

A Review of Investigation Modalities of Lymphedema

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Abstract

Objective: Thanks to the increasing interests in lymphedema surgery, there has been an emergence of new investigation modalities. Apart from making the diagnosis, new investigations are tailored to assess the disease by measuring limb volume and fluid content. There are also studies to assess the lymphatic function and perform lymphatic mapping. This is a review on modern investigation modalities.

Methods: A literature search was performed. Evidence of the following investigation modalities i.e. traditional lymphoscintigraphy, truncated cone formula, computed tomography, magnetic resonance imaging, optoelectronic devices, bioimpedance analysis and indocyanine green lymphangiography will be reviewed.

Results: Traditional lymphoscintigraphy remains an inexpensive, easily available investigation for the establishment of diagnosis. Limb volume calculation is more easily comprehended by patients than limb circumference measurement. ICG lymphangiography has become a valuable investigation for lymphatic bypass surgery mainly because of its handiness and accuracy in localizing subdermal lymphatic vessels.

Conclusion: With the emergence of new investigation modalities of lymphedema, it is important for the health care providers to understand the application of each modalities for proper disease management.

Keywords: *Lymphedema; Investigation; Lymphoscintigraphy; Optoelectronic Study; Bioimpedance Analysis; Indocyanine Green Lymphangiography*

Background

With the increasing popularity of microvascular operations in treating secondary limb lymphedema in the recent two decades, there are new investigation modalities developed with the aims at assisting operation and assessing the lymphatic function and the response to surgery.

Investigations which are able to localize lymphatic vessels can assist operations like lymphaticovenous anastomosis. While, the surgical outcomes can be assessed with investigations which measure parameters such as limb volume and fluid content.

In this review article, the investigation modalities are classified into several categories:

1. Limb volume assessment;
2. Assessment of fluid content;
3. Localization of lymphatic tissue and
4. Assessment of lymphatic function. Their clinical applications, evidences and limitations are discussed.

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Received: October 17, 2016; **Accepted:** December 20, 2016; **Published:** December 22, 2016

Diagnosis of Lymphedema and Lymphoscintigraphy

The diagnosis of secondary lymphedema can usually be made clinically with history taking and physical examination i.e. history of breast or gynecological cancers, lymphadenectomy and corresponding physical findings. Investigation is seldom required for the establishment of diagnosis.

In doubtful secondary cases or suspected primary lymphedema, investigation becomes necessary and the investigation of choice is lymphoscintigraphy.

In lymphoscintigraphy, ^{99m}Tc-labeled nanocolloids contrast material is injected into the subcutaneous layer at the web spaces of the edematous limb. Serial gamma films are then taken. In a normal limb, the major lymphatic vessels appear as a linear structure. The axillary or groin lymph nodes should be visualized in the one-hour film. While in a lymphedema limb, the linear lymphatic uptake is usually replaced by dermal backflow pattern. The groin or axillary lymph node may not be visualized if there is a history of lymphadenectomy [Figure 1] [1-4].

Dermal backflow pattern represents the disease progression in which the lymphatic vessels transform from linear, widely patent channels to tortuous, narrowed channels such that the linear pattern is lost and replaced by diffuse patchy appearance of contrast uptake in lymphoscintigraphy. And when the disease reaches its very late

stage, as there is no functional lymphatic vessel remaining in the limb, there may be a complete stagnation of the radioactive dye at the injection site [Figure 2].

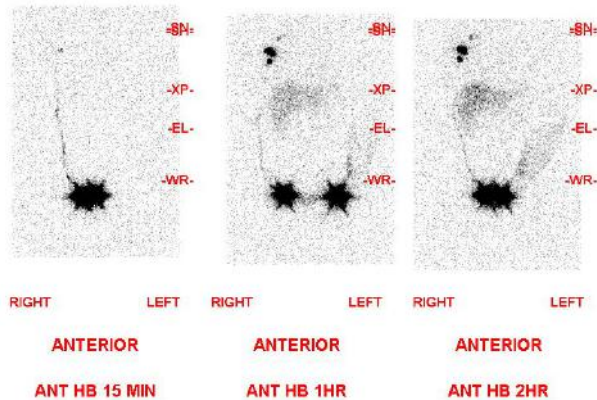


Figure 1: Lymphoscintigraphy of a patient with left upper limb lymphedema after breast cancer treatment. (Left) The lymph nodes at the right axilla were shown up by radioactive contrast as early as 15 minutes. A lymphatic vessel was also visualized. (Middle) The uptake of the right axillary lymph nodes was denser at 1 hour after contrast injection. (Right) In the left upper limb, dermal backflow pattern was shown up to the level of elbow.

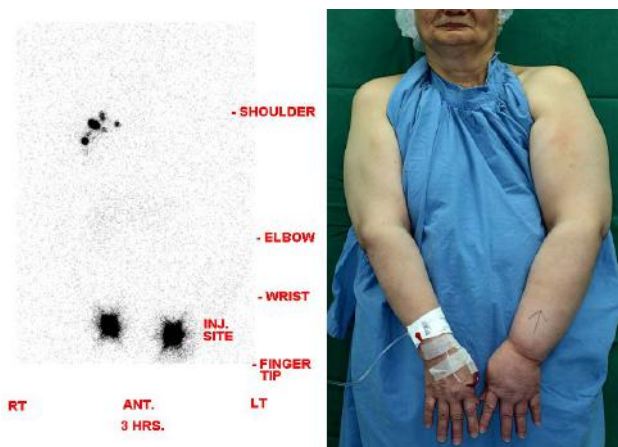


Figure 2: (Right) A patient with left upper limb lymphedema for 10 years after axillary dissection and radiotherapy for breast cancer. The clinical stage of her edema was ISL (International Society of Lymphology) stage II. (Left) Her upper limb lymphoscintigraphy showed a complete stagnation of contrast at 3 hours after contrast injection.

The main advantages of lymphoscintigraphy include the ease of availability and the relatively straightforward interpretation of the study images. The lymphatic function of the limb can also be assessed semi-quantitatively with transport index [5,6]. The obvious disadvantages include use of radiation and inherited suboptimal resolution

Limb Volume

Background

Limb volume is one of the most common methods used by health care providers to follow up the disease progress of lymphedema. On one hand, the total volume of a limb is contributed by the volumes of different components i.e. skin, subcutaneous fat, muscles and bones. On the other hand, the disease process of lymphedema mainly takes place in the skin and subcutaneous layer, while the muscle and bones are spared [7-9].

Therefore, in theory, the disease progression should be more accurately assessed by the change in volume of the skin and subcutaneous fat rather than the total limb volume. The total limb volume can be considered as a measurement of the overall clinical outcome of lymphedema i.e. including musculoskeletal compartment hypertrophy due to heavy limb.

However, since the volume of skin and subcutaneous fat is difficult to be calculated separately, health care providers in general use total limb volume for disease follow-up.

Another precaution of using the limb volume for disease assessment is that the change in patient's body weight has to be taken into consideration for any changes in the limb volume.

The gold standard - water displacement study

Water displacement study has long been considered as the gold standard of limb volume measurement. Therefore, to validate a new investigation modality on limb volume, researchers often compare the findings derived from the new investigation with those derived from water displacement study [10-12].

Water displacement study is easy to be carried out. However, this can be cumbersome to be implemented in the setting of an ordinary clinic e.g. the need of water tank, sizable water collection and measurement container, drainage system and hygienic issues.

Truncated cone formula

A human limb can be imagined as a stack of truncated cones of different shapes. The volume of a truncated cone can be calculated from the height and circumference of the cone i.e. frustum formula. Therefore, the total volume of a limb can be calculated by summing up the volumes of the imaginary truncated cones of each limb segment.

There are two papers in the literatures which studied the calculation of limb volume from circumference measurements [10, 11].

An early study by Karges et al. compared the calculated limb volume with water displacement volume in 14 patients with post-mastectomy upper limb lymphedema. The truncated cone volume was calculated using the frustum formula. The height of each truncated cone, i.e. the interval of circumference measurements, was around 3-4 cm. In this study, the mean calculated limb volume was 2022.90 ml and the mean volume of the limb derived from water displacement was 2118.52 ml. The mean difference between the water displacement volume and the calculated volume was 95.62 ml. It was found that there is a high correlation between the calculated volume and the water displacement volume [10].

Brorson et al. also calculated the limb volume with the truncated cone method. The hand volume was excluded in the calculation. His group has developed Excel-based computer programs to calculate limb volume from circumference measurements. The height of each segment of cone was set at 4 cm. The mean volume of lymphedema limb (including hand volume) from water displacement was 3138 ml. And the calculated mean limb volume was 2972 ml (excluding hand volume). It was found that the findings derived from calculation method correlated with the measurements from water displacement method [11].

The limb volume calculation method appears to be simple and correlates well with the water displacement study.

Computer Tomography (CT) and Magnetic Resonance Imaging (MRI)

CT and MRI volumetry are well-established in volume assessment of certain solid organs e.g. liver, brain volume and muscle [13-17]. In theory, the limb volume can be calculated readily with CT or MRI volumetry. However, in the literature, there was no CT or MRI volumetric study for the assessment of limb volume in lymphedema.

Sagen et al. used CT to measure the cross sectional area of limb in lymphedema patient. Their group compared the cross sectional area with the limb volume obtained from water displacement study [18].

Contrast CT and MRI have been used to study the structural changes of skin and subcutaneous tissue in lymphedema. Honeycombing of the subcutaneous layer is a common finding in both studies, which corresponds to an accumulation of mobile tissue fluid between fibrous septa and fat lobules [Figure 3] [19-21]. Other MRI features of lymphedema include hyperintense dermis and subcutaneous layer in T2-weighted images due to the increase in fluid in these structures [9].



Figure 3: Contrast MRI of a patient with left lower limb lymphedema after treatment of cancer of cervix. Honeycombing of the subcutaneous tissue, hyperintense dermis and subcutaneous layer were shown in this T2-weighted image.

Optoelectronic study

Optoelectronic study is a relatively new investigation modality for the measurement of limb volume. It has been studied to assess the limb volume since the 1990s [12, 22-25]. And Perometer® (Pero-System Messgeräte GmbH, Germany) is one of the well-described commercially available optoelectronic machines in the literature [12, 22, 23, 25].

The essential components of an optoelectronic device are the measurement frame and the computer. The measurement frame is mounted with infrared diodes and infrared receivers. To start the measurement, the patient is instructed to place the limb perpendicular to the plane of the frame. The limb is scanned and the cross sectional information at multiple levels can be obtained while the measurement frame is moved along the long axis of the limb. The limb volume can therefore be computed. Regarding the validation of the machine, Stanton et al. compared the volume

derived from truncated cone formula for standard geometric cylinder and cone models. It was found that Perometer® generated a smaller volume than using truncated cone formula. The difference was 0.8 to 4.6% [25]. A later study by Lee et al. compared Perometer® with water displacement study. In this study, hand volumes of 40 women with Perometer® and water displacement were measured. It was found that there was a high concordance between hand volumes obtained from Perometer® and those from water displacement method [12].

The advantages of optoelectronic device include ease of use and non-invasiveness. It is also less operator-dependent when compared to the truncated cone formula.

Fluid Content of Limb

Background

The severity of edema can be reflected by the fluid content in the limb. Clinically, the more fluid retained in the limb, the limb becomes tense and the edema becomes pitting. On the other hand, when the limb has less fluid, it becomes less tense and the edema becomes less pitting.

Up till now, the only quantitative measurement of the limb fluid content is by bioimpedance analysis.

Bioimpedance analysis

Bioimpedance analysis has been used to assess fluid content of limb since the late 1990s [26-29]. In essence, an electrical current is applied to patient's limb during bioimpedance analysis. The resistance of cellular membranes varies with frequency of the applied current. At lower frequency, the resistance of cellular membranes increases, the current preferentially passes through extracellular fluid. The resistance contributed by the extracellular fluid, i.e. amount of extracellular fluid, can then be assessed. In lymphedema, lymphatic fluid is an excess of fluid in the extracellular compartment. Therefore, by comparing the readings of the edematous and the normal limbs, the bioimpedance findings can be obtained for the edematous limb [30-32].

Warren et al. conducted a case control study with 15 unilateral lymphedema patient and 7 healthy subjects. It was found that there was a significant difference in the bioimpedance analysis findings between the two groups [33].

The advantages of bioimpedance analysis include its non-invasiveness, less operator-dependent and it is the only investigation modality in the literature that studies the fluid content of a limb. The main disadvantage is that the study is not applicable in patients with bilateral disease as the bioimpedance analysis of the edematous limb is the ratio of the edematous limb finding to the healthy limb finding.

Lymphatic Function and Lymphatic Mapping

Background

Although the sites of original insult to the lymphatic system e.g. operation or radiotherapy are usually at the axilla and pelvis, the damages to the lymphatic system are not limited to these lymph node basins. Based on Koshima's study in 1996, the stasis of lymphatic fluid distal to the lymphatic obstruction sites, leads to chronic inflammation, fibrosis and the degeneration of lymphatic smooth

muscle cells. These, in turns, lead to the loss of two important functions of the lymphatic vessels i.e. loss of lymphatic vessels patency and loss of pumping action of the lymphatic vessels. As a result, there will be a decrease in functional lymphatic vessels in the chronic lymphedema, which further worsens the disease. A vicious cycle is therefore created [34].

When the disease progresses, the lymphatic vessels become stenotic, tortuous and completely blocked in the very late stage. Therefore, the function of the limb lymphatic system can be evaluated through the studying of the location, morphology of the lymphatic vessels and the contrast transport time.

Currently, there are three investigation modalities that are able to locate the lymphatic vessels and study their morphology, which include lymphoscintigraphy, indocyanine green lymphangiography and magnetic resonance lymphangiography.

Lymphoscintigraphy has been described in the previous section.

Indocyanine Green (ICG) Lymphangiography

ICG lymphangiography is a relatively new investigation modality to locate and assess the function of lymphatic vessels. Similar to lymphoscintigraphy, ICG solution is injected into the subcutaneous plane at the distal part of the limb. The ICG solution is then absorbed into the lymphatic system.

The formation of image is based on the florescent property of the ICG-protein complex. The ICG-human protein complex in the lymphatic system excites after absorbing near-infrared of 800nm. The excited complex then emits near-infrared of 840nm [35, 36]. Therefore, by picking up the emitted near-infrared signal, the location and anatomy of the subcutaneous lymphatic vessels can be visualized and the lymphatic function can be assessed.

Koshima group derived an ICG lymphangiography staging system where the lymphographic findings are classified into two categories: linear pattern and dermal backflow pattern. The dermal backflow pattern is further divided into splash, stardust, and diffuses patterns [Figure 4]. It was found that this ICG lymphangiography staging system has a significant correlation with clinical stage of lymphedema. In the proximal part of the limb, dermal backflow patterns are more frequently found than linear pattern. And the dermal backflow pattern becomes more widespread with increasing duration of lymphedema [37-39]. After being popularized by the Koshima group, ICG lymphangiography becomes an important investigation modality for preoperative localization of lymphatic vessels in lymphaticovenous anastomosis [40-43].

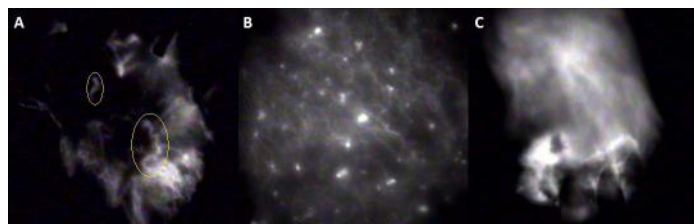


Figure 4: The three dermal backflow patterns in ICG lymphangiography are, in the order of advancing stage of lymphedema, A – splash pattern, tortuous subdermal lymphatic vessels were shown (circle); B – stardust pattern and C – diffuse pattern.

When compared to traditional lymphoscintigraphy, ICG lymphangiography produces a more superior image quality. Color images are now available with newer machines. As opposed to lymphoscintigraphy, ICG lymphangiography does not involve the use of radiation. Therefore, a real time dynamic fluoroscopy can be obtained readily. Moreover, with handier ICG machine, ICG lymphangiography can virtually be performed in any place convenient to both the surgeons and the patients at any time. The main downside is the machine cost. And a whole limb image is not available in ICG lymphangiography as opposed to the other two investigations (traditional lymphoscintigraphy and magnetic resonance lymphangiography).

Magnetic Resonance Lymphangiography (MRL)

The use of MR lymphangiography (MRL) in lymphedema has been described since the early 2000s [44]. In these studies, the MR studies were performed with a 3.0-T MR system. Gadolinium-based contrast agent was required for the production of lymphangiography. The agent was injected intracutaneously at the web spaces as traditional lymphoscintigraphy. The severity and extent of edema was first identified with a heavily T2 -weighted 3D sequence. A dynamic enhanced coronal MRL, T1-weighted images with fat saturation technique was required for lymphatic mapping [Figure 5] [44-50].



Figure 5: Same patient as in Figure 3. Contrast MRL showed a tortuous lymphatic vessel (arrow) at the lateral aspect of the patient's left leg.

Arrivé et al. described a new non-contrast MRL protocol for the evaluation of lymphedema. The lymphangiography required very heavily T2-weighted fast spin echo sequences to obtain a nearly complete signal loss in tissue background and specific display of lymphatic vessels with a long T2 relaxation time [51, 52].

MRL produces images with more superior spatial resolution when compared to traditional lymphoscintigraphy. Information e.g. extent of lymphedema and location of functional lymphatic vessels can be clearly depicted with MRL, which is useful in disease follow-up and preoperative planning for lymphaticovenous anastomosis.

Other Investigation

Lipiodol Lymphangiography

It is worthwhile to mention that lipiodol lymphangiography is an obsolete investigation for lymphedema. This study involves the injection

of radiopaque oily contrast into the lymphatic vessels in order to visualize the lymphatic system of the lymphedema limb. It is observed that this oily contrast causes obliteration of the vessels through inflammatory process or direct blockage by the oily contrast itself [53]. Its current use is mainly restricted to the treatment of intrathoracic chyle leak [54-56].

Conclusion

Although it is common to use limb circumferences for disease follow up, it is more sensible to describe limb size in terms of volume as limb volume is more easily comprehended by patients. Limb volume description also makes the comparison of surgical outcomes amongst different centers possible. Calculation of limb volume from circumference measurement is a good alternative if an optoelectronic system is not available. ICG lymphangiography becomes a valuable investigation for LVA because of its handiness and accuracy in localizing subdermal lymphatic vessels. CT and MRI are still not popular currently mainly because of resources. In doubtful cases of limb swelling, traditional lymphoscintigraphy remains an inexpensive, easily available investigation for the establishment of diagnosis.

Disclosure Statement

No financial interests exist.

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