Evaluation of magnetic resonance lymphangiography for patient's undergoing pre and post microsurgery

Abdullah Almujally, Fabrizio Calliada

University of Pavia, Radiology Department, Pavia, Italy

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ABSTRACT
MR lymphangiography using dynamic contrast-enhanced images is useful in providing high quality images to diagnose many clinical conditions. However, this procedure cannot be used for traumatic patients or patients with severe side effect of using contrast media. Thus the only option available is to develop a protocol for lymphedema without contrast agents in order to reduce the contra indication of the procedure and to extract diagnostic information without contrast medium. The objectives of this study are to evaluate the role of MR-lymphographic for the assessment of lymphedema before and after lymph node self-transplantation. This study was conducted at IRCCS Policlinico San Matteo (PV), Pavia, Italy. A total of 17 patients were investigated for lymphedema evaluation due to primary or secondary lymphedema. All procedures were performed due to justified clinical conditions according to the ethical guidelines. All procedures were performed using two MRI machines: Siemens Symphony 1.5 T and Philips MRI (ingenia) 3.0 T. Early Lymphedema stages diagnosis represents great challenges. Non contrast MRL is used to diagnose accurately the lymphatic system disorder. From studies, the researchers have found non contrast MRL is as a promising methodology in the
diagnosis of lymphatic system disorders with accuracy up to 90%. The study revealed that non-contrast MRL imaging technique can increase the accuracy of lymphedema diagnosis, improve disease prognostication, and provide a more robust marker of treatment response.

**Keywords:** Lymphedema; MRI; Magnetic Resonance Lymphangiography; Lymphatic Imaging, Noncontract MRI

1. INTRODUCTION

The lymphatic system, which is a part of the circulatory system, consists of a complex network various structure consist of organs such as spleen and thymus, tissues (Peyer’s patches and Intraepithelial lymphocytes), lymphatic nodes, vessels and capillaries. The main physiology and importance of the lymphatic system is to gather the lymph fluid from different body tissues organs to maintain body fluids balance, transport some lipids and protein as well as its role in the immune system (leukocytes) in infection fighting and collecting viruses, bacteria and waste products (Breslin et al., 2018). Lymphatic system circulation starts at the level lymphatic capillaries and ducts and connected with cardiovascular system through a large lymph duct (thoracic duct) (Cramer, 2014). Lymphedema or lymphoedema, which is a chronic disorder causing swelling in any body parts due to accumulation of lymph fluid in the interstitial causing prolonged swelling and reactive fibrosis of the affected tissues. It occurs due to congenital or acquired causes cause a blockage in the lymph circulation which diminishes lymphatic return. Lymphedema occur due to developmental causes during infancy caused by faulty genes that affect while secondary lymphedema causes by various causes including infection, trauma, obesity, tumors, cancer treatment (surgical or radiation therapy), filariasis and chronic venous insufficiency (Kayiran et al., 2017). In developed countries, the main etiology of lymphedema is cancer treatment while in developing countries due to infection. The prevalence of lymphedema due to primary causes was estimated to be one cause per one hundred thousand individuals while the prevalence of lymphedema due to secondary cause was estimated to be one out of one thousand individuals (Greene, 2015). Lymphedema can be diagnosed by using different imaging modalities including computed tomography (CT), scintigraphy and magnetic resonance imaging (MRI). All these procedures have various advantages of drawbacks. Traditional techniques for diagnosing lymphedema include pedal lymphangiography (PL), which is replaced by intraoral lymphangiography, because it is invasive procedure and require long time to accomplish the procedure (Nadolski and Itkin 2013). In intradermal pedal lymphoscintigraphy the use of SPECT CT is essential to overcome the limitation of poor spatial resolution. The radiation dose to patient and staff is one of the main concerns of the procedure. MR lymphangiography is used by injection contrast medium (gadolinium) subcutaneously or intradermally. The drawback of this procedure does not provide sufficient findings due to the delusion of the contrast agent (Arrivé et al., 2017). Dynamic contrast-enhanced MR lymphangiography currently used to provide good spatial resolution and dynamic flow of the lymph. This procedure also has limitation regarding imaging of traumatic patients and the side effect of using contrast media for patients with kidney function disorders (Arrivé et al., 2019; Cellina et al., 2019). Thus the only option available is to develop a protocol for lymphedema without contrast agents in order to reduce the contra indication of the procedure and to extract diagnostic information without contrast medium. In addition to that, no previous study, to our knowledge conducted for lymphedema evaluation without contrast medium pre and post-operative. The objectives of this study are to evaluate the role of MR-lymphographic for the assessment of lymphedema before and after lymph node self-transplantation.

2. MATERIALS AND METHODS

**Patient’s populations**

This study was conducted at IRCCS Policlinico San Matteo (PV), Pavia, Italy. A total of 17 patients were investigated for lymphedema evaluation during two years from October 2017 to October 2019. Inclusion criteria are pre and post-surgical operation while MRI contrast medium is a contra indication (Figure 1). The routine patient preparations include suspension of lymphatic drainage for two days and instructed to wear elastic stockings for one day. Patient communication is very crucial in order to maintain patient in the same position during the procedure. Patient is placed in the supine position, feet first, with both legs on a ramp pillow so that the lower extremity is parallel to the main magnetic field and near the most homogeneous area of B0.

**Ethical approval**

All procedures were performed due to justified clinical conditions according to the ethical guidelines according to the Helsinki declaration. The study was approved by the ethics committee approval no RTMU-83746-2017. In addition to regular MRI safety screening check list and consent, an informed consent was obtained from all patients for participation in this research prior the
The consent includes the purpose and duration of the investigation, benefit and risk description, right to enquire or withdraw from the investigation.

**Figure 1** Flow chart Non contrast MRI procedure

**Imaging equipment’s**
All procedures were performed using two MRI machines: Siemens Symphony 1.5 T (Siemens Healthcare, Germany). The machine with bore 60-cm bore delivers a complete range of clinical applications for whole body regions. The second machine is Philips MRI (ingenia). The power magnet of the machine enabled reduction in image acquisition time up to 50%. Both machines were subjected regularly to routine quality control test by a qualified medical physicist to ensure consistency and quality of the images.

**Imaging Protocol**
The imaging protocol is composed of the following sequences, according to Lymph Team protocol IRCCS Policlinico San Matteo (PV), which composed of standard sequences using two MRI Scanners: Siemens Symphony 1.5 T and Philips MRI (ingenia) 3 Tesla. The sequences adopted for MRI machine one (Siemens Symphony 1.5 T) were consist of 3D T2 weighed TSE with SPIR fat suppression. The sequences adopted were D T2 weighed HASTE with SPIR fat suppression. While the sequences used for Philips MRI (ingenia) consist of 3 acquisitions 3D T2 TSE oriented in axial, coronal and sagittal for each of the examined limbs. A single TSE sequence oriented in coronal plane (it is simply MRI cholangiography sequence modified by increasing the values of TR and TE. The parameters of the two types of sequences parameters are described in Table 1. The average time of the exam was about 30-45 min and a semi quantitative analysis of the exam will be used. For each procedure, at least six axial sections of each limb will be investigated, and each of them will be subdivided into four quadrants and evaluated according to specific score. A score of lymphedema severity (from 0 to 2 points) with a maximum of 48 points will be used. The images were assessed by at least two radiologists with experience more than 15 years in addition to one resident. All the images were initially reported by one radiologist and revised by another one (double evaluation of the images).
Table 1 Patient image acquisition parameters according to acquisition type for Philips MRI (ingenia)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient position:</td>
<td>Feet first</td>
<td>Feet first</td>
</tr>
<tr>
<td>Slice Thickness (mm)</td>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td>Repetition time (ms)</td>
<td>1000</td>
<td>4000</td>
</tr>
<tr>
<td>Echo time (ms)</td>
<td>100</td>
<td>890</td>
</tr>
<tr>
<td>Number of averages</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Spacing between slices (mm)</td>
<td>6</td>
<td>0.9</td>
</tr>
<tr>
<td>Echo train length</td>
<td>123</td>
<td>100</td>
</tr>
<tr>
<td>Acquisition matrix</td>
<td>320x280</td>
<td>500x450</td>
</tr>
<tr>
<td>Flip angle</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

3. RESULTS AND DISCUSSION

A total of 15 patients were enrolled in this study. All patients referred to the department for justified clinical conditions. No volunteer were included in this study. The number of patients was determined according to patients flow rate. All patients with pre and post non contrast or post-surgery were included in this study. Exclusion criteria include the use of contrast medium. Out of the 15 patient’s populations, 4 (23.5%) patients were males while 13 (76.5%) patients were females. The mean age and range of patients group is 53.5±13 (26.0-76.0) as shown in Table 2. All patients with normal weight range with body mass index (BMI (kg/m^2)) range from 18.4 to 25.9. Out of the 17 patients, 4 (23.5%) patients had a primary lymphedema while 13 (76.5%) of the sample has a secondary lymphedema resulted from cancer treatment using radiation therapy or surgical intervention. 60% of the patients undergo the procedures pre and post-surgical intervention.

Figures 2 A, B: non contrast MRI for the leg of a patient 37 years old suffering from secondary lymphedema due to radiation therapy.

Figure 3 A.B: non contrast MRI for 34 patients suffering from lymphedema (left arm)
**Figure 4 A, B** Non contrast MRL for 65 years old female patients suffering from secondary lymphedema pre and post-surgery.

**Table 2** patients demographic data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±sd</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>53.5±13</td>
<td>26.0</td>
<td>76.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.1±11</td>
<td>50.0</td>
<td>77.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.0±8</td>
<td>152</td>
<td>178</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.5±3.2</td>
<td>18.4</td>
<td>25.9</td>
</tr>
</tbody>
</table>

Figures 2 A, B show non contrast MRI for the leg of a patient 37 years old suffering from primary lymphedema. Non contrast MR-Lymphographic technique has a capability in providing high-resolution images of the lymphatic system with very good anatomical findings. Thus this promising technique can be used with patients with contra indication to the contrast medium or patients with low Glomerular filtration rate (GFR). Non contrast MRI technique has an excellent potential in providing accurate and reliable diagnosis and planning of microsurgical intervention. Figure 3 showed arm images for non-contrast MRI procedures. Figure 4 A,B show Non contrast MRL for 65 years old female patients suffering from secondary lymphedema pre and post-surgery. 35% of all cases were undergone post-surgery non contrast MRL while 65% of the cases undergone pre and post MRL. All the 17 cases, whom undergone MRI without contrast for lymphedema was diagnosable images and provided acceptable findings, thus no image was rejected or considered poor. Due to the development on MRI technology using string magnetic field with sensitive coils and advanced image processing software, enabled operators to reduce the scan time and increase image quality. As illustrated from the current study results, the vast majority of clinical indications are secondary lymphedema due to acquired cause (radiotherapy or surgery). Primary lymphedema incidence is always for patients below the age 35 years old. However, only 4 patients undergone the procedure suffering from primary lymphedema. The clinical manifestations of primary lymphedema occur in patients from birth to over 25 years of age. Recently Arrivé et al., 2017 reported that non-contrast MRL is useful imaging procedure for the diagnosis of the extremities, patient follow up and severity assessment, classification, and follow-up. The advantages of the contrast medium studies include accurate delineation of the anatomical details of the lymphatic and vascular systems (Hsu & Itkin., 2016). In this study non contrast MRI study was used to evaluate patients’ pre and post microsurgery or physical therapy (Campisi et al., 2006). In agreement with previous studies, and after rigorous assessment of patients using pre and post non contrast imaging, patients were benefited from microsurgery, particularly patents at early stage of the disease by decreasing the swelling and quick recover of patients (Campisi et al., 2006). NCMRL is used for evaluation of lymphedema in literature (Almujally & Calliada, 2020). However, this study provided unique assessment of patient’s pre and post micro surgery. The image acquisition sequences consist of 3D T2-weighted TSE with SPIR fat suppression. The sequences adopted were D T2- weighed HASTE with SPIR fat suppression. While the sequences used for Philips MRI (ingenia) consist of 3 acquisitions 3D T2 TSE oriented in axial, coronal and sagittal for each of the examined limbs. A single TSE sequence oriented in coronal plane (it is simply MRI cholangiography sequence modified by increasing the values of TR and TE. Comparable sequences were reported by arrive et al., 2019. Which include 3D high spatial resolution fast-recovery fast spin-echo (FRFSE). The current imaging sequences enabled acquisition of high image quality (high signal-to-noise ratio (SNR), which means diagnosable image quality while overcoming the contrast medium disadvantages.
4. CONCLUSION
The current study showed that MRL is useful and reliable procedures for the diagnosis and follow up patients with lymphedema pre and post-surgery. The current imaging protocol enabled acquisition of diagnosable MRL images. The current imaging sequences enabled acquisition of high image quality (high signal-to-noise ratio (SNR), which means diagnosable image quality while overcoming the gadolinium disadvantages.

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Conflicts of Interest: The authors declare no conflict of interest.

REFERENCE