

Phlebolympheidema and bioimpedance: general concepts and personal experience

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Abstract Limb phlebolympheidema (PLE) is characterized by an accumulation of fluid in the interstitial space and it is caused by an impairment of venous and lymphatic flow. From the pathophysiology point of view, PLE may be of primary and (more frequently) secondary type; it mostly occurs in post-thrombotic syndrome, after trauma, in varicose veins with dysfunctional centripetal flow pumping mechanisms, in proximal vein obstruction syndromes (e.g. May-Thurner syndrome), in phlebolympatic congenital malformations (e.g. Klippel Trenaunay syndrome). To improve diagnostics of limb PLE, bioimpedance technology has been proposed, both under the form of bioimpedance analysis and under the form of the more accurate bioimpedance spectroscopy (BIS); the latter is based on multiple frequencies which investigate tissues with a higher degree of accuracy, compared to bioimpedance analysis which is usually based on one or two frequencies. By means of BIS it is possible to measure and monitor the variations in the extracellular (interstitial) and intracellular fluids as well as in the tissue composition. More importantly, this biotechnology permits a segmental assessment of the edema, thus both limbs may be individually investigated, as well as the fluid accumulation/tissue conditions of the single limb or part of it may be assessed. Similarly, this method may contribute to monitor therapy outcomes and it may also have a relevant prognostic role after oncologic therapy (e.g. breast cancer treatment) to anticipate the risk of lymphedema/PLE onset. Beside the classical L-Dex index which compares the two limbs in terms of impedance, the analysis of raw data permits to extrapolate absolute figures concerning a series of relevant parameters such as: a) resistance which is the expression of the extracellular fluids, b) reactance and c) cell membrane capacitance (CMC) which are both

indexes of tissue composition/health. Furthermore, BIS provides a wide range of data concerning body composition in terms of fat and lean mass, water and general health (for example through phase angle index); this way, a more comprehensive approach to the possible concomitant chronic diseases (e.g. obesity, cardiovascular diseases, diabetes, cancer) in the PLE patient is pursued.

Keywords bioimpedance, spectroscopy, phlebolympheidema, edema, tissue

Bioimpedance and Phlebolympheidema

Michael Foldi fundamentally considered limb edema always a matter of lymphatic impairment, which may derive from a functional overwhelming of the lymphatic system/transport and/or from a morphologic alteration of the lymphatic system¹. This ingenious and simplified vision helps understanding the relevance of the lymphatic system in any form of edema, both if it is due to lymphatic system disease (lymphedema) and if it is a result of a lymphatic function saturation and overload (edema due to renal/cardiac/metabolic diseases, drugs, etc.)^{1,2}.

By virtue of the innovative data published by Levick and Michel³ which confirm that lymph flow is responsible for the centripetal drainage of the vast majority of interstitial fluid and macromolecules in the limbs, scientific research has increasingly focused on the role of the lymphatic system in the pathophysiology of any edema of limbs, organs and tissues.

About 26 years ago we published a book on phlebolympheidema (PLE)², with the aim of highlighting

the issue of a specific limb edema which features the simultaneous presence of a venous and lymphatic dysfunction and/or morphologic pathology. Furthermore, in that same text we proposed a series of diagnostic and therapeutic approaches to improve the management of this specific limb condition, characterized by an accumulation of fluid in the interstitial space caused by an impairment of the venous and lymphatic drainage.

From the pathophysiology point of view, PLE may be of primary or (more frequently) secondary type⁴; actually, a concomitant lymph and venous stasis mostly occurs in post-thrombotic syndrome (PTS), after trauma, in varicose veins with dysfunctional mechanisms which help propelling centripetally lymph and blood (e.g. dysfunction of leg and diaphragmatic pumps), in proximal vein obstruction syndromes (e.g. May-Thurner syndrome), in phlebolympathic congenital malformations (e.g. Klippel Trenaunay syndrome).

The diagnostic approach to limbs affected by PLE is mainly based on the clinical examination and on a few instrumental exams, such as colour-duplex ultrasound investigation and, more selectively, lymphoscintigraphy. Many more techniques have been proposed in the last decades to quantify limb edema and volumes, as well as to detect the basic pathologies at the root of the edematous limb; however, the vast majority of them are not currently employed in routine clinical practice and still a few limitations exist.

To improve diagnostics of limb PLE, bioimpedance technology has spread among health practitioners, both under the form of bioimpedance analysis and under the form of the more accurate bioimpedance spectroscopy (BIS), the latter being based on multiple frequencies which investigate tissues with a higher degree of accuracy. By means of BIS it is possible to analyze the variations in the extracellular (interstitial) and intracellular fluids, but also in the tissue composition⁵⁻⁷.

More importantly, BIS permits a segmental assessment of the edema, thus the single limb or a part of it may be investigated; basically, by means of multiple frequency bioimpedance it is possible to assess adequately both unilateral and bilateral lymphedema or PLE. This means that each limb or just the thigh, the leg, the forearm etc., may be selectively measured as to the fluid content and as to the changes in their tissues⁵⁻⁸.

Specifically, in a randomized controlled study assessing efficacy and safety of two different compression stocking regimes on 94 patients operated for varicose veins⁸, we assessed a series of clinical and BIS outcomes, so to detect edema and tissue changes. We recorded an improvement of BIS findings 7 days after the intervention in both groups, whereas BIS results deteriorated at 40 days;

more in details leg reactance and limb L-Dex improved in the higher compression group at day seven and 40 ($p=0.039$ and 0.012 respectively), whereas the residual BIS modifications were not statistically significant between the two groups.

Furthermore, this method may contribute to monitor therapy outcomes and it may also have a relevant prognostic role; in fact, BIS may signal, with significant anticipation over the clinical manifestation, the onset of a limb lymph stasis and of tissue changes after specific treatments, for example after breast cancer therapy⁹.

Of interest, it was shown that breast cancer-related upper limb lymphedema itself may be considered as a PLE in the vast majority of the cases, due to the fact that the patients who undergo surgery and radio/chemotherapy show a frequent association of upper extremity lymphedema with some obstruction/reflux in the axillary/subclavian veins^{10,11}.

Similar, even more pronounced, detrimental changes in the lymphatic vessels/nodes have been detected in the vast majority of the lower limbs affected by PTS¹²; after deep vein thrombosis numerous and progressive changes in the satellite lymphatic system of the affected veins have been demonstrated, which explains the occurrence of PLE and tissue changes in the cases of PTS, especially at mid-long term. The predictive value of the BIS exploration could be valuable also in these PTS patients, in order to assess the risk of PLE and principally of skin changes and veno-lymphatic ulcers.

Our personal experience

A number of specific data can be extrapolated from BIS exploration of the total body and especially of the lower and upper limbs. Actually, beside the classical L-Dex (lymphatic index) which is an absolute number and compares the two limbs in terms of ratio of impedances, the analysis of raw data has permitted to extrapolate absolute figures concerning a series of relevant parameters related to the tissue and edema condition: a) resistance, b) reactance and c) cell membrane capacitance (CMC); while resistance is the expression of the extracellular fluids, reactance and CMC are both parameters regarding tissue composition/health^{5-8,13-18}.

In a specific study¹⁶ investigating short-term (6 days) changes of fluid and tissues in lymphedema limbs after an intensive combined treatment, relevant BIS modifications were reported. For example, whole limb L-Dex decreased by 21.5%, total limb resistance at day 0, 3 and 6 was 200.4, 225.7, and 237.5 respectively; leg resistance improved from 117.5 to 150 at the end of the therapy; similar modifications occurred in limb reactance and, of great interest, the correlation volumetry/bioimpedance spectroscopy was

found for all BIS parameters. Furthermore, BIS provides a wide range of data concerning body composition in terms of fat and lean mass, water and general health (for example through phase angle index); this way, a more comprehensive approach to the biologic issues related to several concomitant chronic diseases (e.g. obesity, cardiovascular diseases, diabetes, cancer) in the PLE patient is possibly pursued.

It is expected that PLE has a different tissue composition (at least at the early stages) and a different macro-molecule/water content compared to lymphedema, by virtue of the different etiopathogenesis of these two pathologic conditions; as lymphatic system typically reabsorbs larger molecules (e.g. proteins) from the interstitial matrix, when lymphedema occurs a high-protein stagnating fluid takes place, which is different from the low-protein edema typical of cardiac/renal edema. PLE may have a combined biochemical composition and these different chemical-physical features may be ideally assessed through BIS, for scientific or diagnostic purposes especially, but also for a prognostic evaluation.

One study of ours addressing the issue of PLE changes after nutraceutical administration for 90 days¹⁸ showed an increase in the average value of leg RES from 143.4 to 149.6 ($P < 0.01$) and of leg reactance from 10.4 to 11.1 ($P < 0.04$), whereas a lower and non-significant improvement of RES and REA values was detected for the total limb.

Similarly, a reduction of the dis-homogeneity of the subcutaneous edema was found in limbs affected by edematous lipodystrophy after a specific nutraceutical intake¹⁴; in fact, L-Dex passed from 3.97 at the enrolment to 1.17 at the end of the treatment. Lastly, also the application of a specific electromedical biotechnology in lipedema and lymphedema limbs resulted in an average L-DEX percentage reduction of 21%¹⁵.

Beyond all the hemo-lymphodynamic and fluid issues elicited in PLE and in lymphedema, it was clearly highlighted that the interstice represents a core element in the generation/evolution of any edema and in the consequent tissue derangement. Investigation of tissues and of interstice is possible through a few biotechnologies, among which BIS proved to be probably the most interesting; furthermore, segmental bioimpedance methodology permits to compartment the skin and subcutaneous tissues investigation where necessary (e.g. in the distal area of the lower leg).

Our twenty year experience with BIS started with the L-Dex use, in order to investigate and quantify mainly unilateral lymphedema^{4,7}; subsequently, broader applications of BIS technology were exploited in a series of clinical-instrumental studies that we performed on

patients affected by PLE or lymphedema. Moreover, we assessed limb edema and tissue variations occurring after different forms of treatment, such as varicose vein treatments, complex integrated decongestive treatment for LYM, drugs or nutraceuticals intake, electro-medical device application^{4,7,8,13-18}.

By means of a specific device, L-Dex U400 (ImpediMed, Australia), the lower and upper limbs were investigated to get segmental measurements, but also body data were collected to have a broader picture of the patients. From the technical point of view, the measurement of the impedance of the tissues in the limb and/or in its segment was performed through the passage of alternating current with a maximal 200 μ A amplitude; the multiple frequencies of the current passage (spectrum) ranged from 3 to 1000 kHz.

Notoriously, impedance vector has two components, namely resistance and reactance, which are measured in Ohms through BIS methodology and which respectively express the extracellular fluid content and the trans-cellular membrane opposition to current passage; together with reactance, there is another parameter, CMC, which is extrapolated from raw data to assess quantitatively the tissue composition and specifically the overall cell membrane "health". Lastly, the "older" L-dex parameter was also calculated in order to compare the impedance, thus the fluid and tissue condition, between the two limbs.

Regrettably, L-dex and impedance are significantly influenced by the tissue condition (reactance naturally influences impedance vector calculation), hence an edematous limb with a high degree of fibrosis may result in a high impedance, even in the presence of a relevant fluid content. This limitation has been overcome by the use of the raw data, as per the description above and below.

It is generally accepted that the higher tissue resistance, the lower the fluid content, the higher the tissue reactance and CMC, the "healthier" the tissue^{4,6,8}. Following to the validated protocols, resistance values were usually calculated at the theoretical 0 kHz frequency, whereas reactance and CMC values were extrapolated at the frequency of 50.0078 kHz^{4,6,8,14-17}.

Concerning the detection of edema variations, BIS may elicit fluid changes more reliably than classical volumetry methods (e.g. tape measurement, water volumetry, opto-volumetric or laser-based methods), as bioimpedance technology may potentially discriminate fluids from tissue (e.g. fat/lean mass) variations. Similarly, BIS may overcome some issues of the simpler tonometry investigation.

Overall, BIS proved an extremely useful biotechnology, both for the clinical management of the

patients affected by PLE and lymphedema and for scientific purposes. Further developments are expected to improve

the potentials of this technology in vascular diseases, but also more broadly in biomedical science.

References

- 1) Foldi E., Foldi M, Clodius L. The lymphoedema chaos: a lancet. *Ann Plast Surg* 1989; 22: 505–515.
- 2) Cavezzi A, Michelini S. Phlebolympoedema: From Diagnosis to Therapy. Bologna: Ed. P. R. Communications; 1998:47-53. ISBN: 88-900300-1-1
- 3) Levick JR and Michel CC. Microvascular fluid exchange and the revised Starling principle. *Cardiovasc Res* 2010; 87: 198–210
- 4) Cavezzi, A. (2018). Diagnosis and Management of Secondary Phlebolympoedema. In: Lee BB, Rockson S, Bergan J (eds) *Lymphedema*. Springer, Cham. DOI: [10.1007/978-3-319-52423-8_73](https://doi.org/10.1007/978-3-319-52423-8_73).
- 5) Cornish BH, Chapman M, Hirst C, Mirolo B, Bunce IH, Ward LC, Thomas BJ. Early diagnosis of lymphedema using multiple frequency bioimpedance. *Lymphology*. 2001 Mar;34(1):2-11. PMID: 11307661.
- 6) Cornish BH, Thomas BJ, Ward LC, Hirst C, Bunce IH. A new technique for the quantification of peripheral edema with application in both unilateral and bilateral cases. *Angiology*. 2002 Jan-Feb;53(1):41-7. DOI: [10.1177/000331970205300106](https://doi.org/10.1177/000331970205300106). PMID: 11863308.
- 7) Cavezzi A, Schingale F, Elio C. Limb volume measurement: from the past methods to optoelectronic technologies, bioimpedance analysis and laser based devices. *Int Angiol*. 2010 Oct;29(5):392-4. PMID: 20924339.
- 8) Cavezzi A, Mosti G, Colucci R, Quinzi V, Bastiani L, Urso SU. Compression with 23 mmHg or 35 mmHg stockings after saphenous catheter foam sclerotherapy and phlebectomy of varicose veins: A randomized controlled study. *Phlebology*. 2019 Mar;34(2):98-106. DOI: [10.1177/0268355518776127](https://doi.org/10.1177/0268355518776127). Epub 2018 May 12. PMID: 29754530.
- 9) Kilgore LJ, Korentager SS, Hangge AN, Amin AL, Balanoff CR, Larson KE, Mitchell MP, Chen JG, Burgen E, Khan QJ, O'Dea AP, Nye L, Sharma P, Wagner JL. Reducing Breast Cancer-Related Lymphedema (BCRL) Through Prospective Surveillance Monitoring Using Bioimpedance Spectroscopy (BIS) and Patient Directed Self-Interventions. *Ann Surg Oncol*. 2018 Oct;25(10):2948-2952. DOI: [10.1245/s10434-018-6601-8](https://doi.org/10.1245/s10434-018-6601-8). Epub 2018 Jul 9. PMID: 29987599.
- 10) Svensson WE, Mortimer PS, Tohno E, Cosgrove DO. Colour Doppler demonstrates venous flow abnormalities in breast cancer patients with chronic arm swelling. *Eur J Cancer*. 1994;30A(5):657-60.
- 11) Pain SJ, Vowler S, Purushotham AD. Axillary vein abnormalities contribute to development of lymphoedema after surgery for breast cancer. *Br J Surg*. 2005;92(3):311-315.
- 12) Partsch H, Mostbeck A. Die Mitbeteiligung des Lymphsystems beim postthrombotischen Syndrom [Involvement of the lymphatic system in post-thrombotic syndrome]. *Wien Med Wochenschr*. 1994;144(10-11):210-3. German. PMID: 7856187.
- 13) Cavezzi A, Paccasassi S, Elio C. Lymphedema treatment by means of an electro-medical device based on bioresonance and vacuum technology: clinical and lymphoscintigraphic assessment. *Int Angiol*. 2013 Aug;32(4):417-23. PMID: 23822945
- 14) Elio C, Intilangelo F, Cavezzi A, Dimitrova G, Paccasassi S, Sigismondi G (2014) Treatment of Edematofibrosclerotic Panniculitis (Cellulite) and of Localised Adiposity with Extracts of Birch, Melilotus, Orthosiphon, Bromelin and Red Vine Leukocyanidine: Results from a Single-Centre Observational Prospective Study. *Journal of Cosmetics, Dermatological Sciences and Applications*, 4, 166-172. DOI: [10.4236/jcda.2014.43023](https://doi.org/10.4236/jcda.2014.43023)
- 15) Elio C, Guaitolini E, Paccasassi S, Rosati N, Cavezzi A. Application of microcurrents of bioresonance and transdermal delivery of active principles in lymphedema and lipedema of the lower limbs: a pilot study. *G Ital Dermatol Venereol*. 2014 Dec;149(6):643-7. PMID: 25664822.
- 16) Cavezzi A, Urso SU, Paccasassi S, Mosti G, Campana F, Colucci R. Bioimpedance spectroscopy and volumetry in the immediate/short-term monitoring of intensive complex decongestive treatment of lymphedema. *Phlebology*. 2020 Oct;35(9):715-723. DOI: [10.1177/0268355520938578](https://doi.org/10.1177/0268355520938578). Epub 2020 Jul 6. PMID: 32631170.
- 17) Cavezzi A, Colucci R, Bastiani L. Short-term effects of a maqui-based nutraceutical on heart rate variability, psycho-physical resilience and on a few metabolic biomarkers: a randomized controlled study. *J Complement Integr Med*. 2022 Nov 24;20(2):487-496. DOI: [10.1515/jcim-2022-0292](https://doi.org/10.1515/jcim-2022-0292). PMID: 36420523.
- 18) Campana F, Urso S.U., Paccasassi S, Colucci R, Cavezzi A Preliminary experience with a multicomponent nutraceutical (melilotus, rutin and bromelain) on phlebolympoedema of the lower limbs *Acta Phlebologica* 2017 April;18(1):29-35 DOI: [10.23736/S1593-232X.17.00382-4](https://doi.org/10.23736/S1593-232X.17.00382-4)