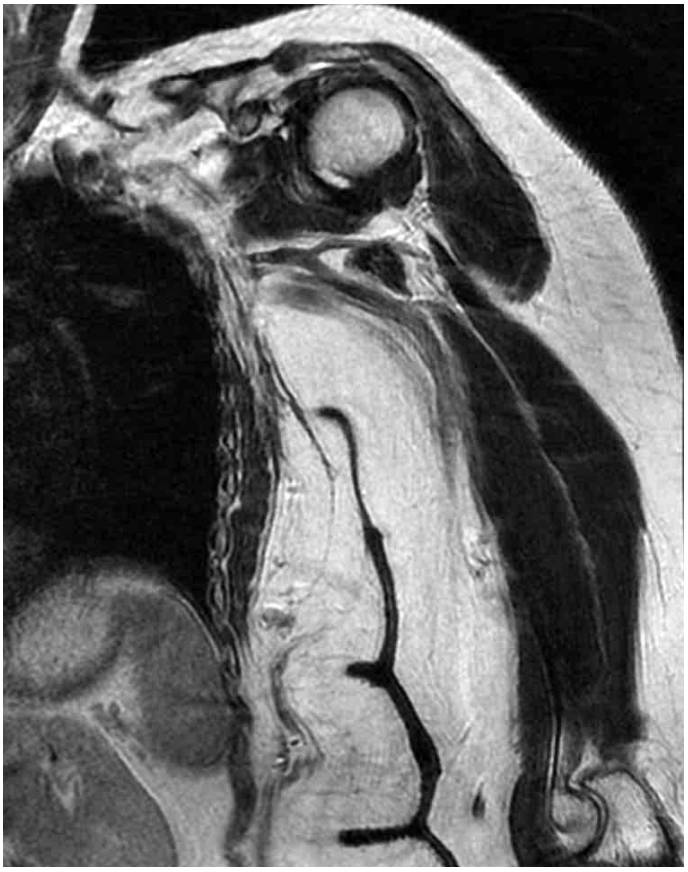


Fig. 9 - Flap will be inserted in the place of the adenectomy to restore the anatomy.

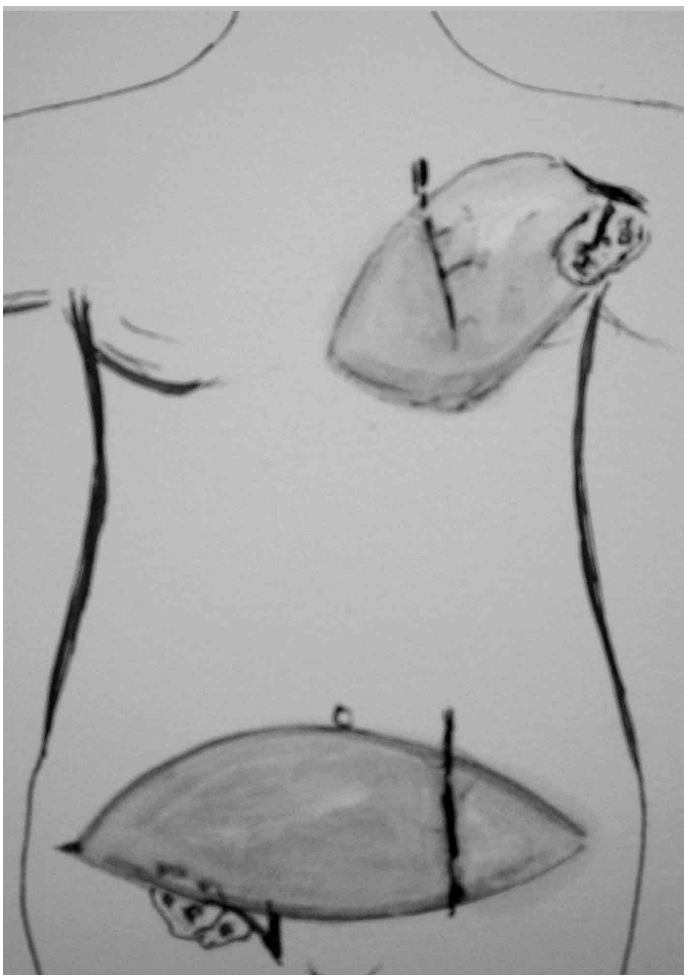


Fig. 10, 11 - Flap can be enlarged and restore the breast by the same time. Modified DIEP.

Post-operative management

Patients are normally discharged on the second post-operative day. Physiotherapy, with manual drainage and compressive bandages are prescribed for two months post-operatively, 3 to 5 days a week on the first month and 3x/week on the second month. Continuation of physiotherapy from the third month on is decided on a case-by-case basis. Compression garments can be used on the first six months. Progressively, new lymphatic vessels, stimulated by the lymph node-produced growing factor VEGF-c, repopulate the limb, replacing progressively the physiotherapy. 20 to 50% percent of patients can be free of physiotherapy in long-term follow-up.

Evaluating results

Standardized evaluation of results is hard due to the great variability of the disease's presentation.
Patients with unilateral lymphedema have a contralateral normal limb to compare results with. Measurements of the normal side should also be made at follow-up consultations.
In cases with bilateral lymphedema, serial measurements of the two affected legs can show the decrease in the circumference of the legs. Results can be compared over time with digital photography.
Results in pediatric patients are difficult to objectively quantify, since the child and the leg will continue to grow continuously after surgery.
Patients are seen for post-operative consultations and follow-up consultations at 6, 12, 18, 24 and 36 months. Repeated lymphoscyntigraphy and/ors MRL can show improvement to the lymphatic system anatomy and function. It can be repeated at follow-up visits once a year after surgery for 3 years (Fig. 12, 13). Patients have to be followed for recurrent episodes of erysipelas. Other improvements referred by patients in long-term follow-up are better skin elasticity and texture. Some patients also refer hair growth. Ability to retake work and cease physiotherapy are the two major objectives of this procedure.

RESULTS

The following results are part of a large personal series (Becker C). It is being analyzed for further publication. Patients were divided into 3 different groups, based on presentation of the lower limb lymphedema:

Group 1 – Distal Lymphedema
Group 2 – Generalized leg lymphedema
Group 3 – Hyperplasic forms

Group 1 - Distal lymphedema (Fig. 1)

Serial perimetry of both affected and non-affected limbs were taken post-operative at the level of the ankle and 10 cm and 20 cm proximally. All patients in this group showed a reduction of the circumference of the treated limb with normalization in 46%. 88% of the patients had no more infections in the follow-up period. Post-operative lymphoscintigraphy in some of these patients showed the following:

- In 50% of the patients, the transplanted lymph nodes were visualized and new lymph drainage pathways appeared;
- In 40% of the patients, lymphangiography improved showing effective lymph drainage pathways;
- In 10% of the patients, no changes at the scintigraphy were seen, even if clinical results were preceived.

MRL was particularly able to show new lymphatic pathways. (Fig. 2).

Group 2 - Generalized limb lymphedema (Fig. 12, 13)

Although improvements in limb perimetry were present in 98% of the patients, only 20% of them achieved complete normalization. In severe and older lymphedemas, a second flap placed at the knee level, at the confluence of the deep and superficial lymphatic pathways further improves the results. The rate of chronic infections decreased from 53 to 4%.
Young patients could go back to work within the two postoperative months. In less severe lymphedema, patients returned to work three weeks after surgery.

Fig. 12, 13 - 11y old girl having lymphedema since birth. Results 1 year after lymphnode transplant..

Group 3 - Hyperplasic forms

Hypertrophic forms of primary lymphedema diagnosed thru MRL and malformations of the thoracic duct are treated by several lymphovenous anastomoses in the inguinal region.
Use of compression garments are mandatory. There seems to be a clinical improvement, with better quality of life and young patients being able to return to work. No radiological improvement is seen on lymphoscintigraphy or MRL.

CONCLUSION

The use of autologous lymph nodes transplantation in hypotrophic forms of primary lymphedema is an innovative and promising treatment. It is a logical approach for the reconstruction of underdeveloped lymph transport system.

The recent discoveries on the VEGF-c lymphangiogenic properties provide a bio molecular explanation for its efficacy. When the lymphedema is not too advanced, complete or near complete recovery is possible.

The use MRL to visualize lymphatic pathways without contrast injection allows clear differentiation between hypotrophic and hypertrophic forms of the disease, allowing precise indications for surgery.

In hyperplasic forms and lesions of the thoracic duct, lymphovenous anastomoses are indicated, but the presence of patent lymphatic vessels is important.

PDE can help identifying these vessels, but in late stages of elephantiasis, they can be obstructed. In theses cases, local resections are needed to remove the skin folds and prevent fungal and/or bacterial infections.

Successful management of these difficult patients depends on good collaboration between a multidisciplinary team (radiologists, reconstructive surgeons and physiotherapists, among others).

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AN ASSOCIATION OF IMMUNO-MODULATORS AND NATURAL LYMPHO-KINETICS IN THE TREATMENT OF POST-MASTECTOMY LYMPHOEDEMA. AN OBSERVATIONAL STUDY

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SUMMARY

Goals: Aim of this study has been to evaluate the effectiveness of the physical treatment of post-mastectomy lymphoedema associated with immune-modulator and lymphokinetic drugs, in the prevention of inflammatory outcomes related to it.

Materials and methods: We selected 20 patients affected with lymphoedema of the upper limb at the second stage of Foldi classification, with preceding lymphangitis occurred from 8 to 13 months after surgery. We treated them for 60 days. All the patients, were submitted to clinical examination with metric measurement of the diameters of the arm starting from the wirst (point 0) every 7 cm till the root; evaluation of subcutaneous thickening, index of fibrosis, by ultrasound; laboratory clinical examinations to show any change in the inflammatory blood index. So, we considered: CBC with PLTS count, INR, PT, PTT, fibrinogen, ESR,CRP, Blood Protein Electrophoresis, Interleukin 1beta and Interleukin 6.
10 patients had only physical therapy, the other 10 added to this a pharmacological supplement of Wobenzym tablets (2 tablets 7 twice/ day) and Lymdiaral drops (30 drops/ twice/ day). The results of clinical and instrumental parameters T0-T30-T60 and the laboratory ones T0-T60 have been compared.

Results: From a clinical point of view, at the end of our observations, we releaved a decrease od the diameters of the arms in all the patient but more evident in the II group (double treatment, phisycal and pharmacological) in comparison with the I. Particularly, at T0 the hand back's diameters of the I group were 21.7 cm, while the II group 22.5 cm; the forearm's diam. were 26.8 cm for the I group and 28.5cm for the II one. These values have been reduced at T30 and T60 of 1.5 cm and 2.3 cm to the hand's back in the I group and 2.2 cm and 3.2 cm in the II one; as regards the forearm the decrease in volume was at T30 and T60 respectively 1.8 cm and 2.7 cm in the I group and 2.7 cm and 4.9 cm in the II group. From a tissue morphological point of view, the subcutaneous thickening is decreased in all the patients, both in the spine that in the forearm. In particular, at Time 0 in the I group it was approx 1.5 cm at the forearm's level and 1.8 cm at the back's level. In the II group it was 1.6 cm at the forearm and 1.7 cm at the hand's back. These values were significantly decreased during the observations, respectively 0.3 cm (T30) and 0.5 cm (T60) at the hand's back and 0.5 cm (T30) and 0.6 cm (T60) at the forearm in the I group, and 0.4 cm (T30) and 0.6 cm (T60) at the hand's back and 0.5 cm (T30) and 0.8 cm (T60) at the forearm in the II group. From a laboratory point of view we noticed a decrease of the ESR, a stability of clotting time, the reactive pr. C, fibrinogen and interleukins within the normal range. At the same time, the increase of beta globulins in the protein electrophoresis, reported a normalization at the end of the protocol.

Conclusions: The associated protocol of kinesis-therapy and drugs with action both on lymphatic drainage and on inflammatory cell mediators has been resulted effective in the treatment of the lymphoedema. It can be observed as in only 60 days of treatment, there have been a decreasing not only of the volume of the limb but also of the subcutaneous thickening, a very important index to define the remitting stage of lymphoedema. Really, the possibility to reach or to stabilize a compressible stage, allows the lymphatic drainage restoring and delays the inflammatory outcomes.
This occurrence in stable post-mastectomy lymphoedema, is equivalent to a less difficult management of the edematous arm and the possibility of a better quality of life for the patients.

INTRODUCTION

Both partial and total ablative surgery on the breast due to cancer, represents a delicate clinical picture in the prognosis and onset of arm's lymphoedema and moreover on its treatment, particularly in a stable and chronic phase.
Besides the complex physical protocol, univocally recognized, the prescription of a pharmacological support is codified and important both in the treatment phase and mainly in the maintenance of the results achieved with the physical therapy. (1)

Generally patients arrive to the observation of the angiologist at overt disease, in a clinical phase of hard-elastic edema with remission low degree, or suffering from acute lymphagitis secondary to iatrogenic or traumatic noxae. Sporadically they arrive to him, as prevention, immediately after the surgery.
The bio-chemical composition of the lymph, protein and lipid, give the clinical features to the lymphedema: softness, changing in different levels up to a stability's level, not compressible (Fig. 1).
By ecography, lymphatic overloading results in linear, hypo-reflective and discontinuous structures, which infiltrate the tissues, altering the normal anatomy. They are often associated to a sub-dermal draining vein: they are lymphatic gaps particularly clear in the lymphedema at the initial phase, with medium protein component or in any case, compressible; otherwise, small gaps, scheduled in a continuous way, reflective, without constant contact with draining veins, inserted into a hypo-reflective tissue, mark out the fibrotic lymphedema with high protein concentration [2].
As regards the differences between the lymph biochemical composition and the blood ones, national and international literatures, mark that lymphedema has a medium concentration of the total proteins less than 45% of the corresponding medium plasma concentration, and a significant decrease of the Ca ion and leukocytes concentration, too. Besides these changes, there are more specifications regarding the inflammatory mediators field, the interleukins, especially the 6, which is particularly high with incoming inflammatory events [3].
It is well known that with post-mastectomy lymphedema, the clinical goal is not to face the increase in volume of the limb (unfortunately expectable sooner or later, due to the ablation of the lymphatic vessels), but to contrast the lymph overloading and its evolution in fibrosis. Really, a lymphatic stagnation, where the drainage of the vessels is insufficient, need the reabsorption of the edema through the cellular way by macrophages. These cells are able to activate the local protein lysis, promoting the fragmentation of the exceeding protein filtrate, in order to facilitate the lympho-venular outflow. This balance can be challenged by the continuous increase of the Oncotic Pressure, due to the saturation of the local adjustment mechanisms of the microcirculatory pressures; this involves a depletion of the proteolytic activity of the tissue drainage operated by macrophages as they undergo a state of hypertrophy with immobilization in the pit. This allows their further integration with the loaded proteins and the activation of fibroblasts; the process causes the tissue's sclerosis, that, stabilizing, promotes local inflammatory reactions chain, which activate permanently the immune system, altering the enzymatic mechanisms adjusting the release of the inflammation inhibitory factors, the cytokines, until they are exhausted [4,5,6]. All this occurs within the interstitial matrix [7]. Being its functions balancing the protein, immunological and volume homeostasis recognized, it is intuitive that a condition of inefficient drainage is impacting the extracellular matrix and particularly the production and maintenance of the correct concentration of GAGs of the interstitial connective [8].

Therefore, in the care of lymphedema, it is very important to act on two fronts: that tissular, blocking the inflammation phenomena and monitoring the expression at the system level by an action on the mediators (cytokines) of the immune response , and the vascular one, by a lymph-kinetic and lymph-tonic activity.

Fig. 1 - Stable post-mastectomy lymphedema.

MATERIALS AND METHODS

Our experience in the lymphatic field comes from a lot of observations on different lymphedema clinical pictures, when treated with physical treatment (lymph-drainage, dressing and pressure therapy) [9,10,11] or with drugs (natural or synthetic coumarin) [12,13,14,15], alone or in combination. The results reached a conclusion that the lymphedema term is understatement, because a deficient activity of lymphatic drainage involves changes both in the blood and in the metabolic level, operating the permanent alterations on the tissue submitted to this injured function. These alterations (presence of interstitial fibroblasts and lymphocytes, hyperplasia and connective laxity, ectasia and tortuosity of the lymphatic collectors with perivascular edema , fibrosis due to the gradual protein accumulation) without objections but detectable constantly in the lymphedema latent phase, predispose to the onset of severe lymphangitis or derma-hypodermis, which can be produced by triggers even of medium size. Thus, edema chronic phase starts. The observation of a specific lifestyle and an antibiotic prophylaxis for a long time are the current way to prevent the recurrence inflammatory.

In this study we focused our attention on the effects of the complex physical treatment of post-neoplastic lymphedema of the upper limb in association to two natural drugs: one with immune-enzymatic activity and the other with lymph-kinetic activity. We analyzed it clinically, in order to get a subjective improvement in

heaviness and swelling symptoms residues to acute inflammatory episodes, and objectively, in order to get a volumetric decrease of the limb, exceedingly on the tissue one, it means on the attainment of a subcutaneous thickness's decrease (index of fibrosis) and consequently of the local tissue pressure (particularly increased in the lymphedema and determining the onset of the lymphatic drainage).
20 patients affected with post-mastectomy lymphoedema since at least 18 months and in pharmacological and kinesis-therapy wash out since at least 3 months (medium 54,7 years old) have been selected. All the patients had a history of acute lymphangitis episodes occurred from 8 to 13 months after the surgery (3 patients had 2 episodes, the others one) and reported lymphedema of the entire upper limb including the hand. Clinically, lymphedema was hard-elastic, little compressible (II stage of Foldi's classification) [16], placed uniformly to the entire limb from the early stages of onset, with greater compactness forearm. Lymph accumulation was more mellow and compressible borne the back of the hand (as it happens in the foot), due to the anatomical characteristics of the extremities. This agrees with most of the clinical observations of stable lymphedema's stage: the presence of a subcutaneous fat layer accounted more in the forearm than arm segments and hand's back, justifies an accumulation and a more rapid organization, with a tendency to fibrosis, particularly in the elbow's area.
This justifies the particular vulnerability of these areas and the fact that they are the choice's sites for lymphangitis or derma-hypodermis. Edema is permanent, and only responsive to the physical therapy, i.e. we get an easier applicability, flexibility and manageability with the manual lymphatic drainage to be kept with elastic compression. These conditions do not correspond to a decrease in volume such as in the case of the arm or more on the back of the hand.
Considering all above mentioned, the therapeutic approach of post-mastectomy lymphedema must be timely and specific. Our study involved the observation of patients by serial controls for 60 days: at Time 0, after 30 or 60 days of treatment.
At recruiting, all the patients were subjected to:

1) Clinical examination, volume (in cm) of the limbs, measuring the back of the hand and, starting from the wrist (point 0), every 7 cm till the root of the limb;
2) Measurement of the skin and subcutaneous thickening, index of fibrosis, by ultrasound of the surface to the hand's back and forearm (in the segment between the first two measurements, i.e. approx 12 cm from the wrist);
3) Laboratory clinical examinations for the study of any change in the inflammatory blood index. These assessments have been carried out at Time0 and after 60 days of treatment. In particular were examine: CBC with PLTS count, INR, PT, PTT, fibrinogen, ESR,CRP, Blood Protein Electrophoresis, Interleukin 1beta and Interleukin 6.

The therapeutic protocol has foreseen 10 patients with complex physical treatment as monotherapy, and 10 patients associating a pharmacological supplements of Wobenzym tablets (2 tablets / twice / day) and Lymdiaral drops (30 drops / twice / day). The results of clinical and instrumental parameters T0-T30-T60 and the laboratory ones T0-T60 have been compared.

RESULTS

At the end of the study, all the patients have been satisfied of this therapeutic way, being it managing and not interfering with the normal daily habits. All patients have reported a subjective decrease of the related symptoms, especially the weight, and enjoyed the great arms touchableness, referring a "softer" feeling.
Our results have met the clinical observation both of the decreasing in volume, and at the same time, of the in the subcutaneous thickness, one. This last condition reveals how the applied treatment protocol promotes a breakdown of the interstitial protein accumulation, avoiding the emergence of new inflammatory events.
Specifically, at the recruiting a volumetric increase of the limb with lymphedema averaging 2.3 cm compared to the other arm, has been detected. All patients complained of an arm heaviness feeling, easy and tiredness feeling and limb's congestion, with deterioration's character during the day.
As regards the volume, at T0 the hand back's diameters of the first group were 21.7 cm, while the second group 22.5 cm; the forearm's diam. were 26.8 cm for the first group and 28.5cm for the second one. These values have been reduced at T30 and T60 of 1.5 cm and 2.3 cm to the hand's back in the first group and 2.2 cm and 3.2 cm in the second one; as regards the forearm the decrease in volume was at T30 and T60 respectively 1.8 cm and 2.7 cm in the first group and 2.7 cm and 4.9 cm in the second group (Fig. 2).
From a tissue morphological point of view, the subcutaneous thickening (index of fibrosis) is decreased in all the patients, both in the spine that in the forearm. In particular, at Time 0 in the first group (treated only with kinesis-therapy) it was approx 1.5 cm at the forearm's level and 1.8 cm at the back's level. In the second group (treated with kinesis-therapeutic and pharmacological protocol) it was 1.6 cm at the forearm and 1.7 cm at the hand's back. These values were significantly decreased during the observations, respectively 0.3 cm (T30) and 0.5 cm (T60) at the hand's back and 0.5 cm (T30) and 0.6 cm (T60) at the forearm in the first group, and 0.4 cm (T30) and 0.6 cm (T60) at the hand's back and 0.5 cm (T30) and 0.8 cm (T60) at the forearm in the second group (Fig. 3).

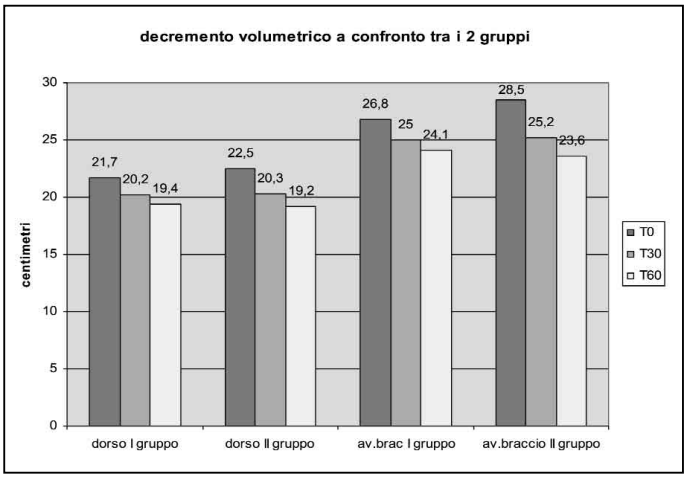

Fig. 2

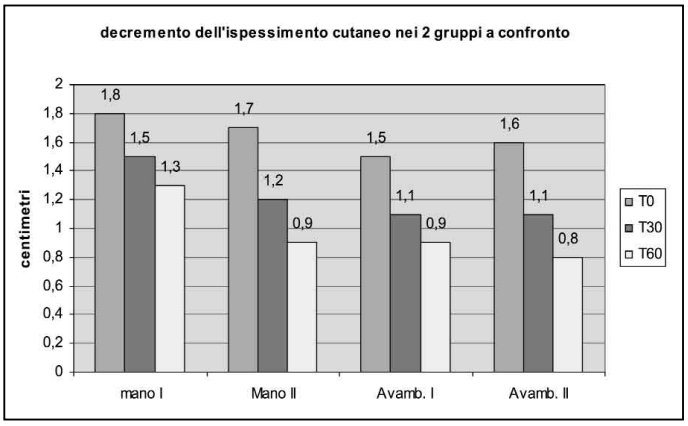

Fig. 3

Examining the laboratory parameters in all the patients we have found: a decrease of the ESR, a stability of the clotting time, the reactive pr. C and fibrinogen within the range of the values test and, particularly, of the inflammation mediators: interleukins 1 beta and 6. Examining the Blood Protein Electrophoresis, the increase in beta globulins at T0 reported a normalization at the end of the Protocol. The results of the above mentioned data are stated in the following table (Tab. 1).

Table 1.

	First Group T0	First Group T60	Second Group T0	Second Group T60
ESR (v.n.: > 15 mm)	29	< 15	31	< 15
PTT (v.n.: 22-36")	29	25	31.46	27
INR (v.n.: 1-1,2)	1,9	0,85	1,15	1,1
Pr. C (v.n.: > 0,5)	0,37	0,30	0,40	0,29
Fibrinogen (v.n.: 150-450)	309	286	370	350
Interleukins 1 (v.n.: < 7)	4,5	3	6,23	3,8
Interleukins 6 (v.n.: < 2)	0,8	0,7	0,9	0,8
Beta globulins (v.n.: 3,2-6,5%)	6,7	4,8	7,3	6,2

COMMENTS

Both psychologically, for the distortion of their image, and functionally, for the use of hand or limb not adaptable to the normal daily activities (bringing the shopping bags, sweing, dressing, grooming, etc), post-mastectomy lymphedema, rather than the impact on a purely clinical aspect (symptoms, possible evolutions of infectious disease, etc), has an impact exponentially mainly on the quality of life of the patients .

The approach to the therapy is always anxious, because it looks for a swift and definitive solution. We know that it is not so. Getting from drugs, a pharmacological support to the physical therapy and a block to the relapse inflammatory, represents already a satisfactory result in the treatment of this disease. It is essential that patients become conscious on this matter.

Our results show that the use of immune-enzymatic drugs in latent chronic inflammation, such as that of secondary lymphedema, is useful and appropriate, in line with the physic-anatomy-pathological characteristics of the secondary lymphoedema. In fact, clinically, in comparison with the neoplasia secondary edema, the onset and the gradual evolution, the uniform distribution to the whole limb, the poor response to the diuretics, the response to the complex physical treatment, the non-excessive increase in volume, if not in association to the inflammatory poussèes, and the hard-elastic character of the post-mastectomy edema give it its own characteristics.

Recent experimental observations of the causes on the base of neoplastic events militate for the occurrence of particular modifications at the tissue level, particularly at the load of extracellular matrix.

It is established that the extracellular matrix is able to turn the Ph of the pericellular environment towards the acidity, to change the oxide-reduction systems, to modify the local temperature; keeping the equilibrium in the chronic stasis' conditions is very important, above all for the prevention of the fearful infectious complications [21].

Therefore, while the onset of lymphedema from lymphatic axillary block is the result from the various traumatic findings (surgical wound, radiotherapy, etc), its evolution and stability depend on biochemical and histological structural changes, which find their expression at the tissue level. In 1896 Unna, describing the "stagnation concept", observed already that the lymph absorbing lipids inhibits the connective tissues. Later De Grot demonstrated how the lymph-node tissue was replaced by a fatty tissue, postulating the tendency of these tissues to become the one another [17]. This supposition reflects the nature of the post-mastectomy lymphedema: a chronic and stable lymphedema, without a particular tendency to remission into an undecline, which is compact, hard-elastic and unpainful. In the past, it met some observations, with Laser Doppler , an useful research system to mark if and how the micro-vessel motility is influenced by the change of the derma characteristics. In fact, where the edema was pasty and unpressable, for example on the hand's back, the chart

described more extensive and frequents waves, already in basic conditions, such as in all the conditions from protein overload. At the level of the forearm or arm, where the edema showed hard-elastic organization characters and it was poorly unpressable, there was a decrease of the base sphygmic parameters and an increase of them after a physical stimulus.

Considering all above mentioned, we came to the conclusions for the effective existence of a substrate's diversity, on which our recordings were performed [18,19,20]. This "static" situation in the clinical practice, takes quickly, if stimulated, the dramatic characters of inflammation: rubor calor, dolor and hyperemia occurs in a bright and debilitating way. Next to the acute event care in the first instance, the use of this therapeutic Protocol has been really efficiency in preventing inflammatory events in patients affected by this particular susceptible clinical picture, subjected to easy infections and sudden increases in volume for trauma of low values (sunburn, insect bites, small injuries during manicure, small household trauma).

From the results of our observations, we can tell how the association of kinesis-therapy and drugs with lymph and immune-stimulating actions, at the onset or stable stages of the post-mastectomy lymphedema, allows a better clinical evolution monitoring and assumes the lymph mobilization and the body component fragmentation, as we can note from the decrease of the subcutaneous thickening and the best treatment of the edema.

An improvement of quality of life is not only referred, but resulted also by the subjective decrease of the heaviness symptom confirmed objectively from the decrease in volume of the swelling in all the patients. All these patients have been satisfied for the recovery of their social life for a remission and a modulation of the reported symptoms.

All above mentioned encourage us to go on, extending this Protocol to a greater number of patients to validate furthermore the effectiveness.

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DRAINAGE PNEUMATIQUE (I-PRESS®) VERSUS DRAINAGE MANUEL IDE LYMPHOEDEME SECONDAIRE DU BRAS MÊME COMPRESSION, MÊME BENEFICE?

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SUMMARY

Pressotherapy is widely used but is often said to have lesser compression yield than manual drainage in upper limb secondary lymphoedema. This idea is difficult to wipe out. One of the main complaints is to find in the anterograde mode of nonprofessional material used or using. Since 1993, some pumps can work in a retrograde mode.

Objective: Our aim was to compare the effects of two light retrograde drainage options: a pneumatic and a manual one's.

Method: Retrograde pneumatic (a seven-compartment i-Press® 10th serial; Electronique du Mazet, France) and manual drainage is successively and randomly carried out on 9 women (71 years old) with an old (14 years) persistent upper limb lymphoedema that appeared 7 years after radio-surgical treatment against breast cancer. All volume variations are recorded continuously with a plethysmograph (JSI, SU4). Mercury gauges are fitted 4 inches (20 cm) above the elbow. The protocol of pneumatic drainage consisted of a standardised retrograde approach with constant pressure (40 mm Hg) (without regressive pressure) at a single to double-level of compression.

Results: By use of Kruskal and Wallis, one-way ANOVA on ranks, the effect of 40 mm Hg was similar (NS) when the drainage was applied manually (0.03 ml/100 mloed/mmHg/min) or using the pneumatic pump (0.03 ml/100 mloed/mmHg/min). After 15 min stopping management, improvement mainly persisted.

Conclusion: Whatever the technique used, there is no better edema reduction at 40 mm Hg: with the help of a same retrograde mode, light drainages give the same benefit.

MOTS CLÉS: drainage manuel, lymphœdème, membre supérieur, pléthysmographie, pressothérapie.

INTRODUCTION

Le drainage d'un œdème est le problème, pas la solution! Il ne peut y avoir une solution, un traitement unique, correct contre un problème qui lui est chronique et évolutif. Cependant, la base du traitement conservateur des œdèmes peut se résumer en trios mots: la répétition d'une compression intermittente. La conjonction de ces objectifs s'obtient par des exercices physiques réalisés sous bandes, par un drainage manuel (DM) ou par un drainage pneumatique (DP). Ces deux dernières techniques ont montré leur bénéfice dans la réduction des lymphœdèmes du membre supérieur. Mais peu a été étudié sur leur efficacité relative. Bien sûr, la comparaison des résultats de différentes études devient vite mission impossible. En effet, les différentes études n'utilisent pas la même définition/stratification des lymphœdèmes, le même type de drainage manuel, le même matériel/programme de drainage pneumatique, le même mode et type des thérapies additionnelles, la même stratégie thérapeutique générale, les mêmes mesures/modes d'objectivation.
Bien sûr, dans le traitement conservateur, il n'est pas possible de réaliser une étude en double aveugle. Par contre, comme les médicaments, un élément peut être comparé à un autre. Le challenge alors revient à ce que l'élément étudié donne de meilleurs résultats que l'autre pris comme gold standard. Pour cette étude, le DM a été pris comme gold standard; le DP comme candidat. En effet, le DM profite, encore aujourd'hui, d'un capital de confiance et de recommandations par consensus interposés. Il doit, probablement, son indication au fait que tout le monde accepte ses principes sans jamais les remettre en question.
Or il faut bien s'en remettre à la réalité clinique dénoncée par la plus grande sommité en la matière qu'est M. Földi: *«il est illusoire de prétendre traiter un lymphœdème par le seul DM»* [1]. Comme quoi, de tous les objectifs, le drainage est le plus difficile à feindre. En d'autres mots, tout consensus, toute recommandation ne fait pas loi. Le traitement d'un LO irréversible donne plus de fil à retordre.

Mais alors que le DM garde, malgré tout, bonne conscience, le DP a, aujourd'hui, encore souvent mauvaise presse. Le désintérêt pour le DP est une conséquence majeure de l'utilisation irréfléchie de pompes à usage domestique et des pompes pseudo-professionnelles. De plus, la première vocation de la pressothérapie pneumatique était la prophylaxie des TVP (1917 – Hartl) [2]. Celle-ci a retardé les progrès en lymphologie et l'abord du membre était limité au seul abord antérograde. Or un lymphœdème irréversible oblige à être abordé par son sommet. Une telle approche rétrograde est employée dans notre service depuis 1975 [3]. Mais il a fallu attendre 1992 pour que M. Quickels développe une nouvelle génération de pompe à multiprogrammations qui répondaient à cette attente. Les dix premiers programmes furent élaborés par Belgrado; les limites

furent étendues à 90 programmes par Theys. Avec un abord pneumatique rétrograde similaire à celui du DM, il devient donc possible de comparer le drainage pneumatique au manuel. Reste à régler la pression exercée à une valeur semblable: 40 mm Hg.

MÉTHODE

Ont complété l'étude prospective 9 femmes (âgées en moyenne de 71 a [54-83]) présentant un lymphœdème (LO) unilatéral (5 gauche; 4 droit) consécutif au traitement du cancer du sein. Le LO est apparu 21 mois [7-35] après le traitement radio-chirurgical. Il s'agit de LO évoluant depuis 14 années [7-32] sans amélioration et sans détérioration. Toutes ont été randomisées pour débuter soit par le DM, soit par le DP. Un intervalle de repos de 15 min est assuré entre chaque session de 16 min de traitement.
La pompe utilisée est un *iPress10f*® à 7 compartiments semi-superposés (Electronique du Mazet™, France). Ses paramètres (de compression, de mode rétrograde, de durée des cycles) sont réglés pour être le plus proche de ceux d'un DM. Le mode rétrograde n'a pas utilisé de gradient de pression. La compression s'exerçait séquentiellement dans une/deux alvéoles. Le drainage débutait à la racine du bras et progressait à reculons vers la périphérie tout en gardant une action centripète.
Afin de pouvoir, ultérieurement, comparer les présents résultats à ceux obtenus par l'emploi d'une autre récente pompe (Hydroven®) qui ne permet pas d'agir par appel-résorption, le choix du mode d'action s'est porté sur un programme de «fragmentation» (Fig. 1).
L'inflation débute dans l'alvéole supérieure, la 7ème; la pression de 40 mm Hg est maintenue 2s. La déflation est de 4s. Une fois dégonflée, la seconde vague reprend à la 6ème alvéole. Après 4s de dégonflement, cette 6ème alvéole est à nouveau gonflée. Et après avoir atteint sa pression de 40 mm Hg, la 7ème enchaine. Ensuite, la 6ème alvéole est dégonflée avant la 7ème. La troisième vague démarre ensuite par l'inflation de la 5ème alvéole. Et ainsi de suite, sans qu'il n'y ait pas plus de deux alvéoles gonflées en même temps, les vagues successives débutent plus bas pour remonter jusqu'à la racine du membre. Ainsi, la résultante des forces draine l'œdème dans le sens du flux de retour. Un cycle complet prend 6min15s.
La pression sélectionnée pour la session de DP a été de 40 mm Hg, soit la valeur supérieure de la marge de pression (30-40 mm Hg) préconisée pour le DM. Afin que le kinésithérapeute soit sensibilisé à une pression de 40 mmHg, il s'est exercé à masser par-dessus un brassard fixé sur le bras opposé, non-œdémateux. Le brassard était d'abord gonflé à 10 mm Hg puis dégonflé à 0 mm Hg. Le kinésithérapeute plaçait alors ses deux mains autour du brassard et le massait pour atteindre les 40 mm Hg requis. Bien sûr, ce n'est qu'une valeur approximative. Une discordance avec la réalité est inévitable ne fut-ce que du fait que la consistance du brassard diffère de celle d'un bras œdémateux. Une discordance peut également apparaître du simple fait qu'il est difficile de tenir compte de la force de glissement, de coulissage de la peau sur le derme, geste qui accompagne les manœuvres.
L'iPress® est équipé d'un contrôle - à deux temps - de la pression intra-alvéolaire. Le premier assure la fermeture de la valve quand

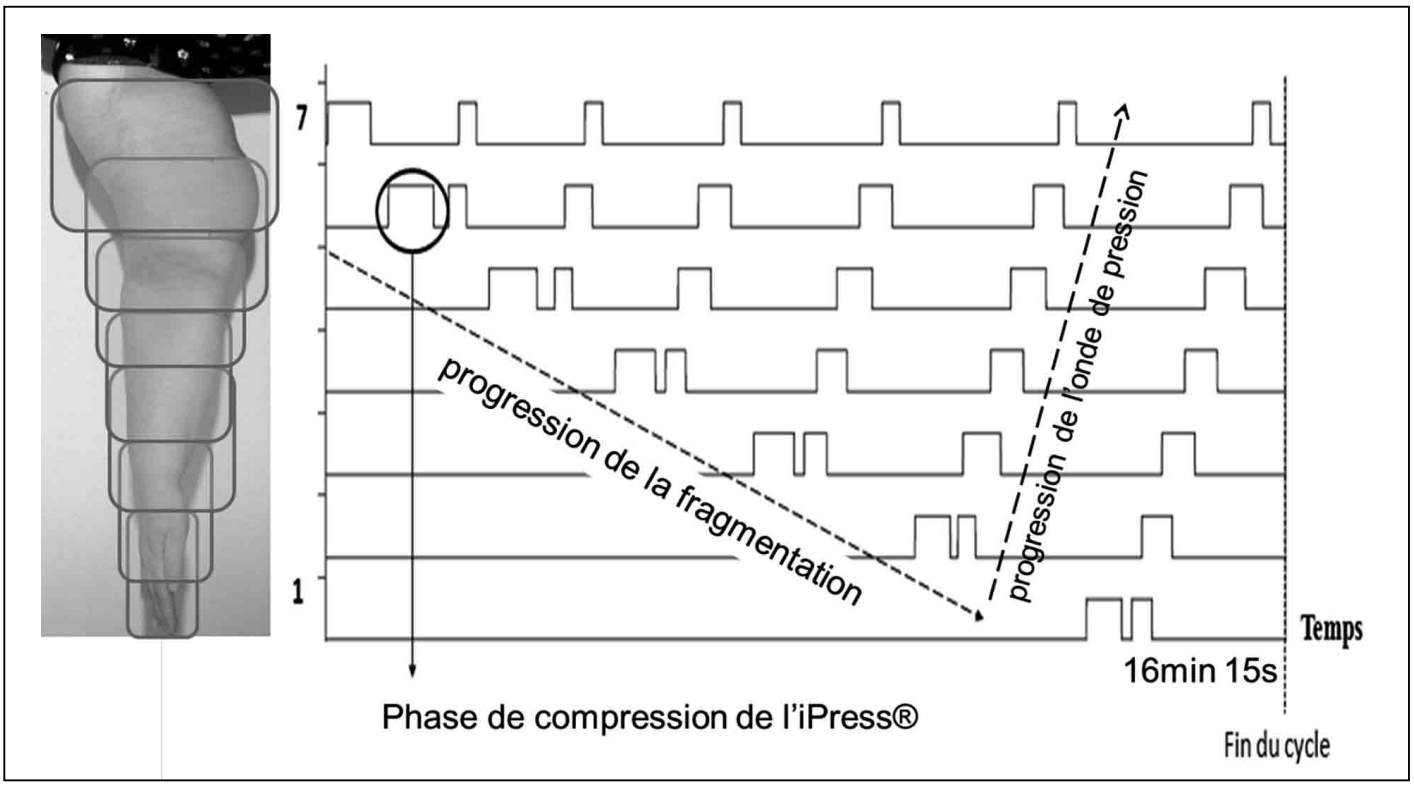

Figure 1 - Progression de l'onde rétrograde de fragmentation et progression de l'onde centripète de pression lors d'un cycle produit par une pompe pneumatique iPress®.

la pression désirée est atteinte. Cette correction permet de suivre la diminution du rayon de courbure due à la fonte de l'œdème. Le second temps corrige le gradient positif de pression produit lors de l'inflation de l'alvéole suivante qui la superpose.
Toutes les variations de volume sont enregistrées en continu par un pléthysmograph e (JSI, SU4). La jauge à mercure (Hg) est enroulée à la racine du bras à ± 20-25 cm au-dessus du coude, à mi-largeur de la 7ème et dernière alvéole pneumatique. Les participantes étaient assises sur une chaise confortable, l'avant-bras reposait sur la table, à hauteur du cœur (plan phlébostatique zéro). Il était en pronation; le coude tendu.
Pour évaluer la réponse du LO, la compliance a été prise comme base. Celle-ci exprime la relation entre la variation relative du volume (% δV/V) et la force (P). A noter que le paramètre «volume du gonflement initial» (Vi = vol segment gonflé – vol segment sain) ne donne pas une valeur précise de l'œdème: en effet, celui-ci est souvent emprisonné dans de la fibrose et de la graisse excédentaire, non-mobilisables. Ces composants ont une élastance très élevée; ce qui fait que – telle une éponge vidée ou remplie d'eau – ils reprennent presqu'immédiatement leur volume initial. Aussi, l'observation est prolongée de 15 min au-delà des 16 minutes des séances. Durant ce temps, quatre possibilités. Le volume revient directement au volume initial; c'est le cas des tissus spongiformes dont on vient de parler. Deux, le volume remonte plus ou moins lentement par réinfiltration des tissus. Trois, le volume reste stable à une valeur inférieure à l'initiale: le drainage du LO a été effectif. Quatre, le volume atteint une valeur supérieure à l'initiale par agglutination du LO et blocage du drainage à la racine du membre.
Pour comparer les deux modes de traitement, l'analyse statistique s'est faite sur base du test de Kruskal et Wallis, d'une ANOVA à deux critères pour mesures répétées.

RESULTATS

Avec un mode de «fragmentation» et une pression de 40 mm Hg, le volume du LO est progressivement mobilisé chez 8 des 9 participantes (Fig. 2). A la fin de la séance, il y eut un seul cas où aucune réponse n'a été produite tant par le DM que par le DP. Par unité d'œdème, de mm Hg et de temps, la décongestion de la

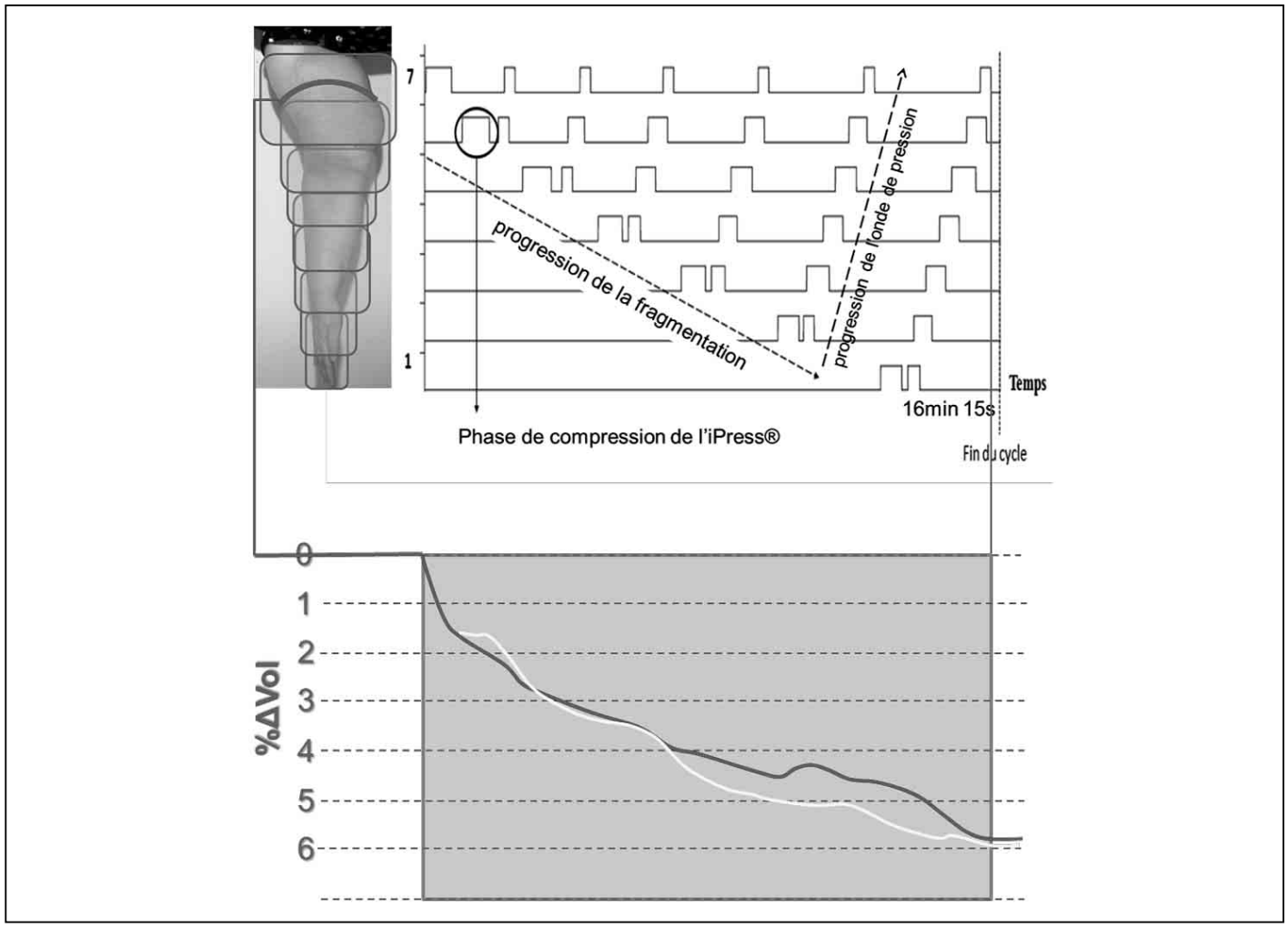

Fig. 2 - Réduction moyenne du volume relatif (%ΔVol ; ligne rouge) du tiers supérieur du bras tout au long d'un cycle de fragmentation pneumatique (iPress®) à 40 mm Hg. En comparaison (en jaune), le résultat obtenu par le drainage manuel (abord rétrograde, onde centripète de pression, ≤ 40 mm Hg).

portion supérieure du bras atteint 0.03 ml/100 mloed/mmHg/min que le drainage soit manuel ou pneumatique. Aucun cas ne montre une augmentation volumétrique ce qui traduirait une agglutination, un engorgement de l'œdème à la racine du bras. L'action ne s'atténue pas après les 16 premières minutes. Nos résultats préliminaires ne dégagent aucune influence de l'ordre de passage du DM/DP (ANOVA; p=0.571).

DISCUSSION

Le rendement d'une onde rétrograde de 40 mm Hg de P est similaire que le drainage soit manuel ou pneumatique. Ceci contredit l'hypothèse selon laquelle le DP est moins efficace que le DM. Au contraire, ces résultats confirment le constat de Forner [4] et autorisent à penser que les pompes /programmes de DP étudiés par ailleurs, étaient inappropriés aux vieux LO du bras tels que ceux étudiés ici.

En contrepartie, les résultats obtenus doivent être analysés avec prudence. En effet, une lecture superficielle pourrait amener à faussement conclure qu'il n'est plus nécessaire d'intégrer le DP dans les protocoles de LO. Or si ces deux techniques produisent le même résultat, le thérapeute ne doit pas oublier qu'un des secrets de la décongestion tient à la longueur de la compression/jour: le taux de réduction de l'œdème doit être supérieur à l'accumulation journalière d'œdème. 1-2 h/jour de drainage à 40 mm Hg sont insuffisants comparativement aux 22-23 h restantes sans compression. Tout au plus, 1-2h de traitement journalier se limitent à éponger l'accumulation quotidienne d'œdème. Avec une telle pauvre efficience, il n'est pas étonnant que Földi conclue que *«seul, le DLM ne réduira jamais un LO»* [1].Une plus grande décongestion nécessiterait l'emploi d'une compression plus élevée [5-7] ou plus longue [6] ce qui peut être obtenu, moins cher, par le DP.

Ainsi, le fait que cette valeur de 40 mm Hg a montrer une action dans nos vieux LO, ne fait pas d'elle la pression optimale, idéale. Celle-ci égale à 33 torr [8-9]. Le talent de cette équation énoncée par Vodder est de faire croire à une valeur quantitative de pression alors qu'elle n'en a pas [10]. En effet, dans la bouche d'un Vodder qui s'était intéressé à l'étude des langues, le nombre 33 pouvait être sans valeur définie. En fait, Vodder dit 33 comme le médecin demande au malade «dite 33» pour lui examiner le fond de la gorge. En fait, le malade n'a pas à dire le nombre 33 mais «n'importe quoi»; aussi, il répond par «aaaaaah».

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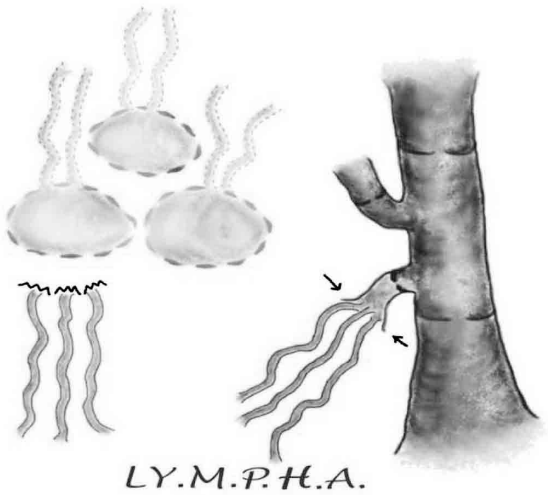

Lymphedema Prevention: from Genetics to Surgery

Searching for Better Lymphedema Patients' Quality of Life

September 25-27, 2014

NH Hotel Marina, Genoa (Italy)

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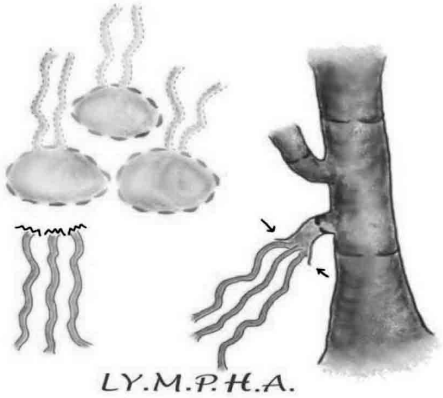

PROGRAM AT A GLANCE

September 25, 2014

11.00 a.m.	ESL Executive Committee Meeting
1.00 p.m.	ISL Executive Committee Meeting
3.30 p.m. - 6.30 p.m.	Congress Scientific Sessions
6.30 p.m. - 7.30 pm	Opening Ceremony
8.00 p.m.	Welcome Cocktail at Aquarium of Genoa

September 26, 2014

8.30 a.m.- 6.30 p.m.	Congress Scientific Sessions
1.00 p.m.	ISL Executive Committee Meeting
6.30 p.m.	ESL Executive Committee Meeting
8.30 p.m.	Gala Dinner at Meridiana Palace

September 27, 2014

8.30 a.m.- 1.30 p.m.	Congress Scientific Sessions
12.45 a.m.	Closing Remarks
2.00 p.m.	ESL General Assembly

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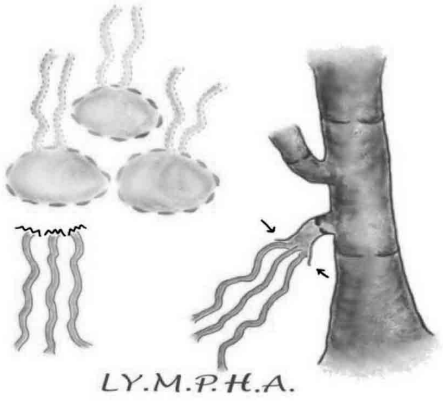

CONGRESS HIGHLIGHTS

- ✓ Genetic and Molecular Bases
- ✓ Anatomic Aspects
- ✓ Epidemiological Studies
- ✓ Pathophysiological Mechanisms
- ✓ Histopathological Findings
- ✓ Diagnostic Tools
- ✓ Therapeutical Options
- ✓ Primary and Secondary Prevention
- ✓ Lymphological Aspects in Pediatrics
- ✓ Quality of Life, Social and Health Aspects

SESSIONS

- ✓ Lectures
- ✓ Symposium
- ✓ Round Tables
- ✓ Summary and Panel Discussions
- ✓ Workshop/Courses
- ✓ Oral Presentations
- ✓ Posters and Videos

IMPORTANT DATES

Abstract Submission	March 31, 2014
Early Registration	June 1, 2014
Hotel Registration	June 1, 2014
Congress	September 25-27, 2014

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CIZETA MEDICALI S.p.A.
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the introduction of

VARISAN® TOP

• KNEE-HIGH WITH LATERAL ZIP

Medical compression stocking RAL certified for leg ulcers (Ccl. 3) 34 to 46 mmHg

GÜTEZEICHEN MEDIZINISCHE KOMPRESSIONS-STRÜMPFE RAL

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Through the establishment of an adequate compression therapy, the mechanisms decisive that cause the formation of an ulcer can be counteracted with great effectiveness and also offers advantages over the more traditional high therapy of bandages both in terms of therapeutic effectiveness (compression constant for all the day) both in terms of convenience of use and management by the patient.

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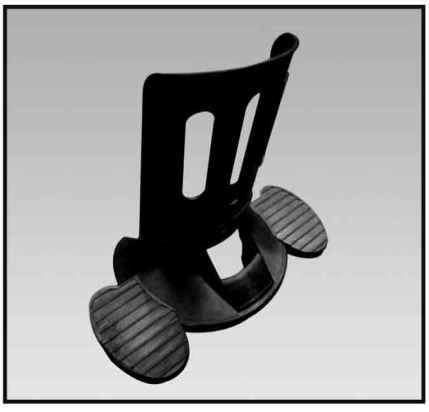

The elastic compression is the only recognized therapy against the chronic venous insufficiency.
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