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Letter to Editor Open Access

Beyond Volume: A Pathophysiology-Driven Approach to Evaluating Physical Treatments for Oedema of Lymphatic Origin — Reflections of the Belgian Society of Lymphology

Bourgeois Pierre*[1], Adriaenssens Nele*[2,3], Barbieux Romain[4], Roman Mirela M[5], Harfouche Joseph[6], Leduc Olivier[4].

[1]Services of Dermatology and Vascular Surgery, Erasme and HIS-IZZ Hospitals, Université Libre de Bruxelles, Brussels, Belgium.
[2]Rehabilitation Research, Vrije Universiteit Brussel, Brussels, Belgium.
[3]Medical Oncology Department, Universitair Ziekenhuis Brussel, Brussels, Belgium.
[4]Lympho-Phlebology Unit, Department of Occupational and Environmental Physiology, Haute Ecole HE2B ISEK, Brussels, Belgium.
[5]Department of Mammo-Pelvic Surgery, CHU St Pierre, Université Libre de Bruxelles, Brussels, Belgium.
[6]Department of Physical Therapy, Delta Hospitals, Brussels, Belgium

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***Correspondence:**
*Dr. Bourgeois Pierre. Services of Dermatology and Vascular Surgery, Erasme and HIS-IZZ Hospitals, Université Libre de Bruxelles, Brussels, Belgium; Email: pierre.bourgeois@outlook.be.
*Prof. Adriaenssens Nele (PT, PhD). Rehabilitation Research, Vrije Universiteit Brussel, Brussels, Belgium; Email: Nele.Adriaenssens@vub.be.

All soft-tissue oedemas result from an imbalance between capillary filtration and lymphatic drainage. When lymphatic transport capacity is insufficient relative to fluid load, the oedema may be considered of lymphatic origin. In superficial tissues, these oedemas initially present as 'liquid' oedemas (with pitting) and may regress or diminish with light pressure. Conversely, oedemas associated with lymphatic lesions, reflux and dermal collateralisation may respond to specific drainage manoeuvres that mobilise fluid and redirect it towards territories with normal drainage. Both actions are incorporated into techniques described as manual lymphatic drainage (MLD) and may be used alone and/or in combination with compression therapy, e.g. intermittent pneumatic compression, bandaging and exercises[1].

However, the interest of MLD manoeuvres remains debated and studies have both supported and questioned their utility, either with negative conclusions (e.g. no benefit of MLD) or positive findings (sometimes reported as limited benefits)[2]. That said, a review of the literature highlights several methodological issues and we believe that an important conceptual issue remains insufficiently addressed: the evaluation of treatment response in oedema of lymphatic origin cannot be reduced to overall limb volume alone. In clinical practice, oedema may be regionally distributed, may involve superficial and deep lymphatic compartments differently, and may respond heterogeneously to treatment depending on the underlying anatomical and functional abnormalities.

This is particularly relevant when interpreting apparently negative trial findings in populations that may be clinically similar at the group level, yet markedly heterogeneous in lymphatic structure and compensatory drainage patterns at the individual level.

The central questions that should be asked for any given oedema, before considering therapeutic management and evaluating their responses - particularly physical treatment - are therefore as follows: which lymphatic lesions and/or functional abnormalities are responsible for this oedema, and can we adapt our physical interventions (MLD for lymphatic stimulation, techniques aimed at fluid resorption, or manoeuvres to open collateral pathways)

to optimise outcomes for the specific patient's oedema? From this perspective, imaging is not merely an adjunct to treatment; it is central to treatment interpretation.

Devoogdt et al.'s approach appears to be of interest[3]. Their use of near-infra-red fluorescence imaging after indocyanine green (ICG) injection (NIRFLI) in the hand for post-therapeutic upper-limb oedema can visualise the superficial lymphatic network but various criticisms and limitations have been raised regarding this technique. It is mainly limited by its inability to provide information on the deep lymphatic system and deep collateral pathways. A peripheral injection may also fail to demonstrate collateral routes at the root of the limb[4] where Medina-Rodriguez et al.[5] have shown opening of such collaterals after manual techniques in some patients using the same methodology but maybe not the same technique of MLD. Medina-Rodriguez et al. are using the MLD Leduc method.

Devoogdt et al. concluded negatively about the interest of MLD[6]. They studied changes in the areas of dermal reflux, the number of vessels and lymph nodes in 3 groups of patients with secondary breast cancer related upper limb edema subjected to different physiotherapeutic protocols (a "placebo" group, a group with traditional MLD and a group with fluoro-guided MLD). They compared the basal situation to those observed after 3 weeks of intensive treatment and 6 months of maintenance treatment. Their initial hypothesis was that patients receiving fluoro-guided drainage would have an increase in the number of lymphatic vessels draining the areas of dermal reflux, a decrease in these areas of reflux and an increase in the number of lymph nodes receiving lymph from these areas of lymphatic stasis. Their results show no difference between the 3 groups and they conclude that MLD has no benefit over the other components of complex physical/decongestive therapy (CP/DT). However, Devoogdt et al.[7] also observed a significant decrease in dermal backflow, lymphatic vessel count, and visible lymph nodes after treatment. They did not discuss these findings, but we argue they may reflect ICG-induced lymphatic dysfunction rather than treatment benefit.

Weiler and Dixon's study[8] appears to be interesting in this context. These authors analysed in vivo the consequences on the function of rat tail lymphatic vessels (at 1, 2 and 4 weeks) of ICG injection (pre-mixed with BSA) and its consequences on the lymph nodes accumulating this tracer. ICG remained visible in the tails of the animals for up to 2 weeks after injection and was accompanied (compared to controls) by significant decreases in lymphatic function at week 1 and enlargement of the lymph nodes draining this ICG (with an increase in size of more than 350% at week 1 and nearly 200% at week 2). The influence of ICG injection on the lymphatic system therefore seems to be delayed rather than immediate and seems to require a long pre-exposure to the molecule to show an effect. The decrease in dermal reflux, lymphatic vessel count, and lymph node numbers observed by Devoogdt et al. could therefore reflect a decrease in the function of the lymphatic system, of the lymphatic vessels to extract ICG from injected tissues and to transport it to and into the lymph nodes.

Table 1. Comparison between lymphoscintigraphy with 99mTc-labelled HSA nanocolloids and near-infra-red fluorescence lymphatic imaging with ICG.

	Lymphoscintigraphy with 99mTc-labelled HSA nanocolloids	**NIR fluorescence lymphatic imaging (NIRFLI) with ICG**
Field of view	Whole-body imaging possible (from feet to head for lower limb oedemas).	Local and regional imaging; field of view limited to camera and injection region.
Depth visualised	Visualises both superficial and deep lymphatic vessels and nodes ('full' anatomy and morphology of the lymphatic system).	Visualises only superficial lymphatic structures; deep lymphatic vessels and nodes are not seen when more than about 2 cm below the skin surface.
Dimensionality	Two- and three-dimensional imaging possible when combined with CT and/or MRI.	Two-dimensional surface imaging; 3D information requires additional techniques.
Quantification	Intrinsically quantitative approach; standardised tracer injection and computer-assisted analysis allow assessment of extraction, time-to-node, nodal accumulation and limb asymmetry.	Primarily qualitative and semi-quantitative; visual assessment of patterns, contractile activity and tracer progression along vessels.
Functional information	Provides global functional assessment of superficial, deep and collateral lymphatic transport depending on injection protocol.	Provides detailed visualisation of superficial vessel contractility, valve competence and local reflux patterns.
Radiation / toxicity	Uses a radioactive tracer and requires a nuclear medicine service; not indicated in young subjects, pregnant or lactating women, or young women of childbearing age.	No ionising radiation but indocyanine green may exert toxic effects on the lymphatic system and can theoretically aggravate oedematous conditions; repeated injections should be used with caution.
Practical aspects	Widely available in nuclear medicine; not "visual" for surgeons at the bedside; costs vary and are reimbursed by some national health insurance systems.	"Visual" and "direct" imaging that is attractive for surgeons; availability still limited in many centres; costs are often not yet reimbursed by national health insurance systems.

Additionally, various criticisms and limitations have been raised regarding this technique, the most important being by its inability to provide information on the deep lymphatic system and deep collateral pathways. Lymphoscintigraphy has been largely used by our group to assess - depending on the injection protocol used - both superficial, deep and collateral lymphatic systems and provide a broader functional view of lymphatic transport[9-13]. Table 1 presents a comparison between lymphoscintigraphy with 99mTc-labelled HSA nanocolloids and near-infra-red fluorescence lymphatic imaging with ICG. Using MLD manoeuvres, we showed that lymphoscintigraphically guided manual lymphatic drainage is more effective than standard 'blindly applied' MLD to mobilize lymphatic loads[11] but also to open collateralization pathways[12].

Accordingly, the key question is not simply whether MLD 'works' in a general sense. Rather, we must determine in whom it works, under which anatomical conditions, and for which therapeutic objective. A given oedema may reflect very different combinations of superficial and deep lymphatic dysfunction, reflux and collateralisation, and each pattern will respond differently to specific drainage manoeuvres. Trials that do not stratify patients according to lymphatic imaging findings therefore risk underestimating treatment benefit in subgroups for whom drainage manoeuvres are physiologically relevant, while diluting effects in those for whom alternative physical strategies are more appropriate.

Negative overall results should not automatically be interpreted as evidence that MLD lacks value in principle; they may instead reflect inadequate phenotyping of the treated population. For instance, a patient with isolated deep lymphatic failure may not respond to superficial MLD, whereas one with superficial dermal backflow might show a clear clinical benefit. We therefore advocate for a more individualised and pathophysiology-driven approach to research in lymphatic oedema. Future studies should incorporate imaging-based characterisation of lymphatic abnormalities, distinguish between superficial and deep transport disorders where possible, and relate treatment choice to the specific drainage pattern observed in each patient. Such an approach would improve patient stratification, strengthen mechanistic interpretation, and provide a more clinically meaningful basis for evaluating physical treatments, including MLD.

In conclusion, evaluation of physical treatments for oedema of lymphatic origin cannot be reduced to changes in limb volume alone. A pathophysiology-driven, imaging-guided approach is required to understand which patients benefit from MLD and related physical interventions, and under which anatomical and functional conditions. Future research should, first, include systematic pre-trial imaging (lymphoscintigraphy or NIRFLI with appropriate caution) to characterise lymphatic lesions, reflux patterns and collateral pathways, and to stratify patients accordingly. Second, studies should distinguish, where possible, between superficial and deep lymphatic transport disorders and analyse treatment responses separately in these phenotypes. Third, drainage pathway counts and other imaging-derived functional parameters should be incorporated as secondary endpoints alongside limb volume, in order to better capture mechanisms of action and true clinical benefit.

Take home messages

- Do not rely on limb volume alone when judging response to physical treatment in lymphatic oedema; always interpret volume change in the context of underlying lymphatic anatomy and function.
- Whenever feasible, obtain imaging (lymphoscintigraphy or NIRFLI with caution) to document superficial, deep and collateral drainage patterns, and use this information to individualise MLD and other physical interventions.
- Be aware that techniques such as NIRFLI may themselves influence lymphatic function, and interpret imaging changes in light of potential tracer-induced toxicity.
- When trial results appear negative, consider whether the studied population was sufficiently phenotyped; a lack of stratification by lymphatic imaging should not be taken as definitive evidence against the usefulness of MLD in well-selected patients.

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