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FACTORIAL ANALYSIS IN RADIONUCLIDE LYMPHOGRAPHY: ASSESSMENT OF THE EFFECTS OF SEQUENTIAL PNEUMATIC COMPRESSION

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ABSTRACT

The effects of intermittent pneumatic compression (IPC) in 12 patients with lower or upper limb lymphedema were studied using a computer-based technique (factorial analysis) of dynamic lymphoscintigraphy. After subcutaneous injection of radiocolloid into the first interdigital web space of the arm or leg, scintigraphic recordings consisted of 40 consecutive one-minute frames of both lower extremities or an edematous upper extremity. Pneumatic compression by Euroduc (6 patients) or by Lymphapress (6 patients) was applied during the final 20 minutes of the recording. A three factors factorial analysis (FA) was performed successively for each extremity. FA allowed "uncontaminated" curves to be displayed distinct from neighboring structures and corresponded to dynamic tracer activity in the interstitium, at the injection site, and within lymphatic vessels.

Based on the results of lymphatic vascular factorial analysis, a beneficial effect of IPC was detected in 18 of 22 limbs examined. FA processing suggested that IPC facilitated radiocolloid transport in the proximal portion of the limb and also propelled tracer from the injection site toward the lymphatics. The effect of IPC was evident as soon as external compression therapy began and was similar with either mechanical unit. Residual tracer activity in peripheral lymphatics 20 minutes after application of IPC was higher in the edematous as compared with the normal limbs.

FA processing is a new and potentially valuable method to evaluate the effects of external pneumatic compression in the management of peripheral lymphedema.

The natural evolution of untreated peripheral lymphedema is persistent swelling and progressive extremity dysfunction. Non-operative therapy usually includes in various combinations manual massage, intermittent pneumatic compression (IPC), elastic sleeves, and circumferential bandaging. Indeed, IPC with a single inflatable chamber was described more than 30 years ago (1).

Several reports document that use of pneumatic devices with a gradient pressure system leads to a reduction in limb volume in most patients (2-4). But, objective data of external compression (pressotherapy) on lymph propulsion are not available. Isotope lymphoscintigraphy, a technique based on the physiologic transport of an interstitially-labeled radiocolloid is theoretically a useful method for demonstrating changes in lymph kinetics after pressotherapy. Most isotopic studies have focused on radiocolloid uptake or disappearance at the injection site (3,5). The present study, however, attempts to assess by dynamic lymphoscintigraphy the effects of IPC on radiocolloid transport through lymphatic vessels.

Interpretation of dynamic lymphoscintigraphy can be performed by the stan-

dard method of regions of interest (ROI's) and time activity curves. Whereas the scintigraphic image represents the plane imaging of a three dimensional space, arbitrarily selected ROI's do not usually correspond to a single anatomic structure. The choice of ROI's is especially difficult in lymphedema as the lymphatic vessels are poorly differentiated from the interstitium. In order to improve imaging of the different spatial structures, including lymphatic vessels and the interstitial space, we used a computer-based-technique, factorial analysis or FA. The methodology and the software of FA have been previously developed by Barber, DiPaola and Bazin (6,7). The algorithm of FA uses the properties of a mathematical method, principal components analysis, to determine the factors by means of the main orthogonal components. The basic hypothesis is that the time evolution of each pixel or unit area in a dynamic study is a linear combination of a limited number of physiological components or factors. The interest of FA processing lies in the possibility of automatically extracting these factors common to a set of dixels, despite anatomic superimposition. The extrapolated factors are described by a factorial curve, time function and by a factorial image which represents the spatial contribution to the factorial curve. The factorial curves are represented superimposed on their corresponding factorial image.

Previous work suggested that FA is a useful method for interpreting lymph transport kinetics in patients with peripheral lymphedema (8,9). The present study examined the effect of IPC on lymph transport kinetics using dynamic lymphoscintigraphy and FA processing.

MATERIALS AND METHODS

A. Clinical Background

Dynamic lymphoscintigraphy was performed in 12 patients with either lower or upper extremity lymphedema. During the recording, IPC was applied using either a "Euroduc" or a "Lymphapress" mechanical device in 6 patients each, respectively.

The "Euroduc" unit consists of a five-compartment boot and produces intermittent and graded external compression. The compartments successively inflate and deflate. The highest pressure is delivered to the most distal part of the limb. A compression pressure less than 40mmHg is general used.

The "Lymphapress" unit consists of 10-12 overlapping cells. After complete inflation, all cells automatically deflate and then reinflate thereby creating a "milking" pressure gradient. The inflation-deflation cycle is short and allows the application of 70-90mmHg pressure without undue patient discomfort (2).

The patient population based on clinical data including venous Doppler examinations included two patients with upper limb lymphedema secondary to treatment of breast cancer (mastectomy and radiotherapy), and ten patients with lower limb lymphedema of which five were bilateral. Lymphedema was secondary to injury in one patient and was associated with venous dysfunction in six patients.

B. Scintigraphic protocol

Tc-99m rhenium sulfur-colloid (111MBq) was subcutaneously injected into the first interdigital space of both feet or one hand. (We prefer this injection site to an intradermal injection because the occasional puncture of a cutaneous blood vessel is more easily avoided.) Imaging of both legs and the edematous upper limb superior to the injection site was performed with a large field gamma-camera (General Electric 520T) connected to a data processing system (Sopha Simis V). The recording consisted of 40 consecutive one-minute frames of the limbs immediately after injection. The pressotherapy apparatus was assembled before injection and external compression was applied from 21 to 40 minutes after radiocolloid injection.

C. Recording analysis

The FA processing was applied to the dynamic image series of both legs or the edematous upper limb. It was performed successively for each leg, after "masking" the contralateral leg. A search for three factors was performed in each instance. The size of the trixel (elemental search unit) was 4x4 pixels. The calculation of the factors was done on the basis of the curves supplied by each of the studied trixels; the factorial curves were scaled to a common maximum value of 100. FA provided better curves, with less fluctuations, than curves gathered with ROI's. The analysis of factorial curves and images led to a recognition of independent physiological components contained in the dynamic lymphoscintigraphic recording.

RESULTS

The three factors extracted from dynamic recording FA were different in each patient. The physiological significance of the factors was determined by the activity distribution on the factorial image and by the shape of the associated factorial curve. It was possible thereby to identify factors corresponding to lymphatic vessels, localized tracer diffusion from the injection site and the interstitial space. Whereas the injection site factor was represented by a "decreasing" curve and the interstitial factor displaying the activity in soft tissues was represented by an "increasing" curve, the vessel factor curve depicting tracer influx into lymphatics was variable.

Aiming at a more thorough analysis of the effect of pressotherapy on lymph kinetics, we focused on curves displaying interstitial space or lymphatic vessel activity. We did not focus on curves displaying injection site activity because the concomitant images did not include the total area of the injection site; the imaging was performed superior to the injection site to avoid saturation effects of a high radioactivity source counting. Two examples of FA processing are shown in *Figs. 1 and 2.*

The mean factorial curves displaying the effects of IPC are shown in *Figs. 3-7*; they were smoothed by point averaging to eliminate activity fluctuations and to better depict pressotherapy effects.

A. Lymphatic factorial curves

Two types of response to IPC were identified from the lymphatic factorial curve analysis: the first type was a fall off of activity; the second type was increased radioactivity, which occurred as soon as IPC began.

1. Curves with IPC induced fall off of activity

Sixteen curves with a fall off of radioactivity after application of IPC was seen in 9 of 12 patients. These "drop off" curves were seen in 4 or 5 normal limbs and in 12 of 17 edematous limbs.

The mean curve showed a clear fall off in radioactivity immediately after IPC therapy started *(Fig. 3)*. The depletion rate (DR) of radioactivity in lymphatic vessels was determined by the ratio between the radioactivity reduction during the first 5 minutes of IPC therapy and lymphatic activity just before compression started or:

$$DR = \frac{\text{Activity (A) 20 min - A 25 min}}{\text{A 20 min}}$$

$\overline{DR}$ (mean ± SD) = 0.53±0.2.

There was no significant difference in the ratio of $\overline{DR}$ between the edematous and normal limbs (0.50±0.19 and 0.61±0.20, respectively). However, the mean curves diverged after five minutes of IPC therapy *(Fig. 4)*, with radioactivity regularly diminishing to zero in normal limbs but remaining largely constant in the edematous limbs.

The $\overline{DR}$ values associated with Euroduc (6 curves) and Lymphapress (10 curves) were similar (0.53±0.14 and 0.53±0.23, respectively).

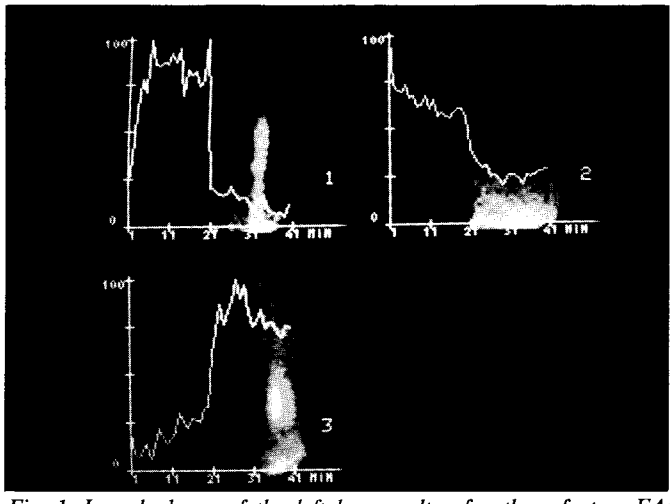

Fig. 1. Lymphedema of the left leg; results of a three factors FA; maximum count rate of each curve = A_M = 100. Factor 1: early radiocolloid influx into lymphatics with sharp fall in radioactivity at 21 minutes, one minute after the onset of intermittent pneumatic compression (IPC); A_{20} = 100, A_{25} = 17, A_{40} = 11. Factor 2: localized tracer diffusion from the injection site with slightly decreasing radioactivity at 21 minutes; A_{20} = 56, A_{25} = 30, A_{40} = 28. Factor 3: lymph influx at 21 minutes in another lymphatic pathway with segmental dilatation, A_{20} = 33, A_{25} = 87, A_{40} = 74.

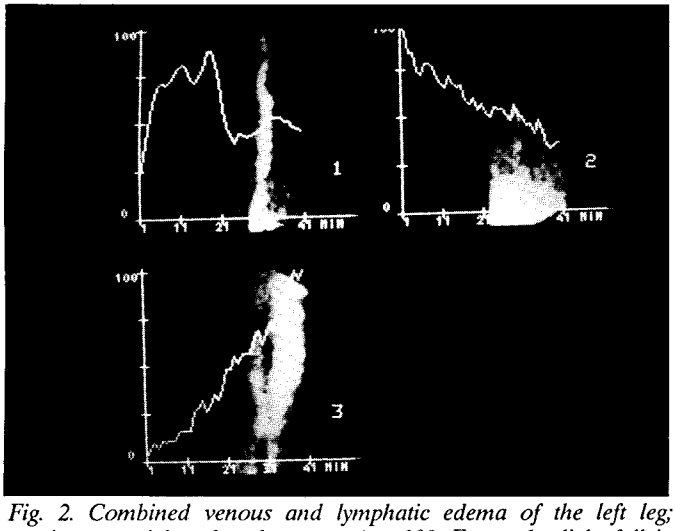

Fig. 2. Combined venous and lymphatic edema of the left leg; maximum activity of each curve = A_M = 100. Factor 1: slight fall in radioactivity in lymphatic vessel at 21 minutes, one minute after the onset of IPC; A_{20} = 90, A_{25} = 48, A_{40} = 42. Factor 2: localized tracer diffusion from the injection site; A_{20} = 55, A_{25} = 51, A_{40} = 35. Factor 3: increasing radioactivity in the interstitial space; A_{20} = 40, A_{25} = 48, A_{40} = 100.

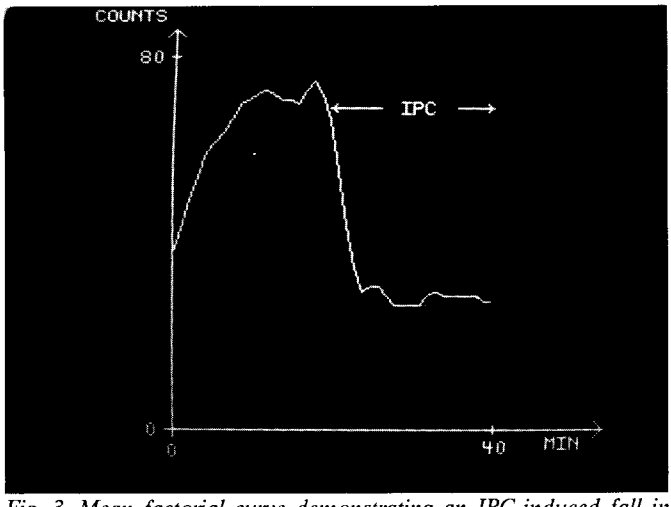

Fig. 3. Mean factorial curve demonstrating an IPC-induced fall in radioactivity of lymphatic vessel, in patients with or without edema; $A_{20}=64$, $A_{25}=30$, $A_{40}=27$.

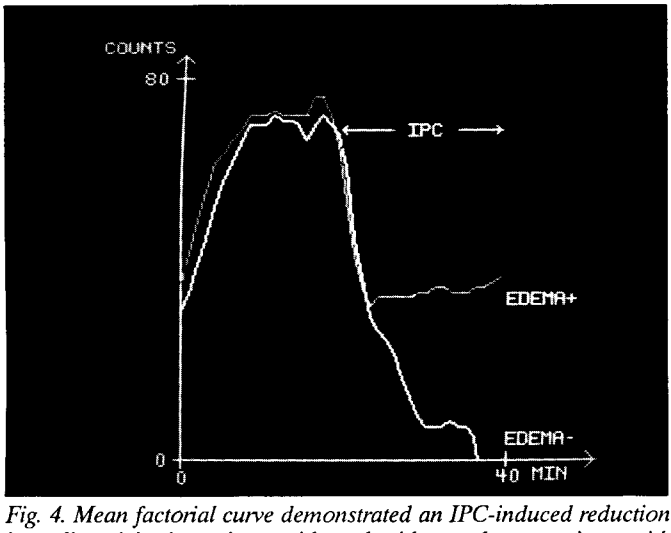

Fig. 4. Mean factorial curve demonstrated an IPC-induced reduction in radioactivity in patients with and without edema; patients with edema $A_{20}=68$, $A_{25}=34$, $A_{40}=38$; patients without edema $A_{20}=69$, $A_{25}=27$, $A_{40}=1$.

2. *Curves with IPC induced rise in activity*

Eleven curves in 7 patients displayed a rise in radioactivity and represented lymph influx secondary to pressotherapy. This curve pattern was identified in 8 of 17 edematous limbs and in 3 of 5 normal limbs *(Fig. 5)*.

The filling rate (FR) was determined by the ratio between tracer activity increase during the first 5 minutes after beginning IPC and activity at 25 minutes or:

$$FR = \frac{A\ 25\ min - A\ 20\ min}{A\ 25\ min}$$

$\overline{FR}$ (mean ± SD) was 0.64±0.21.

The $\overline{FR}$ values were similar in normal and edematous limbs (0.64±0.16 and

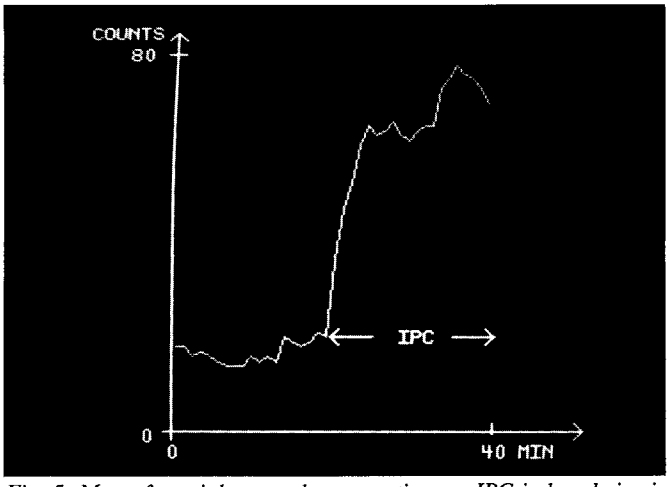

Fig. 5. Mean factorial curve demonstrating an IPC-induced rise in radioactivity of lymphatic vessel, in patients with or without edema, $A_{20}=23$, $A_{25}=64$, $A_{40}=69$.

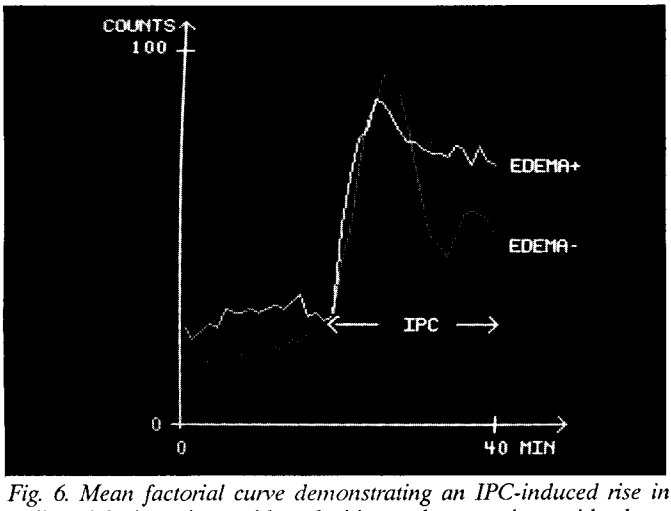

Fig. 6. Mean factorial curve demonstrating an IPC-induced rise in radioactivity in patients with and without edema; patients with edema $A_{20}=30$, $A_{25}=82$, $A_{40}=67$; patients without edema $A_{20}=30$, $A_{25}=84$, $A_{40}=49$.

0.63±0.24, respectively). On the other hand, the residual tracer activity 20 minutes after lymph influx was much more prominent in non-edematous limbs *(Fig. 6)*.

The $\overline{FR}$ associated with the Euroduc unit (6 curves), namely, 0.49±0.03 was lower than the $\overline{FR}$ value associated with the Lymphapress unit (5 curves) 0.81±0.20 ($P<0.01$).

B. Interstitial space curves

Thirteen curves representing interstitial space tracer kinetics were identified in 4 normal and in 9 edematous limbs. The mean curve is shown in *Fig. 7*. In order to evaluate if IPC displaced lymph towards the interstitial space, we compared the rate of activity increase between 4 minutes before and after starting pressotherapy or:

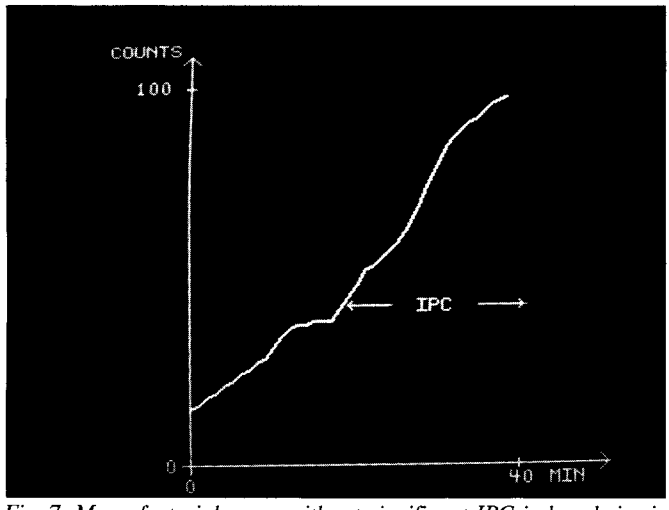

Fig. 7. Mean factorial curve without significant IPC-induced rise in interstitial radioactivity; $A_{16}=34$, $A_{20}=43$, $A_{21}=47$, $A_{25}=55$, $A_{40}=95$.

$$\frac{\text{A 20 min - A 16 min}}{\text{A 20 min}}$$

or

$$\frac{\text{A 25 min - A 21 min}}{\text{A 25 min}}$$

The values (mean ±SD) were 0.21±0.22 and 0.145±0.126, respectively, supporting that pressotherapy did not increase fluid movement through the interstitium.

C. *Global analysis of pressotherapy*

Factorial analysis demonstrated a beneficial effect of pressotherapy in 18 of 22 limbs studied either in propelling lymph from the leg to the calf (16 patients) or in propelling lymph from the injection site up the leg (11 patients). FA failed to display a change in lymph kinetics in 4 patients (2 with venous insufficiency, 1 with lymphatic hypoplasia, and 1 with lymphedema secondary to mastectomy with no identifiable axillary lymphatics).

DISCUSSION

Pressotherapy devices are widely used to manage peripheral lymphedema. This non-operative treatment modality is thought to mobilize excess interstitial fluid from subcutaneous tissues (2). Theoretically pressotherapy promotes tissue fluid flow through the interstitium or existing lymphatics (10) or, alternatively, induces opening of natural lymphatic-venous communications (11). Results of isotopic studies regarding the effects of IPC on tissue clearance of radiolabeled proteins are controversial. Partsch and Leduc suggest that the effect of IPC on limb volume is to facilitate primarily the resorption of water, and that the concentration of interstitial proteins are not diminished (5,12). Zelikovski, on the other hand, maintains that the tissue transport of radiolabeled albumin is increased after external compression and furthermore claims that the reduction in limb volume is accompanied by a greater clearance of interstitial proteins (3).

The principle of lymphoscintigraphy is based upon the physiological transport of interstitially injected radiolabeled macromolecules. Approximately 90% of injected colloidal particles are phagocytosed locally and transported into lymphatics by macrophages (13). The movement of radioactive particles through lymphatic vessels involves both diffusion and the migration rate of macrophages in lymph and indirectly therefore gauges the transport of lymph fluid.

Using factorial analysis we extracted from the dynamic lymphoscintigraphy the effects of IPC on lymph kinetics and peripheral tissues. Factorial curves and images demonstrated that IPC facilitated lymph propulsion cephalad through lymphatics, enhanced lymph transport from the injection site to lymphatic collectors but did not augment the movement of extracellular fluid from the injection site into the interstitium. In other words, the primary effect of external compression therapy was to promote an increased tissue fluid--lymph flux through existing lymphatics.

Based on the factorial curves, the greatest benefit of pressotherapy occurs during the first 5 minutes of external compression and seems to depend on the compliance of lymphatic collectors. Residual radioactivity in the lymphatic vessels, 20 minutes after the beginning of external compression, is higher in the edematous as compared with the normal limbs. Accordingly, to circumvent overloading of lymphatics at the base of the extremity and to facilitate pressotherapy, external compression may need to be combined with manual massage, both before and after pneumatic pressotherapy.

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