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MAGNETIC RESONANCE LYMPHOGRAPHY (MRL): POINT AND COUNTER-POINT

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ABSTRACT

Two preeminent lymphologists debate the findings, implications, interpretations, and value of magnetic resonance lymphography (MRL) in the evaluation of peripheral lymphedema. Their contrasting views are discussed in the context of different lymphatic imaging modalities including MRL, lymphoscintigraphy, and microscopic anatomy.

Keywords: imaging, magnetic resonance lymphography, lymphoscintigraphy, anatomy, lymphatic vessels

POINT

(Dr. Waldemar Olszewski)

The article published by Ningfei Liu and colleagues "Magnetic Resonance Lymphography Demonstrates Spontaneous Lymphatic Disruption and Regeneration in Obstructive Lymphedema" (1) presents MRI lymphographies demonstrating disruption and regeneration of lymphatics of limbs in obstructive lymphedema.

This article prompted me not only to point to flaws in interpretation of MR imaging but also to bring up the problem of proper discrimination of anatomical structures such as: a) lymphatics, b) veins, c) perivascular spaces, d) tissue channels accumulating excess tissue fluid, and e) limb regions accumulating macrophages with phagocytized tracer. An additional problem is the reported size of structures evaluated on images compared with those seen in actual live human tissues. The field of lymphatic imaging is continuously evolving, and technological advances combined with the development of new contrast agents, although impressive, should be confirmed with actual morphology and physiology of the investigated tissues. Otherwise, incorrect interpretation will be made, memorized, and possibly adversely affect our clinical reasoning leading to improper decisions.

The authors carried out MRI imaging on 45 patients with obstructive lymphedema of lower and upper limbs using gadobenate dimeglubine (Gd-BOPTA) injected into the digital web spaces. The main problem for visualization of lymphatics with this tracer is uptake by the venous system caused by diffusion of its small molecules (2). The lymphatic vessels in the lower/upper leg and inguinal lymph nodes show a tendency to have the highest contrast material uptake in the later acquisitions, compared with the veins, however, diffusion through the lymphatic walls and in the interstitial space, virtually increases the size of the contrasted structures.

1. Examining *Fig. 1*, I find some important highlighted findings which need to be examined. In panel a, the spot pointed by

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arrow is not "disruption of lymphatics," but a network of lymphatics at the site of inflammation or trauma, etc. Furthermore, the typical site of development of ulcers is on the calf and never developing in the thigh. In addition, leakage of tracer from "disrupted" lymphatic does not form a network, lymphatics are extremely resistant to traction and tearing, and their disruption is very unlikely (3). They can stand pressures over 200-300mmHg due to small diameter (surface) and low tension on the wall (law of Laplace). In panel b, arrowhead points to a branch of saphenous vein and not a lymphatic. In panel c, arrows point to a network of dilated preexisting lymphatic subepidermal plexus at the site of pathological changes. There is nothing specific in the image indicating that there is "regeneration." In fact, regenerating capillaries grow longitudinally bridging the gap. This is a confluent pattern suggesting accumulation of macrophage take-up of the tracer. In panel d, there is a diffuse accumulation of the tracer in the subepidermal lymphatic plexus and not a "backflow." In obstruction of main lymphatic trunks, stagnant lymph accumulates under the epidermis as this is the site of least resistance to tissue expansion (4).

2. Examining *Fig. 2*, there is superimposition of the venous and lymphatic epifascial systems, with predominance of veins. If this an anterior-posterior view, the contrasted vessels are not lymphatics as they are located on the lateral side of the calf.

3. In *Fig. 3b,* the arrow on the left leg points to a vein and not a lymphatic. The structure of lymphatic vessels is different with typical narrowings at the valves and much smaller diameters.

4. In the text (p.58), there is the statement "lymphatic collectors diameter ranges from 0.7-10mm in lower limbs". The 10mm wide vessels would be wider than the femoral artery! This is unrealistic. This quantitative evaluation of the MR image is misleading due to lateral scattering of the signal. Human limb lymphatics have a normal diameter of 0.1 to 1.5mm and in lymphedema up to 2.0mm. The diameters reported by the authors do not correspond to actual morphology. In my experience performing over 2,000 operations on limbs for lympho-venous shunts and debulkings, I have never dissected a lymphatic wider than 2mm.

These remarks are not a criticism of authors' observations, but of inaccurate interpretations of images due to lack of comparison with actual anatomy of human tissues seen during surgery or in atlases of anatomy based on tissue dissection (5). The new imaging techniques prompt us to contribute to the interpretation with our own experience to optimize the method.

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COUNTER-POINT
(Dr. Ningfei Liu)

High quality lymphatic imaging is extremely important for the diagnosis and management of lymphatic disease. MR lymphangiography (MRL) with high resolution has been proven to be useful in the diagnosis of peripheral lymphatic system

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disorders in the clinic. The outstanding advantage of MRL is its capability to produce high-quality, real-time imaging of the lymphatics and lymph nodes, and therefore to help clinic workers make morphological and functional judgment of the lymphatic system (1). However, as a relatively new technique which has not yet been widely used, MRL imaging can present as a difficult and not well understood technique by people lacking information and practice. In response to Dr. Olszewski, we provide additional information on MRL techniques and imaging by clarifying what was interpreted as "the flaws in interpretation of MR imaging" in our article.

There are two major mistakes in Dr. Olszewski's statement. First "perivascular spaces and tissue channels" are not the observation items in MRL. Actually, they cannot be visualized with current MRI, nor with our MRL. Perivascular spaces and tissue channels have never been the target of our study. The purpose for us developing our MRL is for observation of the lymphatic system. Also, "perivascular spaces and tissue channels" are closer to terms used for describing microscopic examination. Second, the phenomenon "limb regions accumulating macrophages with phagocytyzed tracer" cannot be seen during our MRL examination, and this also is a microscopic description. Further, the mechanism of contrast absorption between lymphoscintigraphy and MRL is different. Unlike the tracer which is taken up by macrophages in lymphoscintigraphy, the contrast (Gd-BOPTA) which is injected intradermally in MRL is quickly absorbed and transported by primary lymphatic vessels because of its small molecules. This can be confirmed by visualizing highlights of lymphatic channels within minutes after contrast injection and a fast contrast flow-in and flow-out of contrast in lymph nodes.

The purpose of developing a new imaging method is to have a realistic picture of pathological changes of the lymphatic system in the lymphedematous limbs. Compared with previous and present imaging tests, the MRL we developed produces images of the lymphatic system with much higher resolution and are of much better quality. There were no "false pictures" presented in our article. The so-called "false picture" may be the result of a misunderstanding of the image by an observer who is not familiar with MRL imaging. After more than 1,200 tests, we have learned a great deal about the pathology of the lymphatic system in lymphatic circulatory disorders, and the explanations of our published pictures are based on the accumulation of our experience and knowledge over 6 years. MRL examination has significantly improved diagnoses of lymphatic system disorders at our clinic, and it has not yet resulted in an improper clinical decision. None of our published pictures as yet require reinterpretation, but we welcome discussion and learning from those with experience and a sound understanding of the technique.

With respect, Dr Olszewski has mistakenly reinterpreted some aspects of the lymphatic network depicted in our images (2). With careful examination of *Fig. 1d*, one is able to see what the lymphatic network actually looks like, and *Fig. 1a* does indeed show a "disrupted" lymphatic with leakage of contrasted lymph and not a lymphatic network. This patient never had inflammation, trauma, or an ulcer in her edematous leg. I agree that lymphatic vessels may resist traction and tearing and can be extremely dilated in locations with softer tissue protection (i.e., the thigh). This lymphatic disruption was only seen in the anterior tibial region where the lymphatic collector had little protection and was found to be damaged, as reported in our article.

Fig. 2 shows an interrupted lymphatic. It is easy to distinguish the lymphatic from veins on the MRL picture by its much higher signal intensity, larger size, and irregular shape. The veins show much lighter signal intensities, are straighter in shape, and are

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located behind the lymphatic in this picture. The disrupted vessel is not a saphenous vein as Dr. Olszewski suggests. This is in fact an "acute" obstructive lymphedema case with inguinal lymph node metastasis, severe lymphedema, and significant dilatation of lymphatic channels.

The MRL technique we have developed cannot display either the "subepidermal plexus" of lymphatic vessels or macrophages. The leg scan in the original article (*Fig. 2*) was taken 10-20 min after the injection of the contrast. It is therefore not possible, to the best of the authors' knowledge, for macrophages to take up the tracer and move quickly up the leg and accumulate. Contrast injected intradermally is diffused into initial lymphatics in the MRL technique and transported with lymph through lymphatics and lymph nodes. The quick fill-in and fill-out of the contrast through lymph nodes in healthy limbs (about 30 min after contrast injection) (3) does not support Dr. Olszewski's claim of macrophages absorbing the contrast. The regenerated lymphatic network identified in *Fig. 1c* and *Fig. 4* was confirmed with repeated MRL over a 1½ year follow-up period in patients with lymphatic disruption as shown in *Fig. 3*. The patient never had an inflammatory attack or trauma to the leg, and therefore it is hard to speculate some kind of pathological change other than lymphatic disruption.

"Dermal backflow" is the most common term used to describe pathological changes in lymphedematous skin, and means "stagnant lymph accumulating under the epidermis." Because of its high resolution, MRL is capable of differentiating between "false dermal backflow" (the shadow of isotopic tracer in the collectors) with lymphoscintigraphy and "real dermal backflow," as evidenced by a number of cases (4). The dilatation of "subepidermal lymphatic plexus" in chronic lymphedema should be extremely common as a result of long-term lymph stagnation. However, the dermal backflow phenomenon seen in *Fig. 1d* was only observed in some of the patients. The only interpretation for the characteristic imaging seen in *Fig. 1d* is lymphedematous skin (epidermis) massively diffused with contrast on the MRL image, i.e., dermal backflow. As far as we know, "subepidermal lymphatic plexus" is only seen with fluorescent indirect lymphangiography with a test probe on the skin (5) or with microscopy after monoclonal antibody staining (6). We, therefore, wonder why Dr. Olszewski feels so sure that the spots are "subepidermal lymphatic plexus."

There are no errors in marking the lymphatics in *Figs. 2 and 3* in our original paper (2). With the very first test we performed, we found that the greatest advantage of MRL is its ability to produce images that clearly demonstrate lymphatic vessels. This is because MRL imaging produces lymphatic vessels with much higher signal intensity and a larger size than veins in lymphedematous limbs. This is likely because: a) lymph flow is much slower in obstructed lymph vessels than blood flow in veins; b) contrast is injected intradermally in MRL tests and this ensures that the contrast can be absorbed to a great extent by the initial lymphatic thereby avoiding diffusion of the contrast into veins; and c) enhanced lymph flow in lymphatics and lymph nodes is monitored in real-time during examination in every patient, and dilated vessels with high signal intensities, which we identified as lymphatics, flow into (connect with) lymph nodes. These are the simplest and most important characteristics for correct identification of lymphatic vessels. With experience, using MRL makes it very difficult to mistake the lymphatics.

Lymphatic diameters range between 0.7-10mm in the lower limbs. This observation is the result of direct measurement using MRL imaging. There might be some diffusion of contrast through the vessel wall and increases in the size of the vessel, but it does not affect the overall morphology of the lymphatic system. In the attached *Fig. 1*,

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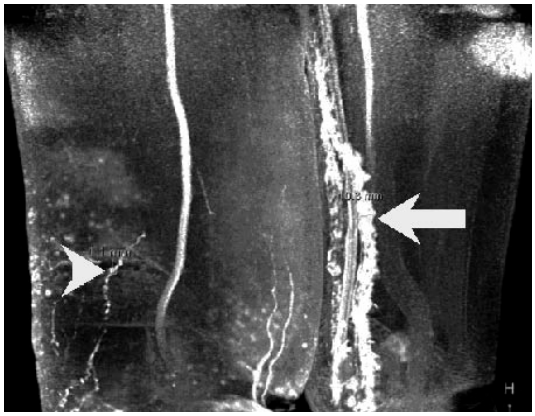

Fig. 1. MRL imaging in a woman with malignant lymphedema due to inguinal lymph node metastases. The arrow head in the right limb points to a lymphatic with 1.1 diameter, and the arrow in the left limb points to an extremely dilated lymphatic 10mm in diameter.

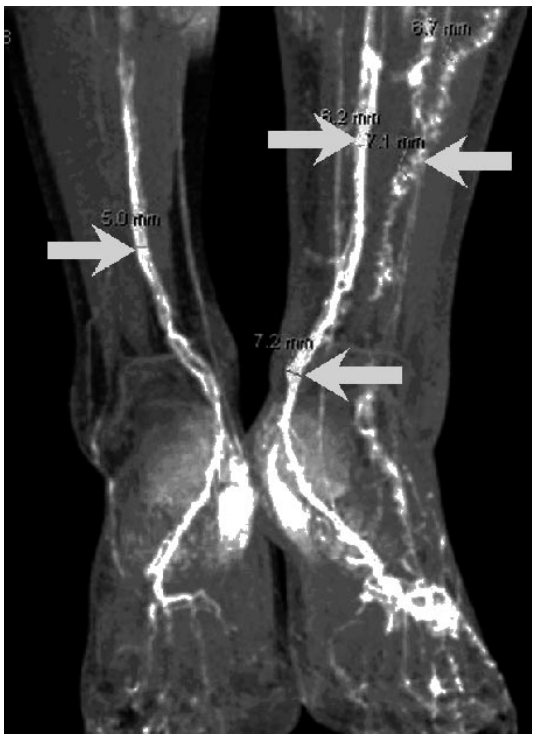

Fig. 2. MRL imaging of lymphatic system in a woman diagnosed with acute lymphedema caused by inguinal lymph node metastasis. The diameters of dilated lymphatic vessels are between 5-7mm in the lower legs.

contrast-enhanced lymphatic vessels are seen with sharp differentiation of sizes in a patient with bilateral lymphedema. The diameter of the lymphatic vessel is 1.1mm in the right limb and 10mm in the left limb. This confirms that MRL can be used to observe lymphatic vessels with significant differences in size. Lymphatic vessels with a diameter >5mm were commonly seen in "acute" lymphedema due to tumor metastasis or surgical procedures which blocked almost all upstream lymphatics in a short period of time as shown in the attached *Fig. 2.* Lymphatic vessels also have the ability to increase size under high pressure, and this could be an physiologic reaction of the body.

Every new technology goes through a learning and development process whereby techniques become better known and more familiar, and those using it gain experience and practice. MRL is no exception. Based on >1,200 tests over the past 6 years, we feel confident that the MRL we use is among the most sensitive and accurate image modality at present for diagnosis of lymphatic disorders. This MRL technique and the images it produces are highly valuable and will become familiar to those involved in the field with wide application in the future.

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